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THE COURSE OF SELECT LECTURES ON EXCEPTIONAL PHARMACOLOGY

Educational manual

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Представлены клинические вопросы частной фармакологии с целью научного обоснования принципов лекарственной терапии. Подробно рассмотрены фармакокинетика, фармакодинамика, показания к применению таких лекарственных средств, как производные серотонина, простагландины, тиреоидные гормоны и препараты для лечения сахарного диабета, средства, влияющие на свертывающую систему крови. Курс лекций позволяет студентам воспользоваться современными сведениями по клинической фармакологии отдельных препаратов и предоставляет информацию для понимания роли каждого лекарственного препарата в терапии заболеваний.

Для студентов 3–6 курсов факультета подготовки специалистов для зарубежных стран.

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5-HYDROXYTRYPTAMINE, ITS ANTAGONISTS AND DRUG THERAPY OF MIGRAINE

5-HYDROXYTRYPTAMINE (5-HT, Serotonin)

Serotonin was the name given to the vasoconstrictor substance which appeared in serum when blood clotted *and Enteramine* to the smooth muscle contracting substance present in entero-chromaffin cells of gut mucosa. In the early 1950s both were shown to be *5-hydroxytryptamine* (5-HT). About 90% of body's content of 5-HT is localized in the intestines; most of the rest is in platelets and brain. It is also found in wasp and scorpion sting and widely distributed in invertebrates and plants (banana, pear, pineapple, tomato, stinging nettle, cowhage).

SYNTHESIS AND DESTRUCTION

5-HT is β-aminoethyl-5-hydroxyindole. It is synthesized from the aminoacid tryptophan and degraded primarily by MAO and to a small extent by a dehydrogenase.

There is close parallelism between CAs and 5-HT. The decarboxylase is non-specific, acts on DOPA as well as 5-HTP to produce NA and 5-HT respectively. Like NA, 5-HT is actively taken up by an amine pump which operates at the membrane of platelets (therefore 5-HT does not circulate in free form in plasma) and serotonergic nerve endings and is inhibited by tricyclic antidepressants. Platelets do not synthesize but acquire 5-HT by uptake during passage through intestinal blood vessels. Again like CAs, 5-HT is stored within storage granules and its uptake at the granular membrane is inhibited by reserpine—causes depletion of CAs as well as 5-HT. The degrading enzyme MAO is also common for both. The isoenzyme MAO-A preferentially metabolizes 5-HT.

SEROTONERGIC (5-HT) RECEPTORS

Gaddum and Picarelli (1957) classified 5-HT receptors into musculotropic (D type) and neurotropic (M type) on the basis of pharmacological criteria. The classical 5-HT antagonists methysergide and cyproheptadine blocked D type receptors. Subsequently 5-HT receptors were differentiated by their high or low affinity for [^{3}H] 5-HT in radioligand binding studies. The present system of classifying 5-HT receptors is based on molecular characterization and cloning of the receptor cDNAs.

Four families of 5-HT receptors (5-HT_1, 5-HT_2, 5-HT_3, 5-$HT_{4\text{-}7}$) comprising of 14 receptor subtypes have so far been recognized. However, only some of these have been functionally correlated or their selective agonists/antagonists defined. Knowledge of subtypes of 5-HT receptors has assumed importance because some newly developed therapeutically useful drugs can only be described as 5-HT receptor subtype selective agonists or antagonists.

All 5-HT receptors (except 5-HT_3) are G protein coupled receptors which function through decreasing (5-HT_1) or increasing (5-HT_4, 5-HT_6, 5-HT_7) cAMP production or by generating IP_3/DAG (5-HT_2) as second messengers. The 5-HT_3 is a ligand gated cation (Na^+,K^+) channel which on activation elicits fast depolarization.

5-HT_1 Receptors Five subtypes (5-$HT_{1A, B, D, E, F}$) have been identified. The 5-HT_{1c} receptor is now designated 5HT_{2c}. All subtypes of 5-HT_1 receptor inhibit adenylyl cyclase; 5-HT_{1A} in addition activates K^+ channels (resulting in hyperpolarization) and inhibits Ca^+ channels. These receptors function primarily as autoreceptors in brain—inhibit firing of 5-HT neurones or release of 5-HT from nerve endings.

The most important location of 5-HT_{1A} receptor are raphe nuclei of brain stem and hippocampus. The anti-anxiety drug *buspirone* acts as a partial agonist of 5-HT_{1A} receptor. The 5-HT_{1D} receptor has been shown to regulate dopaminergic tone in substantia nigra-basal ganglia, and 5-$HT_{1B/1D}$ to cause constriction of cranial blood vessels. The antimigraine drug *sumatriptan* is a selective 5-$HT_{1B/1D}$ agonist. Other functions subserved by 5-$HT_{1\,D}$ receptors are inhibition of NA release from sympathetic nerve endings and that of inflammatory neuropeptides from nerve endings in cranial blood vessels.

5-HT_2 Receptors There are 3 subtypes of 5-HT_2 receptor; all are coupled to phospholipase C and function through generation of IP_3/DAG. 5-HT_{2A} receptor also inhibits K^+ channels resulting is slow depolarization of neurones, α-methyl 5-HT is a selective agonist for all 3 subtypes.

5-HT_{2A} is the most widely expressed postjunctional 5-HT receptor (D type) located on vascular and visceral smooth muscle, platelets and cerebral neurones specially prefrontal cortex. It mediates most of the direct actions of 5-HT like vasoconstriction, intestinal, uterine and bronchial contraction, platelet aggregation and activation of cerebral neurones. *Ketanserin* is a 5-HT_2 antagonist more selective for 5-HT_{2A}.

Contraction of rat gastric fundus is mediated by 5-HT_{2B} receptor.

5-HT_{2C} receptor is located on vascular endotheliumelicits vasodilatation through EDRF release. Choroid plexus expresses large number of 5-HT_{2C} receptors.

5-HT_3 Receptor This is the neuronal 5-HT receptor which rapidly depolarizes nerve endings by opening the cation channel located within it and corresponds to the classical M type receptor. It mediates the indirect and reflex effects of 5-HT:

(i) Somatic and autonomic nerve endings → pain, itch, coronary chemo reflex (bradycardia, fall in BP due to withdrawal of sympathetic tone, respiratory stimulation or apnoea elicited by stimulation of receptors in the coronary bed), other visceral reflexes.

(ii) Nerve endings in myenteric plexus → augmentation of peristalsis, emetic reflex.

(iii) Area postrema and nucleus tractus solitarious in brain stem → nausea, vomiting.

Ondansetron is a selective 5-HT_3 antagonist which inhibits vomiting by blocking these receptors in brainstem as well as in gut wall. 2-Methyl 5-HT is a selective 5-HT_3 agonist.

5-HT_{4-7} Receptors The 5-HT_4 receptor has been demonstrated in the mucosa, plexuses and smooth muscle of gut → probably involved in augmenting intestinal secretion and peristalsis. It is also located in brain, specially hippocampus and the colliculi where it causes hyperpolarization by decreasing K^+ conductance.

Cisapride and *renzapride* are selective 5-HT_4 agonists.

The recently cloned 5-HT_5, 5-HT_6 and 5-HT_7 receptors are closely related to the 5-HT_4 receptor. These are mainly located in specific brain areas, but their functional role is not known. An interesting finding is that *clozapine* (atypical neuroleptic) has high affinity for 5-HT_6 and 5-HT_7 receptors in addition to being a 5-$HT_{2A/2C}$ antagonist.

ACTIONS

5-HT is a potent depolarizer of nerve endings. It thus exerts direct as well as reflex and indirect effects. Tachyphylaxis is common with repeated doses of 5-HT. The overall effects therefore are often variable.

1. CVS Arteries are constricted (by action on smooth muscle) as well as dilated (through EDRF release) by direct action of 5-HT, de-

pending on the vascular bed and the basal tone. In addition, it releases Adr from adrenal medulla, affects ganglionic transmission and evokes cardiovascular reflexes. The net effect is complex. Larger arteries and veins are characteristically constricted. In the microcirculation 5-HT dilates arterioles and constricts venules: capillary pressure rises and fluid escapes. The direct action to increase capillary permeability is feeble.

Isolated heart is stimulated by 5-HT: both directly and by release of NA from nerve endings. In intact animals, bradycardia is mostly seen due to activation of coronary chemoreflex (Bezold Jarisch reflex) through action on vagal afferent nerve endings in the coronary bed, evoking bradycardia, hypotension and apnoea. BP: a triphasic response is classically seen on i.v. injection of 5-HT in animals.

Early sharp fall in BP—due to coronary chemoreflex.

Brief rise in BP—due to vasoconstriction and increased cardiac output.

Prolonged fall in BP—due to arteriolar dilatation and extravasation of fluid.

However, 5-HT is not involved in the physiological regulation of BP.

Important 5-HT Receptor Subtypes

5-HT_1: Autoreceptors; inhibit serotonergic neural activity in brain.
5-HT_{1A}—present in raphe nuclei and hippocampus; buspirone may act through these receptors.
5-$HT_{1B/1D}$—Constricts cranial blood vessels and inhibits release of inflammatory neuropeptides in them; sumatriptan acts through these receptors.

5-HT_{2A}: Previously D type receptor; most important postjunctional receptor mediating direct actions of 5-HT like vascular and visceral smooth muscle contraction, platelet aggregation, neuronal activation in brain; ketanserin blocks these receptors.

5-HT_3: Previously M type receptor; depolarizes neurones by gating cation channels; elicits reflex effects of 5-HT—emesis, gut peristalsis, bradycardia, transient hypotension, apnoea, pain, itch; ondansetron acts by blocking these receptors.

5-HT_4: Mediate intestinal secretion, augmentation of peristalsis. Renzapride is a selective 5-HT_4 agonist.

2. Smooth muscles 5-HT is a potent stimulator of g.i.t., both by direct action as well as through enteric plexuses. Several subtypes of 5-HT receptors are present in the gut. Peristalsis is increased and diarrhoea can occur (also due to increased secretion). It constricts bronchi, but is less potent than histamine. Action on other smooth muscles in man are feeble and inconsistent.

3. Glands 5-HT inhibits gastric secretion of acid and pepsin, but increases mucus production. It thus has ulcer protective property. Effect on other glandular secretions is not significant.

4. Nerve endings and adrenal medulla Afferent nerve endings are activated—tingling and pricking sensation, pain. Depolarization of visceral afferents elicits respiratory and cardiovascular reflexes, nausea and vomiting. 5-HT is less potent than histamine in releasing CAs from adrenal medulla.

5. Respiration A brief stimulation of respiration (mostly reflex from bronchial afferents) and hyperventilation are the usual response, but large doses can cause transient apnoea through coronary chemoreflex.

6. Platelets 5-HT causes changes in shape of platelets and is a weak aggregator through 5-HT_{2A} receptors. However, it does not induce the release reaction.

7. CNS Injected i.v., 5-HT does not produce central effects because it poorly crosses blood brain barrier. However, it serves as a transmitter, primarily inhibitory. Direct injection in the brain produces sleepiness, changes in body temperature, appetite and a variety of behavioural effects.

PATHOPHYSIOLOGICAL ROLES

1. *Neurotransmitter* 5-HT is a confirmed neu-rotransmitter in the brain; brain 5-HT has a fast turnover rate. Cells containing 5-HT are present in the raphe nuclei of brainstem, substantia nigra and few other sites—send axons rostrally (to limbic system, cortex and neostriatum) as well as caudally to spinal cord. 5-HT is probably involved in sleep, temperature regulation, thought, cognitive function, behaviour and mood (imbalance may result in affective disorders and schizophrenia), vomiting and pain perception. Some serotonergic fibres are present in intestines also.

2. *Precursor of melatonin* in pineal gland. It is believed to regulate biological clock and maintain circadian rhythm.

3. *Neuroendocrine function* The hypothalamic neurones that control release of anterior pituitary hormones are probably regulated by serotonergic mechanism.

4. *Nausea and vomiting* Specially that evoked by cytotoxic drugs or radiotherapy is mediated by release of 5-HT and its action on 5-HT_3 receptors in the gut, area postrema and nucleus tractus solitarious.

5. *Migraine* 5-HT is said to initiate the vasoconstrictor phase of migraine and to participate in neurogenic inflammation of the affected blood vessels. Methysergide (5-HT antagonist) is an effective prophylactic and sumatriptan (5-$HT_{1B/1D}$ agonist) can control an attack. However, the role of 5-HT in this condition is not precisely known.

6. *Haemostasis* Platelets release 5-HT during aggregation at the site of injury to blood vessel. Acting in concert with collagen and other mediators this 5-HT accelerates platelet aggregation and clot formation—serves to amplify the response. Its contractile action appears to promote retraction of the injured vessel. Both the above actions contribute to haemostasis.

7. *Raynaud's phenomenon* Release of 5-HT from platelets may trigger acute vasospastic episodes of larger arteries. Ketanserin has prophylactic value in Raynaud's.

8. *Variant angina* Along with thromboxane A_2, 5-HT released from platelets has been implicated in causing coronary spasm and variant angina. However, the inefficacy of anti 5-HT drugs in this condition points to involvement of other mediators.

9. *Hypertension* Increased responsiveness to 5-HT as well as its reduced uptake and clearance by platelets has been demonstrated in hypertensive patients. Ketanserin has antihypertensive property. 5-HT has been held responsible for preeclamptic rise in BP.

10. *Intestinal motility* Enterochromaffin cells and 5-HT containing neurones may regulate peristalsis and local reflexes in the gut through activation by intestinal distension and vagal efferent activity.

11. *Carcinoid syndrome* The carcinoid rumours produce massive quantities of 5-HT. Bowel hypermotility and bronchoconstriction in carcinoid is due to 5-HT but flushing and hypotension are probably due to other mediators. Pellagra may occur due to diversion of tryptophan for synthesizing 5-HT.

DRUGS AFFECTING 5-HT SYSTEM

1. ***5-HT precursor*** Tryptophan increases brain 5-HT and produces behavioural effects because tryptophan hydroxylase in brain is not saturated by the amount of tryptophan available physiologically.

2. ***Synthesis inhibitor*** p-Chlorophenylalanine (PCPA) selectively inhibits tryptophan hydroxylase (rate limiting step) and reduces 5-HT level in tissues. It is not used clinically due to high toxicity.

3. *Uptake inhibitor* Tricyclic antidepressants inhibit 5-HT uptake along with that of NA. Some like fluoxetine, sertraline are selective serotonin reuptake inhibitors (SSRI).

4. *Storage inhibitor* Reserpine blocks 5-HT (as well as NA) uptake into storage granules and causes depletion of all monoamines. Fenfluramine selectively releases 5-HT and has anorectic property.

5. *Degradation inhibitor* Nonselective MAO inhibitor (tranylcypromjne) and selective MAO-A inhibitor (chlor-giline) increase 5-HT content by preventing its degradation.

6. *Neuronal degeneration 5,* 6 dihydroxytryptamine selectively destroys 5-HT neurones.

7. *5-HT Receptor agonists* A diverse range of compounds producing a variety of actions have been found to activate one or more subtypes of 5-HT receptors. Notable among these are:

(i) *D-Lysergic acid diethyl amide (LSD)*—Synthesized as an ergot derivative LSD was found to be an extremely potent hallucinogen. It is a nonselective 5-HT agonist—activates many subtypes of 5-HT receptors including 5-HT_{1A} on raphe cell bodies, 5-$HT_{2A/2C}$ (probably responsible for the hallucinogenic effect) and 5-$HT_{5–7}$ in specific brain areas. However, it antagonizes 5-HT_{2A} receptors in the ileum. A number of other hallucinogens also interact with brain 5-HT receptors.

(ii) *Azapirones* like buspirone, gepirone and ipsapirone are a new class of antianxiety drugs which do not produce sedation. They act as partial agonists of 5-HT_{1A} receptors in the brain.

(iii) *8-Hydroxydipropylamino tetraline (8-OH DPAT)* is a highly selective 5-HT_{1A} agonist which is used only as an experimental tool.

(iv) *Sumatriptan* and other triptans are selective 5-$HT_{1B/1D}$ agonists, constrict cerebral blood vessels and have emerged as the most effective treatment of acute migraine attacks.

(v) *Cisapride* This prokinetic drug which increases gastrointestinal motility has now been found to be a selective 5-HT_4 agonist. Renzapride is still more selective for 5-HT_4 receptors.

(vi) *m-chlorophenyl piperazine (mCPP)* It is an active metabolite of the antidepressant drug trazodone; found to be an agonist of 5-HT_{1B} as well as 5-$HT_{2A/2C}$ receptors in the brain. In human volunteers it induces anxiety and enhances release of prolactin, ACTH, and growth hormone.

8. *5-HT receptor antagonists* A variety of drugs block serotonergic receptors; many are nonselective, but some newer ones are highly subtype selective.

5-HT ANTAGONISTS

The ability to antagonise atleast some actions of 5-HT is found in many classes of drugs, e.g. ergot derivatives (ergotamine, LSD, 2-bromo LSD, methysergide), adrenergic α blockers (phenoxybenzamine), antihistaminics (cyproheptadine, cinnarizine), chlorpromazine, morphine etc., but these are nonselective and interact with several other receptors as well. Many are partial agonists or antagonize certain actions of 5-HT but mimic others. The salient features of drugs which have been used clinically as 5-HT antagonists and some newly developed selective antagonists are described below:

1. Cyproheptadine It primarily blocks 5-HT_{2A} receptors and has additional H_1 antihistaminic, anticholinergic and sedative properties. Like other antihistaminics, it has been used in allergies and is a good antipruritic but the anti 5-HT action has no role in these conditions. It increases appetite and has been recommended in children and poor eaters to promote weight gain. An action on growth hormone secretion has been suggested for this.

The anti 5-HT activity of cyproheptadine has been utilized in controlling intestinal manifestations of carcinoid and postgastrectomy dumping syndromes and in antagonizing priapism/orgasmic delay caused by 5-HT uptake inhibitors like fluoxetine and trazodone.

Side effects drowsiness, dry mouth, confusion, ataxia, weight gain.

2. Methysergide It is chemically related to ergot alkaloids; antagonizes action of 5-HT on smooth muscles including that of blood vessels, without producing other ergot like effects: does not interact with a adrenergic or dopamine receptors. It is neither emetic nor oxy-

tocic. Methysergide is a potent 5-$HT_{2A/2C}$ antagonist with some tissue specific agonistic actions as well; but is nonselective—acts on 5-HT_1 receptors also. It has been used for migraine prophylaxis, carcinoid and postgastrectomy dumping syndrome.

Side effects Nausea, abdominal pain, diarrhoea, nervousness and other CNS effects. Prolonged use has caused abdominal, pulmonary and endocardial fibrosis, because of which it has gone into disrepute.

3. Ketanserln It is the prototype of a class of 5-HT antagonists having selective 5-HT_2 receptor blocking property with negligible action on 5-HT_1, 5-HT_3 and 5 HT_4 receptors and no partial agonistic activity. Among 5-HT_2 receptors, blockade of 5-HT_{2A} is stronger than 5-HT_{2C} blockade. 5-HT induced vasoconstriction, platelet aggregation and contraction of airway smooth muscle are antagonized but not contraction of guineapig ileum or rat stomach. It has additional weak α_1, H_1 and dopaminergic blocking activities.

Ketanserin is an effective antihypertensive, but the mechanism underlying is undecided; α_1 adrenergic blockade appears to be causative rather than 5-HT_{2A} blockade. In normotensives fall in BP is minimal, and side effects are mild—dizziness, tiredness, nausea, dry mouth.

Trials of Ketanserin in vasospastic conditions in which 5-HT released locally from platelets has been implicated have shown symptomatic improvement only in Raynaud's disease. It has been marketed in some European countries.

Ritanserin is a relatively more 5-HT_{2A} selective congener of ketanserin.

4. Clozapine In addition to being a dopaminergic antagonist (weaker than the typical neuroleptics), this atypical antipsychotic is a 5-$HT_{2A/2C}$ blocker. Blockade of cerebral 5-$HT_{2A/2c}$ receptors may account for its efficacy in resistant cases of schizophrenia.

5. Risperidone This recently developed atypical antipsychotic is a combined 5-HT_{2A} + dopamine D2 antagonist, similar to clozapine. Like the latter it specially ameliorates negative symptoms of schizophrenia and produces extrapyramidal side effects only at higher doses.

6. Ondansetron It is the prototype of the new class of selective 5-HT_3 antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of highly emetic anticancer drugs and radiotherapy.

Granisetron and *Tropisetron* are the other selective 5-HT_3 antagonists.

ERGOT ALKALOIDS

Ergot is a fungus *Claviceps purpurea* which grows on rye, millet and some other grains. The grain is replaced by a purple, hard, curved body called 'sclerotium'. Epidemics of ergot poisoning (ergotism), due to consumption of contaminated grains, have been recorded from the beginning of history. It still occurs in epidemic and sporadic forms. Dry gangrene of hands and feet which become black (as if burnt) is the most prominent feature. Miscarriages occur in women and cattle A convulsive type is also described.

Ergot had been used by midwives to quicken labour since the middle ages. This use received medical sanction in the 19th century, but its dangers were recognized by the beginning of the present century and then it was advocated only after delivery. Dale and Barger (1906 onwards) isolated the ergot alkaloids and studied their pharmacology. Ergometrine was isolated in 1935.

Ergot contains a host of pharmacologically active substances—alkaloids, LSD, histamine, ACh, tyramine and other amines, sterols, etc.

Natural ergot alkaloids These are tetracyclic indole containing compounds which may be considered as derivatives of *lysergic acid.* They are divided into—

(a) *Amine alkaloid* Ergometrine (Ergonovine): Oxytocic

(b) *Amino acid alkaloids* Ergotamine, Ergotoxine (mixture of ergocristine + ergocornine + ergocryptine): Vasoconstrictor and a adrenergic blocker.

Other semisynthetic derivatives

(a) Dihydroergotamine (DHE), Dihydroergotoxine (Codergocrine): antiadrenergic, cerebro-active.

(b) 2-Bromo-α-ergocryptine (Bromocriptine): dopaminergic.

(c) Methysergide: anti 5-HT.

Synthetic non-lysergic acid derivatives which pharmacologically resemble ergot alkaloids are—Lisuride, Pergolide, Lergotrile and Metergoline.

The ergot related compounds have diverse pharmacological properties. They act as agonists, partial agonists and antagonists on certain subtypes of α adrenergic, serotonergic and dopaminergic receptors: activity differing depending on the tissue.

Actions

Ergotamine It acts as a partial agonist and antagonist at α adrenergic and all subtypes of 5-HT_1 and 5-HT_2 receptors, but does not interact with 5-HT_3 or dopamine receptors: produces sustained vasoconstriction, visceral smooth muscle contraction, vasomotor centre depression and antagonizes the action of NA and 5-HT on smooth muscles. The overall effect of oral/rectal doses of ergotamine on BP is insignificant. It is a potent emetic (through CTZ) and moderately potent oxytocic. At high doses CNS stimulation and paresthesias may be experienced. On chronic exposure vasoconstriction is accompanied by damage to capillary endothelium—thrombosis, vascular stasis and gangrene occurs in ergot poisoning.

Dihydroergotamine (DHE) Hydrogenation of ergotamine reduces serotonergic and α-adrenergic agonistic actions, but enhances α-receptor blocking property. Consequently DHE is a less potent vasoconstrictor; primarily constricts capacitance vessels and causes less intimal damage. It is a weaker emetic and oxytocic (action on uterus evident only during pregnancy), has some antidopaminergic action as well.

Dihydroergotoxine (Codergocrine) This hydrogenated mixture of ergotoxine group of alkaloids is a more potent α blocker and a very weak vasoconstrictor. In the brain, a variety of partial agonistic/antagonistic actions on 5-HT receptors, metabolic and vascular effects and enhancement of ACh release in cerebral cortex have been demonstrated—advocated for treatment of dementia.

Bromocriptine The 2 bromo derivative of ergocryptine is a relatively selective dopamine D2 agonist on pituitary lactotropes (inhibits prolactin release), in striatum (antiparkinsonian) and in CTZ (emetic—but less than ergotamine). In certain brain areas weak antidopaminergic action has also been shown. It has very weak anti 5-HT or α blocking actions and is not an oxytocic.

Ergometrine (Ergonovine) This amine ergot alkaloid has very weak agonistic and practically no antagonistic action on α adrenergic receptors: vasoconstriction is not significant. Partial agonistic action on 5-HT receptors has been demonstrated in uterus, placental and umbilical blood vessels and in certain brain areas. It is a moderately potent 5-HT_2 antagonist in g.i. smooth muscle and a weak dopaminergic

agonist on the pituitary lactotropes as well as CTZ; emetic potential is low. The most prominent action is contraction of myometrium; used exclusively in obstetrics.

Pharmacokinetics Oral bioavailability of aminoacid ergot alkaloids and their hydrogenated derivatives is poor (<1%) due to slow and incomplete absorption as well as high firstpass metabolism. Bioavailability is better after sub-lingual and rectal administration, but still often erratic. They are metabolized in liver and excreted primarily in bile. Ergotamine is sequestrated in tissues—produces longer lasting actions compared to its plasma t½ of 2 hours. Ergot alkaloids effectively cross blood-brain barrier.

Adverse effects Nausea, vomiting, weakness, paresthesias, coronary and other vascular spasm, chest pain are the frequent side effects. These drugs are contraindicated in presence of sepsis, ischaemic heart disease, peripheral vascular disease, hypertension, pregnancy, liver and kidney disease.

Preparations and dose

Ergotamine: For migraine 1–3 mg oral/sublingual, repeat as required (max 6 mg in a day); rarely 0.25–0.5 mg i.m. or s.c.; ERGOTAMINE, GYNERGEN, INGAGEN 1 mg tab, 0.5 mg/ml and 1 mg/ml inj.

Dihydroergotamine: For migraine 2–6 mg oral (max 10 mg/day), 0.5–1 mg i.m., s.c. repeat hourly (max 3 mg); DIHYDERGOT, DHE 1 mg tab, MIGRANIL 1 mg/ml inj. Also used for postural hypotension, herpes zoster, mumps. Dihydroergotoxine (codergocrine) For dementia 1–1.5 mg oral or sublingual, 0.15–0.6 mg i.m., HYDERGINE 1.5 mg tab, CERELOID 1 mg tab.

DRUG THERAPY OF MIGRAINE

Migraine is a mysterious disorder characterized by pulsating headache, usually restricted to one side, which comes in attacks lasting 4–48 hours and is often associated with nausea, vomiting, sensitivity to light and sound, vertigo, loose motions and other symptoms. Two major types are—*migraine with aura* (classical migraine) in which headache is preceded by visual or other neurological symptoms, and *migraine without aura* (common migraine). Pulsatile dilatation of certain large cranial vessels is the immediate cause of pain. The pathogenic mechanisms are not well understood. The *Vascular theory* holds that

initial vasoconstriction or shunting of blood through carotid arteriovenous anastomoses produces cerebral ischaemia and starts the attack. The *Neurogenic theory* considers it to be a spreading depression of cortical electrical activity followed by vascular phenomena. Some triggering event appears to produce neurogenic inflammation of the affected blood vessel wall which is amplified by retrograde transmission in the afferent nerves and release of mediators like 5-HT, neurokinin, substance P, calcitonin gene related peptide (CGRP), nitric oxide etc.

Changes in blood/urinary levels of 5-HT and its metabolites during migraine attack, its precipitation by 5-HT releasers and efficacy of drugs having actions in the serotonergic system to prevent/abort/terminate migraine attacks suggests a pivotal role of 5-HT in this disorder.

Drug therapy of migraine has to be individualized: severity and frequency of attacks and response of individual patients to various drugs determine the choice. The strategy mostly adopted is summarized in the box.

Mild migraine Cases having fewer than one attack per month of throbbing but tolerable headache lasting upto 8 hours which does not incapacitate the individual may be classified as mild migraine.

(i) *Simple analgesics* like paracetamol (500mg) or aspirin (300–600 mg) taken at the first indication of an attack and repeated 4–6 hourly abort and suppress most mild attacks.

(ii) *Nonsteroidal antiinflammatory drugs (NSAIDs) and their combinations* Drugs like ibuprofen (400–800 mg 8 hourly), naproxen (500 mg followed by 25 mg 8 hourly), diclofenac (50 mg 8 hourly), mephenamic acid (500 mg 8 hourly), indornethacin (50 mg 6–8 hourly) either alone or combined with paracetamol/codeine/diazepam or another sedative/diphenhydramine or another antihistaminic/caffeine are found more satisfactory by some patients. These drugs are more effective in migraine without aura, but certain patients of migraine with aura also prefer them over ergot alkaloids. Drugs are taken only till the attack passes off. They also have a prophylactic effect, but long term treatment on a regular schedule to ward off migraine attacks is not advised.

(iii) *Antiemetics* Metoclopramide (10 mg oral/i.m.) is frequently used: relieves nausea, vomiting and gastric stasis. Domperidone (10–20 mg oral) and prochlorperazine (10–25 mg oral/i.m.) are also effective. Diphenhydramine or promethazine exert sedative as well as antiemetic action.

Moderate migraine Migraine may be labelled as moderate when the throbbing headache is more intense, lasts for 6–24 hours, nausea/vomiting and other features are more prominent and the patient is functionally impaired. One or more attacks occur per month.

Simple analgesics are usually not effective, but stronger NSAIDs or their combinations mentioned above are beneficial in many cases. The remaining are treated with an ergot preparation or sumatriptan. Antiemetics are almost regularly needed. Prophylactic therapy is advised only when attacks are more frequent than 2–3 per month.

Severe migraine These patients suffer more than 2–3 attacks per month of severe throbbing headache lasting 12–48 hours, often accompanied by vertigo, vomiting and other symptoms; the subject is grossly incapacitated during the attack.

Analgesics/NSAIDs and their combinations usually donot afford adequate relief—specific drugs like ergot alkaloids/sumatriptan have to be prescribed along with antiemetics. Prophylactic regimens lasting 6 months or more are recommended.

Severity	*Drug therapy*
Mild	: Simple analgesics/NSAIDs or their combinations (± antiemetic)
Moderate	: NSAIDs combinations/ergot alkaloids/sumatriptan (+ antiemetic)
Severe	: Ergot alkaloids /sumatriptan (+ antiemetic) + Prophylaxis

- Propranolol/other β blockers
- Amitriptyline/other tricyclic antidepressants
- Flunarizine/other Ca^{2+} channel blockers
- Methysergide/Cyproheptadine

Ergotamine It is the most effective ergot alkaloid for migraine. Given early in attack, relief is often dramatic and lower doses suffice, but when pain has become severe—larger doses are needed and control may be achieved only after few hours. Oral/sublingual route is preferred, 1 mg is given at half hour intervals till relief is obtained or a total of 6 mg is given. Patients who vomit can be given the drug per rectum as suppository. Parenteral administration, though rapid in action is generally not employed because it is more hazardous. An inhalational preparation is available in some countries.

Ergotamine probably acts by constricting the dilated cranial vessels. Reduced shunting of blood flow from carotid artery by specific constriction of the A-V shunt channels is another proposed mechanism. Ergotamine and DHE have also been shown to reduce neurogenic inflammation and leakage of plasma in duramater that occurs due to retrograde stimulation of perivascular afferent nerves. These actions appear to be mediated through partial agonism at 5-$HT_{1B/1D}$ receptors in and around cranial vessels.

Dihydroergotamine (DHE) It is nearly as effective as ergotamine and preferred for parenteral administration because injected DHE is less hazardous. Orally it is a safer alternative to ergotamine in patients who respond to this drug. Ergot alkaloids should be discontinued when relief is obtained. They have no prophylactic value: regular use is not justified—may itself produce a dull background headache and an attack may be precipitated on discontinuation. Ergot poisoning is also the risk. *Caffeine* 100 mg taken with ergotamine enhances its absorption from oral and rectal routes and adds to the cranial vasoconstricting action. Many combination preparations are available.

MIGRANIL: Ergotamine 1 mg, caffeine 100 mg, belladonna dry ext 10 mg, paracetamol 250 mg tab. MIGRIL: Ergotamine 2 mg, caffeine 100 mg, cyclizine 50 mg tab.

VASOGRAIN: Ergotamine 1 mg, caffeine 100 mg, paracetamol 250 mg, prochlorperazine 2.5 mg tab. ERGOPHEN: Ergotamine 0.3 mg, belladonna dry ext. 10 mg, phenobarbitone 20 mg tab.

Sumatriptan This novel selective 5-$HT_{1B/1D}$ receptor agonist; activates other subtypes of 5-HT_1 receptors only at very high concentrations, and does not interact with 5-HT_2, 5-HT_3, 5-$HT_{4–7}$, α or β adrenergic, dopaminergic, cholinergic or GABA receptors. Administered at the onset of an attack sumatriptan is as effective and better tolerated than ergotamine. About ¾ patients obtain complete/significant relief within 2–3 hours. However, recurrence of headache within 24 hr has been noted in 20–40% patients, probably due to short t½ of sumatriptan. It tends to suppress nausea and vomiting of migraine, while ergotamine accentuates these symptoms.

The antimigraine activity of sumatriptan has been ascribed to 5-$HT_{1B/1D}$ receptor mediated constriction of dilated cranial extracerebral blood vessels, especially the arterio-venous shunts in the carotid artery, which

express 5-$HT_{1B/1D}$ receptors. Dilatation of these shunt vessels during migraine attack is believed to divert blood flow away from brain parenchyma. In addition it can reduce 5-HT and inflammatory neuropeptide release around the affected vessels as well as extravasation of plasma proteins across dural vessels. Like ergotamine, the triptans have been found to suppress neurogenic inflammation of cranial vessels. Suppression of impulse transmission in the trigeminovascular system has also been implicated.

Pharmacokinetics: Sumatriptan is absorbed rapidly and completely after s.c. injection. Oral bioavailability averages 15%. It is rapidly metabolized by MAO-A isoenzyme and metabolites are excreted in urine; elimination t½ is ~2 hours.

Side effects: to sumatriptan are usually mild. Tightness in head and chest, feeling of heat and other paresthesias in limbs, dizziness, weakness are short lasting but dose related side effects, more common after s.c. injection which is painful. Slight rise in BP occurs, but has little clinical relevance, because sumatriptan is not a drug for regular use. Bradycardia, coronary vasospasm and risk of myocardial infarction are the serious but infrequent adverse effects. Few cases of sudden death have been ascribed to sumatriptan. Seizures and hypersensitivity reactions are rare.

Contraindications: are in patients with ischaemic heart disease, hypertension, epilepsy, hepatic or renal impairment and during pregnancy. Patients should be cautioned not to drive.

Sumatriptan and ergotamine should not be administered within 24 hours of each other. Interaction with 5-HT uptake inhibitors, MAO inhibitors and lithium has been reported.

Dose: 6 mg s.c., 50–100 mg oral at the onset of migraine attack, may be repeated once within 24 hours if required. Those not responding to the first dose should not be given the second dose.

MIGRATAN, SUMITREX 50, 100 mg tabs, SUMINAT 25, 50, 100 mg tab, 60 mg/5 ml inj.

Prophylaxis of Migraine

Regular medication to reduce the frequency and/or severity of attacks is recommended for moderate to severe migraine when more than 2–3 attacks occur per month. Diverse classes of drugs are used but none is effective in all cases, and none abolishes the attacks totally. It may be prudent to discontinue pophylaxis every 6 months to check whether its continuation is needed or not. It is important to avoid the precipitating factor(s).

(i) *β-Adrenergic blockers* Propranolol is the most commonly used drug: reduces frequency as well as severity of attacks in upto 70% patients. Effect is generally seen in 4 weeks and is sustained during prolonged therapy. The starting dose is 40 mg BD, which may be increased upto 160 mg BD if required. The mechanism of action is not clear; that it is due to β adrenergic blockade has been questioned. Other nonselective (timolol) and β_1 selective (metoprolol, atenolol) agents are also effective, but pindolol and others having intrinsic sympathomimetic action are ineffective.

(ii) *Tricydic antidepressants* Many tricyclic compounds of which amitriptyline has been most extensively tried (25–50 mg at bed time) reduce migraine attacks. It is effective in many patients but produces more side effects than propranolol. It is not known whether its 5-HT (and other monoamine) uptake blocking property is causally related to the prophylactic effect. The antimigraine effect is independent of antidepressant property, but this class of drugs are better suited for patients who also suffer from depression.

(iii) *Calcium channel blockers* Verapamil was found to reduce migraine attacks, but was judged inferior to propranolol. *Flunarizine* is a relatively weak Ca^{2+} channel blocker that also inhibits Na^{+} channels. It is claimed to be as effective as propranolol, but convincing proof is lacking. Frequency of attacks is often reduced, but effect on intensity and duration of attacks is less well documented. It is claimed to be a cerebroselective Ca^{2+} channel blocker; may benefit migraine by reducing intracellular Ca^{2+} overload due to brain hypoxia and other causes. Side effects are sedation, constipation, dry mouth, hypotension, flushing, weight gain and rarely extrapyramidal symptoms.

Dose: 10–20 mg OD, children 5 mg OD, NOMIGRAIN, FLUNARIN 5 mg, 10 mg caps/tab, (iv) *5-HT antagonists Methysergide* is a nonsubtype selective 5-HT antagonist more potent on $5\text{-}HT_{2A/2C}$ receptors. Its prophylactic effect in migraine is less impressive than that of propranolol and side effects are more frequent. Continuous treatment can produce retroperitoneal fibrosis: a gap of 1 month is generally given after 5 month treatment. It has been preferred in cluster headaches.

Cyproheptadine is a combined 5-HT, histamine and cholinergic antagonist which has been used for migraine prophylaxis, but efficacy is low.

Future Trends

Knowledge of the location and functions subserved by specific subtypes of 5-HT receptors is likely to be crystallized further. The introduction of several 5-HT receptor subtype selective drugs for migraine, anxiety and vomiting has boosted efforts to unravel the role of specific 5-HT receptors in complex functions like behaviour, mood, sleep, eating patterns, g.i. motility etc., and to develop drugs tailored to correct disorders of these functions. Drugs with combined activity on dopaminergic and serotonergic receptors are being developed as novel therapeutic agents. Limitations of sumatriptan like low oral bioavailability, frequent headache recurrence (possibly due to its short t½ and contraindication in coronary artery disease have prompted search for better congeners. *Zolmitriptan, Rizatriptan* and *Namtriptan* have been marketed in Western countries. Others like eletriptan, almotriptan and frovatriptan are in advance stages of clinical development. However, because these drugs have been developed to act on a specific 5-HT receptor subtype, pharmacodynamic differences among them are minor and clinical efficacy is almost comparable, but there are important pharmacokinetic differences. All have superior oral bioavailability. Rizatriptan appears to act faster due to more rapid oral absorption. Fewer headache recurrences are reported with naratriptan, probably due to its longer t½. Frovatriptan with a t½ of -24 hr is particularly long acting. It is likely that the gene responsible for migraine will be soon identified. Such discovery may render this mysterious disorder amenable to gene therapy as well as help development of more effective and safer remedies.

PROSTAGLANDINS, LEUKOTRIENES (EICOSANOIDS) AND PLATELET ACTIVATING FACTOR

PROSTAGLAND

Prostaglandins (PGs) and Leukotrienes (LTs) are biologically active derivatives of 20 carbon atom poryunsaturated essential fatty acids that are released from cell membrane phospholipids. They are the major lipid derived autacoids.

In the 1930s human semen was found to contract isolated uterine and other smooth muscle strips and to cause fall in BP in animals. The active principle was termed 'prostaglandin', thinking that it was derived from prostate. Only in 1960s it was shown to be a mixture of closely related compounds, the chemical structures were elucidated and widespread distribution was revealed. In 1970s it became clear that aspirin like drugs act by inhibiting PG synthesis, and that in addition to the classical PGs (Es and Fs), throm-boxane (TX), prostacyclin (PGI) and leukotrienes (LTs) were of great biological importance. Bergstrom, Samuelsson and Vane got Nobel prize in 1982 for their work on PGs and LTs. Over the past 40 years they have been among the most intensely investigated substances.

CHEMISTRY, BIOSYNTHESIS AND DEGRADATION

Chemically, PGs may be considered to be derivatives of *prostanoic acid,* though prostanoic acid membered ring and two side chains projecting in opposite directions at right angle to the plane of the ring. There are many series of PGs and TXs designated A, B, C…..I, depending on the ring structure and the substituents on it. Each series has members with subscript 1, 2, 3 indicating the number of double bonds in the side chains.

Leukotrienes are so named because they were first obtained from leukocytes *(leuko)* and have 3 conjugated double bonds *(triene).* They have also been similarly designated A, B, C.....F and given subscripts 1, 2, 3, 4.

PROSTANOIC ACID

In the body PGs, TXs and LTs are all derived from eicosa (referring to 20 C atoms) tri/tetra/penta enoic acids. Therefore, they can be collectively called *eicosanoids.* In human tissues, the fatty acid re-

leased from membrane lipids in largest quantity is *5, 8, 11, 14 eicosa tetraenoic acid (arachidonic acid)*. During PG, TX and prostacyclin synthesis, 2 of the 4 double bonds of arachidonic acid get saturated in the process of cyclization, leaving 2 double bonds in the side chain. Thus, subscript 2 PGs are most important in man, e.g. PGE_2, PGF_{2a}, PGI_2, TXA_2. No cyclization or reduction of double bonds occurs during LT synthesis—the LTs of biological importance are LTB_4, LTC_4, LTD_4.

Eicosanoids are the most universally distributed autacoids in the body. Practically every cell and tissue is capable of synthesizing one or more types of PGs or LTs.

There are no preformed stores of PGs and LTs. They are synthesized locally at rates governed by the release of arachidonic acid from membrane lipids in response to appropriate stimuli. These stimuli activate hydrolases, including phospholipase A, probably through increased intracellular Ca^{2+}.

The *cydooxygenase* (COX) pathway generates eicosanoids with a ring structure (PGs, TXs, prostacyclin) while *lipoxygenase* (LOX) produces open chain compounds (LTs). All tissues have COX—can form cyclic endoperoxides PGG_2 and PGH_2 which are unstable compounds. Further course in a particular tissue depends on the type of isomerases or other enzymes present in it. PGE_2 and $PGF_{2\alpha}$ are the primary prostaglandins (name based on the separation procedure: PGE partitioned into Ether while PGF into phosphate [Fosfat in Swedish] buffer; a in $PGF_{2\alpha}$ refers to orientation of OH group on the ring). PGs A, B and C are not found in the body: they are artifacts formed during extraction procedures. Lung and spleen can synthesize the whole range of COX products. Platelets primarily synthesize TXA_2 which is—chemically unstable, spontaneously changes to TXB_2. Endothelium mainly generates prostacyclin (PGI_2); also chemically unstable and rapidly converts to 6-keto $PGF_{l\alpha}$.

Cyclooxygenase is now known to exist in two isoforms COX-1 and COX-2. While both isoforms catalyse the same reactions, COX-1 is a constitutive enzyme in most cells—its activity is not changed once the cell is fully grown. On the other hand COX-2 normally present in insignificant amounts but is inducible by cytokines, growth factors and other stimuli during the inflammatory response. It is believed that eicosanoids produced by COX-1 participate in physiological (house keeping) functions such as secretion of mucus for protection of gastric

mucosa, haemostasis and maintenance of renal functions, while those produced by COX-2 lead to inflammatory and other pathological changes. However, certain sites in kidney and brain constitutively express COX-2 which may play physiological role.

Lipoxygenase pathway appears to operate mainly in the lung, WBC and platelets. Its most important products are the LTs, (generated by 5-LOX) particularly LTB_4 (potent chemotactic) and LTC_4, LTD_4 which together constitute the 'slow reacting substance of anaphylaxis' (SRS-A) described in 1938 to be released during anaphylaxis. A membrane associated transfer protein called FLAP (five lipoxygenase activating protein) carrys arachidonic acid to 5-LOX, and is essential for the synthesis of LTs. Platelets have only 12-LOX.

HPETEs produced by LOX can also be converted to *hepoxilins, trioxilins* and lipoxins. A third enzymatic pathway involving cytochrome P450 can metabolize arachidonic acid into *19-and 20-HETEs* and *epoxyeicosatrienoic acids.* Free radicals can attack arachidonic acid to produce *isoprostanes* nonenzymatically. Brain cells couple arachidonic acid with ethanolamine to produce *anandamide* which has cannabinoid like action. The above named metabolites of arachidonic acid have a variety of vascular, inflammatory and other actions, but their pathophysiological role is not clear.

Inhibition of synthesis Synthesis of cyclooxy-genase products can be inhibited by nonsteroidal antiinflammatory drugs (NSAIDs). Aspirin acetylates COX at a serine residue and causes irreversible inhibition while other NSAIDs are competitive and reversible inhibitors. Most NSAIDs are nonselective COX-1 and COX-2 inhibitors, but some newer ones like celecoxib, rofecoxib are selective for COX-2.

The sensitivity of COX in different tissues to inhibition by these drugs varies; selective inhibition of formation of some products may be possible at lower doses. NSAIDs do not inhibit the production of LTs: this may even be increased since all the arachidonic acid becomes available to the LOX pathway.

Glucocorticosteroids inhibit the release of arachidonic acid from membrane lipids (by stimulating production of proteins *calledannexins* or *lipocortins* which inhibit phospholipase A_2)—indirectly reduce production of all eicosanoids—PGs, TXs and LTs. Moreover, they inhibit the induction of COX-2 by cytokines at the site of inflammation.

Degradation of arachidonates occurs rapidly in most tissues, but fastest in the lungs. Most PGs, TXA_2 and prostacyclin have plasma t½ of few seconds to few minutes. First a specific carrier mediated uptake into cells occurs, the side chains are then oxidized and double bonds are reduced in a stepwise manner to yield inactive metabolites. Metabolites are excreted in urine. PGI_2 is catabolized mainly in the kidney.

ACTIONS AND PATHOPHYSIOLOGICAL ROLES

Prostaglandins, Thromboxanes and Prostacyclin

The cyclic eicosanoids produce a wide variety of actions depending upon the particular PG (or TX or PGI), species on which tested, tissue, hormonal status and other factors. PGs differ in their potency to produce a given action and different PGs sometimes have opposite effects. Even the same PG may have opposite effects under different circumstances. Since virtually all cells and tissues are capable of forming PGs, they have been implicated as mediators or modulators of a number of physiological processes and pathological states.

1. CVS PGE_2 and $PGF_{2\alpha}$ cause vasodilatation in most, but not all, vascular beds. In isolated preparations, they are more potent vasodilators than ACh or histamine. $PGF_{2\alpha}$ constricts many larger veins. Fall in BP occurs when PGE_2 is injected i.v., but $PGF_{2\alpha}$ has little effect on BP.

- PGI_2 is uniformly vasodilatory and is more potent hypotensive than PGE_2.
- TXA_2 consistently produces vasoconstriction.
- PG endoperoxides (G_2 and H_2) are inherently vasoconstrictor, but often produce vasodilatation or a biphasic response due to rapid conversion to other PGs, especially PGI_2 in the blood vessels themselves.
- PGE_2 and $F_{2\alpha}$ stimulate heart by weak direct but more prominent reflex action due to fall in BP. The cardiac output increases.

Role

(i) PGI_2 is probably involved in the regulation of local vascular tone as a dilator.

(ii) PGE_2 and PGI_2 are believed to be continuously produced locally in the ductus arteriosus during foetal life—keep it patent; at birth their synthesis is inhibited and closure occurs. Aspirin and indomethacin have been found to induce closure when it fails to occur spontaneously. These PGs may also be important in maintaining placental blood flow.

(iii) PGs, along with LTs and other autacoids may mediate vasodilatation and exudation at the site of inflammation.

2. Platelets TXA_2, which can be produced locally by platelets, is a potent inducer of aggregation and release reaction. The endoperoxides PGG_2 and PGH_2 are also proaggregatory. On the other hand PGI_2 (generated by vascular endothe-lium) is a potent inhibitor of platelet aggregation. PGD_2 has antiaggregatory action, but much less potent than PGI_2. PGE_2 has inconsistent effects.

Role TXA_2 (along with PGG_2 and H_2) and PGI_2 probably constitute a mutually antagonistic system: preventing aggregation of platelets while in circulation and inducing aggregation on injury, when plugging and thrombosis are needed.

Aspirin interferes with haemostasis by inhibiting platelet aggregation which is due to TXA_2 production. Before it is deacetylated in liver, aspirin acetylates COX in platelets while they are in portal circulation. Further, platelets are unable to regenerate fresh COX (lack nucleus: do not synthesize protein), while vessel wall is able to do so (fresh enzyme is synthesized within hours). Thus, in low doses, aspirin selectively inhibits TXA_2 production and has antithrombotic effect lasting >3 days.

3. Uterus PGE_2 and $PGF_{2\alpha}$ uniformly contract human uterus, pregnant as well as nonpregnant *in vivo.* The sensitivity is higher during pregnancy and there is a further modest increase with progress of pregnancy. However, even during early stages uterus is quite sensitive to PGs though not to oxytocin. PGs increase tone as well as amplitude of uterine contractions.

When tested *in vitro,* $PGF_{2\alpha}$ consistently produces contraction while PGE_2 relaxes nonpregnant but contracts pregnant human uterine strips. At term, PGs at low doses soften the cervix and make it more compliant.

Role

(i) Foetal tissues produce PGs and at term $PGF_{2\alpha}$ has been detected in maternal blood. It has been postulated that PGs mediate initiation and progression of labour. Aspirin has been found to delay the initiation of labour and also prolongs its duration.

(ii) Because PGs are present in high concentration in semen and can be rapidly absorbed when lodged in the vagina at coitus, it is believed that they so coordinate movements of the female genital tract that transport of sperms and fertilization is facilitated.

(iii) Dysmenorrhoea in many women is associated with increased PG synthesis by the endometrium. This apparently induces incoordinated uterine contractions which compress blood vessels → uterine ischaemia → pain. Aspirin group of drugs are highly effective in relieving dysmenorrhoea in most women.

4. Bronchial muscle $PGF_{2\alpha}$, PGD_2 and TXA_2 are potent bronchoconstrictors (more potent than histamine) while PGE_2 is a powerful bronchodilator. PGI_2 produces mild dilatation. Asthmatics are more sensitive to constrictor as well as dilator effects of PGs. PGE_2 and PGI_2 also inhibit histamine release and are effective by aerosol—but produce irritation of the respiratory tract and have a brief action.

Pole Asthma may be due to an imbalance between constrictor PGs ($F_{2\alpha}$, PGD_2, TXA_2) and LTs on one hand and dilator ones (PGE_2, PGI_2) on the other. In few individuals aspirin like drugs consistently induce asthma while in another small subgroup they relieve bronchoconstriction. However, in allergic human asthma, LTs are more important and COX inhibitors are without any effect in most patients.

5. GIT

(i) In isolated preparations, the longitudinal muscle of gut is contracted by PGE_2 and $PGF_{2\alpha}$ while the circular muscle is either contracted (usually by $PGF_{2\alpha}$) or relaxed (usually by PGE_2). Propulsive activity is enhanced in man, specially by PGE_2 → colic and watery diarrhoea are important side effects. PGE_2 acts directly on the intestinal mucosa and increases water, electrolyte and mucus secretion. PGI_2 does not produce diarrhoea and infact opposes PGE_2 and toxin induced fluid movement.

Role PGs may be involved in mediating toxin induced increased fluid movement in secretory diarrhoeas. In certain diarrhoeas, aspirin can reduce stool volume, but is not uniformly effective. PGs appear to play a role in the growth of colonic polyps and cancer. Association of low incidence of colon cancer with regular intake of aspirin is now established. NSAIDs afford relief in familial colonic polyposis by reducing polyp formation.

(ii) PGE_2 markedly reduces acid secretion in the stomach. Volume of juice and pepsin content are also decreased. It inhibits fasting as well as stimulated secretion (by feeding, histamine, gastrin). The gastric pH may rise upto 7.0. PGI_2 also inhibits gastric secretion, but is less potent. Secretion of mucus in stomach and mucosal blood flow are increased—antiulcerogenic.

Role PGs (specially PGI_2) appear to be involved in the regulation of gastric mucosal blood flow. They may be functioning as natural ulcer protectives. The ulcerogenic action of NSAIDs may be due to loss of this protective influence.

6. Kidney PGE_2 and PGI_2 increase water, Na^+ and K^+ excretion and have a diuretic effect. PGE_2 has been shown to have a furosemide like inhibitory effect on Cl^- reabsorption as well. They cause renal vasodilatation and inhibit tubular reabsorption. PGE_2 antagonizes ADH action, and this adds to the diuretic effect. In contrast, TXA_2 causes renal vasoconstriction. PGI_2, PGE_2 and PGD_2 evoke release of renin.

Role

(i) PGs appear to function as intrarenal regulators of blood flow as well as tubular reabsorption. The NSAIDs tend to retain salt and water. The diuretic action of furosemide is blunted by indomethacin—indicating a facilitatory role of PGs by increasing renal blood flow and/or augmenting inhibition of tubular reabsorption.

(ii) Renin release in response to sympathetic stimulation and other influences may be facilitated by PGs.

(iii) Bartter's syndrome, characterized by decreased sensitivity to AII is associated with increased PG production; many of the manifestations are improved by prolonged use of NSAIDs.

7. CNS PGs injected i.v. penetrate brain poorly and central effects are not prominent. However, injected intracerebroventricularly PGE_2 produces a variety of effects — sedation, rigidity, behavioral changes and marked rise in body temperature. $PGF_{2\alpha}$ is not pyrogenic.

Roles

(i) PGE_2 may mediate bacterial or other pyrogen induced fever and malaise at the level of hypothalamus. Aspirin and other inhibitors of PG synthesis are antipyretic. However, a number of findings are against such a role of PGs.

(ii) PGs may be functioning as neuromodula-tors in the brain by regulating neuronal excitability.

8. ANS Depending on the PG, species and tissue, both inhibition as well as augmentation of NA release from adrenergic nerve endings has been observed.

Role PGs may modulate sympathetic neuro-transmission.

9. Peripheral nerves PGs (especially E_2 and I_2) sensitize afferent nerve endings to pain inducing chemical and mechanical stimuli. They irritate mucous membranes and produce long lasting dull pain on intradermal injection. Inhibition of PG synthesis is a major antiinflammatory mechanism.

Role PGs probably serve as algesic agents during inflammation. They cause tenderness and amplify the action of other algesics. Aspirin injected locally decreases pain produced by injection of bradykinin at the same site.

10. Endocrine system PGE_2 facilitates the release of anterior pituitary hormones—growth hormone, prolactin, ACTH, FSH and LH as well as that of insulin and adrenal steroids. It has a TSH like effect on thyroid.

$PGF_{2\alpha}$ causes luteolysis and terminates early pregnancy in many mammals, but this effect is not significant in humans. Though PGs can terminate early pregnancy in women, this is not associated with fall in progesterone levels.

11. Metabolism PGEs are antilipolytic, exert an insulin like effect on carbohydrate metabolism and mobilize Ca^{2+} from bone: may mediate hyper-calcaemia due to bony metastasis.

Leukotrienes

The straight chain lipoxygenase products of arachidonic acid are produced by a more limited number of tissues (LTB_4 mainly by neutrophils; LTC_4 and LTD_4—the cysteinyl LTs—mainly by macrophages) but probably they are pathophy-siologically as important as PGs.

1. CVS and blood LTC_4 and LTD_4 injected i.v. evoke a brief rise in BP followed by a more prolonged fall. The fall in BP is not due to vasodilatation as no relaxant action has been seen on blood vessels. It is probably a result of coronary constriction induced decrease in cardiac output and reduction in circulating volume due to increased capillary permeability. These LTs markedly increase capillary permeability and are more potent than histamine in causing local edema formation. LTB_4 is highly chemotactic for neutrophils and monocytes; this property is shared by HETE but not by other LTs. Migration of neutrophils through capillaries and their clumping at sites of inflammation in tissues is also promoted by LTB_4.

Role LTs are important mediators of inflammation. They are produced (along with PGs) locally at the site of injury. While LTC_4 and D_4 cause exudation of plasma, LTB_4 attracts the inflammatory cells which reinforce the reaction. 5-HPETE and 5-HETE may facilitate local release of histamine from mast cells.

Table 2.1

A summary of the actions of major prostaglandins, prostacyclin and thromboxane

Organ	*Prostaglandin E_2 (PGE_2)*	*Prostaglandin* $F_{2\alpha}$ ($PGF_{2\alpha}$)	*Prostacyclin (PGI_2)*	*Thromboxane A_2 (TXA_2)*
1. Blood vessels	Vasodilatation, ↓ BP	Vasodilatation (mostly), larger veins constrict, little effect on BP	Vasodilatation (marked and wide spread), ↓↓ BP	Vasoconstriction
2. Heart	Weak inotropic, Reflex cardiac stimulation	Weak inotropic	—	—
3. Platelets	Variable effect	—	Antiaggregatory	Aggregation and Release reaction
4. Uterus	Contraction *(in vivo),* Relaxes non gravid human uterus *in vitro,* softening of cervix	Contraction *(in vivo* and *in vitro),* softening of cervix	—	—
5. Bronchi	Dilatation, Inhibit histamine release	Constriction	Dilatation (mild), Inhibit histamine release	Constriction
6. Stomach	↓ acid secretion, ↑ mucus production	—	↓ acid secretion (weak), mucosal vasodilatation	—
7. Intestine	Contracts longitudinal & relaxes circular muscles, ↑ peristalsis, ↑ Cl- & water secretion	Spasmogenic, ↑ fluid & electrolyte secretion (weak)	Weak spasmogenic, Inhibit toxin induced fluid secretion	Weak spasmogenic
8. Kidney	Natriuresis, ↓ Cl^- reabsorption, Inhibit ADH action, Vasodilatation, Renin release	—	Natriuresis, Vasodilatation, Renin release	Vasoconstriction
9. CNS	Pyrogenic, Variety of effects on i.c.v. inj.	—	—	—
10. Release of NA	↑ or ↓	↑ or ↓	—	—
11. Afferent nerves	Sensitize to noxious stimuli → tenderness	—	same as PGE_2	—
12. Endocrine system	Release of ant. pituitary hormones, steroids, insulin; TSH like action	Release of gonadotropins & prolactin, Luteolysis (in animals)	—	—
13. Metabolism	Antilipolytic, Insulin like action, Mobilization of bone Ca^{2+}	—	—	—

2. Smooth muscle LTC_4 and D_4 contract most smooth muscles. They are potent bronchoconstrictors and induce spastic contractions of g.i.t. at low concentrations.
They also increase mucus secretion in the airways.

Pole The cysteinyl LTs (C_4 and D_4) are the most important mediators of human allergic asthma. They are released along with PGs and other autacoids during AG: AB reaction in the lungs. In comparison to other mediators, they are more potent and are metabolised slowly in the lungs, exert a long lasting action. LTs may also be responsible for abdominal colics during systemic anaphylaxis.

3. Afferent nerves Like PGE_2 and I_2, the LTB_4 also sensitizes afferents carrying pain impulses—contributes to pain and tenderness of inflammation.

PROSTANOID RECEPTORS

PGs, TX and prostacyclin act on their own specific receptors located on cell membrane. Five major types of prostanoid receptors have been designated, each after the natural PG for which it has the greatest affinity. This has been supported by receptor cloning. All prostanoid receptors are G-protein coupled receptors which utilize the IP3/DAG or cAMP transducer mechanisms. Some selective antagonists of prostanoid receptors have been produced. The prostanoid receptors are:

DP Has greatest affinity for PGD_2, but PGE_2 also acts on it; activation increases cAMP which inhibits platelet aggregation.

EP Has greatest affinity for PGE_2; *enprostil* is a selective agonist. It has been subdivided into EP_1 which causes smooth muscle contraction through IP_3/DAG pathway and EP_2 which mediates smooth muscle relaxation by increasing cAMP. Cloning studies have identified two more subtypes EP_3 and EP_4. PGE_2 enhances Cl^- and water secretion in intestinal mucosa also by increasing cAMP. However, in some tissues (adipocytes) PGE_2 inhibits cAMP formation—responsible for its antilipolytic action. EP_1 receptors are activated by $PGF_{2\alpha}$ also.

FP Has greatest affinity for $PGF_{2\alpha}$; *fluprostenol* is a selective agonist. The most prominent effect of activation of this receptor is smooth muscle contraction mediated through IP_3/DAG formation.

IP Has greatest affinity for PGI_2; PGE also acts on it and *cicaprost* is a selective agonist. It functions by activating adenylyl cyclase in platelets (inhibiting aggregation) and smooth muscles (relaxation).

TP Has greatest affinity for TXA_2; PGH_2 also acts on it. K utilizes IP_3/DAG as second messengers which mediate platelet aggregation and smooth muscle contraction.

LEUKOTRIENE RECEPTORS

Separate receptors for LTB_4 and for the cysteinyl LTs (LTC_4, LTD_4) have been defined. Two subtypes *cys* LT, and *cys* LT_2 of the cysteinyl LT receptor have been cloned. All LT receptors function through the IP_3/DAG transducer mechanism. Many cys LT_1 receptor antagonists, *viz. Montelukast, Zafirlukast* etc are now valuable drugs for bronchial asthma.

USES

Clinical use of PGs and their analogues is rather restricted because of limited availability, short lasting action, cost, side effects and other practical considerations. Their approved indications are:

1. *Abortion* During first trimester, termination of pregnancy by transcervical suction is the procedure of choice: PGs are not used as the primary abortifacient. However, intravaginal PGE_2 pessary inserted 3 hours before attempting dilatation can minimise trauma to cervix by reducing resistance to dilatation.

PGs do have a place in midterm abortion, missed abortion and molar gestation, though delayed and erratic action and incomplete abortion are a problem. The initial enthusiasm has given way to more considered use. PGs convert the oxytocin resistant midterm uterus to oxytocin responsive one: a single extra amniotic injection (PGE_2) followed by i.v. infusion of oxytocin or intraamniotic ($PGF_{2(t}$) with hypertonic solution produces 2nd trimester abortion in a high percentage without undue side effects. Pretreatment with mifepristone improves the efficacy of PGE as abortifacient. Methotrexate administered along with misoprostol is also highly successful in inducing abortion in the first few weeks of pregnancy.

2. *Induction/augmentation of labour* PGs do not offer any advantage over oxytocin for induction of labour at term. They are less reliable and show wider individual variation in action. PGE_2 and $PGF_{2\alpha}$ (rarely) have been used in place of oxytocin in toxaemic and renal failure patients, because they do not cause fluid retention. PGE_2 may also be

used to augment labour, if it is slow, in primipara. Intravaginal route is preferred now: side effects are milder. Oral and i.v. routes have been practically abandoned and extra/intra amniotic route is infrequently used.

3. *Cervical priming* Applied intravaginally or in the cervical canal, low doses of PGE_2 which do not affect uterine motility make the cervix soft and compliant. This procedure has yielded good results in cases with unfavourable cervix. If needed labour may be induced 12 hours later with oxytocin: chances of failure are reduced.

4. *Postpartum haemorrhage (PPH)* Carboprost (15-methyl $PGF_{2\alpha}$) injected i.m. is an alternative for control of PPH due to uterine atony, specially in patients unresponsive to ergometrine and oxytocin.

PGE_2 (Dinoprostone) PROSTTN-E_2 for induction/ augmentation of labour, midterm abortion.

Vaginal gel (1 mg or 2 mg in 2.5 ml) 1 mg inserted into posterior fornix, followed by 1-2 mg after 6 hour if required.

Vaginal tab (3 mg) 3 mg inserted into posterior fornix, followed by another 3 mg if labour does not start within 6 hour.

Extra amniotic solution (10 mg/ml in 0.5 ml amp.) infrequently used.

Intravenous solution (1 mg/ml in 0.75 ml amp., 10 mg/ml in 0.5 ml amp) rarely used.

Oral tablet PRIMIPROST 0.5 mg tab, one tab. hourly till induction, max 1.5 mg per hr; rarely used.

Cervical gel CERVIPRIME (0.5 mg in 2.5 ml prefilled syringe) 0.5 mg inserted into cervical canal for preinduction cervical softening and dilatation in patients with poor Bishop's score.

Gemepmst CERVAGEM 1 mg vaginal pessary: for softening of cervix in first trimester—1 mg 3 hr before attempting dilatation; for 2nd trimester abortion/molar gestation—1 mg every 3 hours, max. 5 doses.

$PGF_{2\alpha}$ (Dinoprost) PROSTIN F_2 ALPHA intraamniotic injection 5 mg/ml in 4 ml amp. for midterm abortion/ induction of labour (rarely used).

15-methyl $PGF_{2\alpha}$ *(Carboprost)* PROSTODIN 0.25 mg in 1 ml amp; 0.25 mg i.m. every 30–120 min for PPH, midterm abortion, missed abortion.

5. *Peptic ulcer* Stable analogues of PGE_1 (misoprostol, rioprostil) and PGE_2 (enprostil) are occasionally used for healing peptic ulcer, specially in patients who need continued NSAID therapy or who continue to smoke.

6. *Glaucoma* Topical $PGF_{2\alpha}$ analogues like *latanoprost* and *isopropyl unoprostone* are gaining usage as 2nd choice/adjunctive drugs in glaucoma.

7. *To maintain patency of ductus arteriosus* in neonates with congenital heart defects, till surgery is undertaken. PGE, (Alprostadil) is used; apnoea occurs in few cases.

PROSTIN VR 0.5 mg in 1 ml amp; dilute and infuse i.v.

8. *To avoid platelet damage* PGI_2 (Epoprostenol) can be used to prevent platelet aggregation and damage during haemodialysis or cardippulmonary bypass. It also improves harvest of platelets for transfusion. Few cases of primary pulmonary hypertension have been successfully maintained on epoprostenol infusion.

FLOLAN 0.5 mg vial for reconstitution.

The other suggested uses of PGs are:

1. *Peripheral vascular diseases* PGI_2 (or PGE_1) infused i.v. can relieve rest pain and promote ulcer healing in severe cases of intermittent claudication. Benefit has also been noted in Rayna'ud's disease.

2. *To reduce infarct size* In the immediate post myo-cardial infarction period a continuous i.v. infusion of PGI_2 or its analogues carbacyclin or iloprost can reduce the area that ultimately undergoes necrosis. However, outcome benefits are not proven.

3. *Impotence* Alprostadil (PGE_1) injected into the penis causes erection lasting 1–2 hours. Priapism occurring sometimes with papaverine/phentolamine injection used for the same purpose has not been noted with PGE_1 Local tenderness may occur.

4. *Menstruation inducing contraceptive* Applied intravaginally within 2 weeks of missed period, PGs may dislodge the early embryo, producing an apparent 'late heavy period'. However, efficacy is modest and side effects like uterine cramps have discouraged use.

5. *Bronchial asthma* Aerosolized PGE_2 can abort an attack of bronchial asthma. Clinical utility is limited by its irritant action on bronchial mucosa.

SIDE EFFECTS

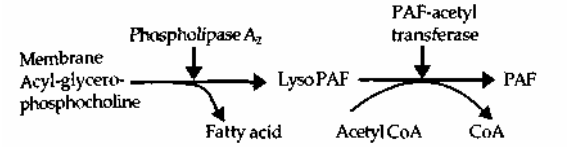
Side effects are common in the use of PGs, but their intensity varies with the PG, the dose and the route. These are: nausea, vomiting, watery diarrhoea, uterine cramps, unduely forceful uterine contractions, vaginal bleeding, flushing, shivering, fever, malaise, fall in BP, tachycardia, chest pain.

PLATELET ACTIVATING FACTOR (PAF)

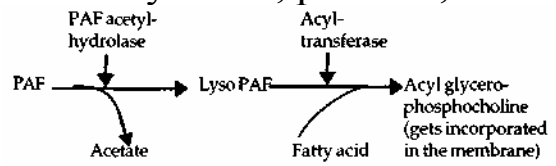
Like eicosanoids, platelet activating factor (PAF) is a cell membrane derived polar lipid with intense biological activity; discovered in 1970s and now recognized to be an important signal molecule. PAF is acetyl-glyceryl ether-phosphoryl choline.

Synthesis and Degradation PAF is synthesized from precursor phospholipids present in cell membrane by the following reactions:

PAF is degraded in the following manner:



The second step is rate limiting. Antigen-antibody reaction and a variety of mediators stimulate PAF synthesis in a Ca^{2+} dependent manner on demand: there are no preformed stores of PAF. In contrast to eicosanoids, the types of cells which synthesize PAF is quite limited—mainly WBC, platelets, vascular endothelium and kidney cells.



Actions PAF has potent actions on many tissues/organs.

Platelets Aggregation and release reaction; also releases TXA_2; i.v. injection results in intravascular thrombosis.

WBC Chemotactic to neutrophils, eosinophils and monocytes. It stimulates neutrophils to aggregate, to stick to vascular endothelium and migrate across it to the site of infection. It also prompts release of lysosomal enzymes and LTs and generation of superoxide radical by the polymorphs. The chemotactic action may be mediated through release of LTB_4. It induces degranulation of eosinophils.

Blood vessels Vasodilatation probably mediated by release of EDRF → fall in BP on i.v. injection. Decreased coronary blood flow has been observed on intracoronary injection, probably due to formation of platelet aggregates and release of TXA_2.

PAF is the most potent agent known to increase vascular permeability. Wheal and flare occur at the site of intradermal injection.

Injected into the renal artery PAF reduces renal blood flow and Na^+ excretion by direct vasoconstrictor action, but this is partly counteracted by local PG release.

Visceral smooth muscle Contraction by direct action as well as through release of LTC_4, TXA_2 and PGs. Aerosolized PAF has been found to be a potent bronchoconstrictor. In addition, it produces mucosal edema, secretion and a delayed and long lasting bronchial hyperresponsiveness. It also stimulates intestinal and uterine smooth muscle.

Stomach Ulcerogenic: erosions and mucosal bleeding occur shortly after i.v. injection of PAF. The gastric smooth muscle contracts.

Mechanism of action Membrane bound specific PAF receptors have been identified. The PAF receptor is a G-protein coupled receptor which exerts most of the actions through intracellular messengers $IP_3/DAG \rightarrow Ca^{2+}$ release.

As mentioned above, many actions of PAF are mediated/ augmented by PGs, TXA_2 and LTs which may be considered its extracellular messengers. PAF also acts intracellularly, specially in the endothelial cells; rise in PAF concentration within the endothelial cells is associated with exposure of neutrophil binding sites on their surface. Similarly, its proaggregatory action involves unmasking of fibrinogen binding sites on the surface of platelets.

PAF antagonists A number of natural and synthetic PAF receptor antagonists have been investigated. Important among these are ginkgolide B (from a Chinese plant), and some structural analogues of PAF. The PAF antagonists have manyfold therapeutic potentials like treatment of stroke, intermittent claudication, sepsis, myocardial infarction, shock, g.i. ulceration, asthma and as contraceptive. Some of them have been tried clinically but none has been found worth marketing. Alprazolam and triazolam antagonise some actions of PAF.

Pathophysiological roles PAF has been implicated in many physiological processes and pathological states, specially those involving cell to cell interaction. These are:

1. Inflammation: Generated by leukocytes at the site of inflammation PAF appears to participate in the causation of vasodilatation, exudation, cellular infiltration and hyperalgesia.

2. Bronchial asthma: Along with LTC_4 and LTD_4, PAF appears to play a major role by causing bronchoconstriction, mucosal edema and secretions. It is unique in producing prolonged airway hyperreactivity, so typical of bronchial asthma patient.

3. Anaphylactic (and other) shock conditions: are associated with high circulating PAF levels.

4. Haemostasis and thrombosis: by promoting platelet aggregation.

5. Rupture of mature graffian follicle and implantation: Early embryos which produce PAF have greater chance of implanting; PAF antagonists may have contraceptive potential.

6. Labour PAF produced by foetus at term may be involved in progression of labour by directly contracting uterine muscle as well as releasing PGE_2. PAF antagonists delay parturition in animals.

7. Ischaemic states of brain, heart and g.i.t., including g.i. ulceration.

Future Trends

Molecular cloning of several genes controlling eicosanoid biosynthesis and action has paved the way for defining the exact role of each signal/regulatory molecule. The successful introduction of selective COX-2 inhibitors has led to further studies delineating the role of COX-1 and COX-2 at various sties and in different pysiological/pathological processes. The possibility of using COX-2 inhibitors for prevention of colon cancer is being explored. Drugs that interrupt PG and/or LT biosynthesis at different steps are being searched. The cysteinyl LT receptor antagonists have opened another approach to asthma treatment; their clinical status is being defined. Selective agonists/antagonists of subtypes of prostanoid receptor are being searched in the hope of finding disease specific drugs, eg. *Sulotroban* and *vapiprost* are TP receptor antagonists—inhibit platelet aggregation and have potential use in cardiovascular, renal and allergic diseases. Clinically useful PAF antagonists are yet to be developed.

THYROID HORMONE AND THYROID INHIBITORS

THYROID HORMONE

The thyroid gland secretes 3 hormones—thyroxine (T_4), triiodothyronine (T_3) and calcitonin. The former 2 are produced by thyroid follicles, have similar biological activity and the term 'thyroid hormone' is restricted to these only. *Calcitonin* produced by interfollicular 'C cells is chemically and biologically entirely different. It is considered along with parathormone, with which it regulates calcium metabolism.

The physiological significance of thyroid gland was recognized only after Graves and Basedow (1835, 1840) associated the clinical features of the 'Graves' disease' with swelling of thyroid gland and Gull (1874) correlated myxoedema with its atrophy. Kendall (1915) obtained crystalline thyroxine and suggested its chemical formula which was confirmed in 1926. Thyroxine was the first hormone to be synthesized in the laboratory. Later, as T_4 could not account for all the biological activity of thyroid extract, search was made and more potent T_3 was discovered in 1952.

Chemistry and Synthesis

Both T_4 and T_3 are iodine containing derivatives of *thyronine* which is a condensation product of two molecules of the amino acid *tyrosine. Thyroxine;* is 3,5,3′, 5'-tetraiodothyronine while *T_3* is 3,5,3' triiodothyronine.

The thyroid hormones are synthesized and stored in the thyroid follicles as part of *thyroglobulin* molecule—which is a glycoprotein synthesized by thyroid cells, MW 660 KDa, contains 10% sugar. The synthesis, storage and release of T_4 and T_3 is summarized and involves the following processes.

1. Iodide uptake The total body content of I_2 obtained from food and water, is 30–50 mg, out of which about 1/5 is present in the thyroid. Concentration of iodide in blood is low (0.2–0.4 μg/dl) but thyroid cells have an active transport process (Na^+: I^- symporter or NIS) to concentrate this anion; this trapping is stimulated by TSH to exceed a gradient of more than 100 fold. The I_2 content of thyroid gland somehow regulates the uptake mechanism: meagre store activating and large store inhibiting it. The iodide concentrating mechanism is not peculiar to thyroid; skin, salivary glands, gastric mucosa, intestine, mammary glands and placenta also possess it, but uptake in these organs is not stimulated by TSH.

2. Oxidation and iodination Iodide trapped by follicular cells is oxidized by a peroxidase enzyme located at the apical membrane, with the help of H_2O_2 to iodinium (I^+) ions or hypoiodous acid (HOI) or enzyme linked hypoiodate (E-OI). These forms of iodine combine avidly with tyrosil residues of thyroglobulin, apparently without any enzymatic intervention, to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) while the residues are still attached to the thyroglobulin chains.

3. Coupling Pairs of iodinated tyrosil residues couple together to form T_3 and T_4.

Normally much more T_4 than T_3 is formed, but during I_2 deficiency relatively more MIT is available and a greater proportion of T_3 is formed. Thus, more active hormone is generated with lesser amount of I_2.

Coupling is an oxidative reaction and is catalysed by the same thyroid peroxidase. Thyroglobulin is the most efficient protein in supporting coupling by providing favourable spatial configuration to facilitate the reaction. Oxidation of iodide and coupling are both stimulated by TSH.

4. Storage and release Thyroglobulin containing iodinated tyrosil and thyronil residues is transported to the interior of the follicles and remains stored as thyroid colloid till it is taken back into the cells by endocytosis and broken down by lysosomal proteases. The T_4 and T_3 so released is secreted into circulation while MIT and DIT residues are deiodinated and the iodide released is reutilized. The uptake of colloid and proteolysis are stimulated by TSH: the quiescent gland has follicles distended with colloid and cells are flat or cubical, while the TSH stimulated gland has columner cells and colloid virtually disappears.

Normal human thyroid secretes 60–90 ug of T_4 and 10–30 μg of T_3 daily.

5.Peripheral Conversion of T_4 to T_3 Peripheral tissues, specially liver and kidney, convert T_4 to T_3. About ⅓ of T_4 secreted by thyroid undergoes this change and most of the T_3 in plasma is derived from liver. Target tissues take up T_3 from circulation for their metabolic need, except brain and pituitary which take up T_4 and convert it to T_3 within their own cells. Almost equal amounts of 3,5,3' triiodothyronine (normal T_3: active) and 3,3', 5' triiodothyronine (reverse T_3: inactive) are produced in the periphery. Propylthiouracil (but not carbimazole), propranolol (high doses), amiodarone and glucocorticoids inhibit peripheral conversion of T_4 to T_3 (except in brain and pituitary).

Transport, Metabolism and Excretion

Thyroid hormones are avidly bound to plasma proteins — only 0.03–0.08% T_4 and 0.2–0.5% of T_3 are in the free form. Almost all protein bound iodine (PBI) in plasma is thyroid hormone, of which 90–95% is T_4 and the rest T_3. Binding occurs to 3 plasma proteins. In order of affinity for T_4, these are:

(i) Thyroxine binding globulin.

(ii) Thyroxine binding prealbumin (transthyretin).

(iii) Albumin.

The normal concentration of PBI is 4–10 μg/ dl; only 0.1–0.2 μg/dl of this is T_3, rest is T_4. During pregnancy thyroxine binding globulin is increased—PBI levels are elevated, but there is no effect on thyroid status as the concentration of free hormone remains unaltered.

Only the free hormone is available for action as well as for metabolism and excretion. Metabolic inactivation of T_4 and T_3 occurs by deiodination and glucuronide/sulfate conjugation of the hormones as well as of their deiodinated products. Liver is the primary site (also salivary glands and kidneys). The conjugates are excreted in bile. A significant fraction is deconjugated in intestines and reabsorbed (enterohepatic circulation) to be finally excreted in urine.

Plasma t½ of T_4 is 6–7 days, while that of T_3 is 1–2 days. The half lives are shortened in hyperthyroidism and prolonged in hypothyroidism due respectively to faster and slower metabolism.

Regulation of Secretion

The secretion of hormones from thyroid is controlled by anterior pituitary by the elaboration of thyrotropin. The negative feedback by the thyroid hormones is exercised directly on the pituitary as well as through hypothalamus. The action of TRH on pituitary and that of TSH on thyroid cells is mediated by enhanced cAMP synthesis. High concentration of TSH also acts *via* IP_3/DAG-increased intracellular Ca^{2+} pathway in the thyroid cells.

ACTIONS

The actions of T_4 and T_3 are qualitatively similar and are nicely depicted in the features of hypo and hyperthyroidism. They affect the function of practically all body cells.

1. Growth and development T_4 and T_3 are essential for normal growth and development. The most remarkable action is metamorphosis of tadpole to frog: the tail is used up to build lungs, limbs and other organs. The action cannot be broadly labelled as catabolic or anabolic. It is probably exerted through a critical control of protein synthesis in the translation of the genetic code. Congenital deficiency of T_4 and T_3 resulting in cretinism emphasizes their importance. The milestones of development are delayed and practically every organ and tissue of the body suffers. The greatest sufferer, however, is the nervous system. Retardation and nervous defecit is a consequence of paucity of axonal and dendritic ramification, synapse formation and impaired myelination. In adult hypothyroidism also, intelligence is impaired and movements are slow.

2. Intermediary metabolism Thyroid hormones have marked effect on lipid, carbohydrate and protein metabolism.

Lipid T_4 and T_3 indirectly enhance lipolysis by potentiating the action of catecholamines and other lipolytic hormones, probably by suppressing a phosphodiesterase → increased cAMP: plasma free fatty acid levels are elevated. Lipogenesis is also stimulated. All phases of cholesterol metabolism are accelerated, but its conversion to bile acids dominates. Thus, hyperthyroidism is characterized by hypocholesterolemia. LDL levels in blood are reduced.

Carbohydrate Carbohydrate metabolism is also stimulated. Though utilization of sugar by tissues is increased (mainly secondary to increased BMR), glycogenolysis and gluconeogenesis in liver as well as faster absorption of glucose from intestines more than compensate it → hyperglycaemia and diabetic like state with insulin resistance occur in hyperthyroidism.

Protein Synthesis of certain proteins is increased, but the overall effect of T_4 is catabolic—increased amounts of protein being used as energy source. Prolonged action results in negative nitrogen balance and tissue wasting. Weight loss is a feature of hyperthyroidism. T_3/T_4 in low concentrations inhibit mucoprotein synthesis which so characteristically accumulates in myxoedema.

3. Calorigenesis T_3/T_4 increase BMR by stimulation of cellular metabolism and resetting of the energystat. This is important for maintaining body temperature. However, metabolic rate in brain, gonads, uterus, spleen and lymph nodes is not significantly affected. The

mechanism of calorigenesis was believed to be uncoupling of oxidative phosphorylation: excess energy being released as heat. However, this occurs only at very high doses and is not involved in mediating the physiological actions of T_3/T_4. Dinitrophenol uncouples oxidative phosphorylation, but has no thyroid like activity.

4. CVS T_3/T_4 cause a hyperdynamic state of circulation which is partly secondary to increased peripheral demand and partly due to direct cardiac actions. Heart rate, contractility and output are increased resulting in a fast, bounding pulse. T_3/T_4 stimulate heart by direct action on contractile elements (increasing the myosin fraction having greater Ca^{2+} ATPase activity) and probably by up regulation of β adrenergic receptors. Auricular fibrillation and other irregularities are common in hyperthyroidism. It can also precipitate CHF and angina. BP, specially systolic, is often raised. Myocardial O_2 consumption can be markedly reduced by induction of hypothyroidism.

5. Nervous System T_3/T_4 have profound functional effect on CNS. Mental retardation is the hallmark of cretinism; sluggishness and other behavioral features are seen in myxoedema. Hyperthyroid individuals are anxious, nervous, excitable, exhibit tremors and hyperreflexia.

6. Skeletal muscle Muscles are flabby and weak in myxoedema while thyrotoxicosis produces increased muscle tone, tremor and weakness due to myopathy.

7. GIT Propulsive activity is increased by T_3/ T_4. Hypothyroid patients are often constipated while diarrhoea is common in hyperthyroidism.

8. Kidney T_3/T_4 do not cause diuresis in euthyroid individuals, but the rate of urine flow is often increased when myxoedematous patients are treated with it.

9. Haemopoiesis Hypothyroid patients suffer from some degree of anaemia which is restored only by T_4 treatment. Thus, T_4 appears to be facilitatory to erythropoiesis.

10. Reproduction Thyroid has an indirect effect on reproduction. Fertility is impaired in hypothyroidism and women suffer from oligomertorrhoea. Normal thyroid function is required for maintenance of pregnancy and lactation.

Mechanism of Action

T_3 (and T_4) penetrate cells and combine with a nuclear receptor. A specific DNA sequence called *'thyroid hormone response element'* has been

identified in the regulatory region of specific genes to which the T_3-receptor complex binds → derepression of gene transcription or in some cases direct activation of gene transcription. This results in expression of predetermined genetically coded pattern of protein synthesis.

Many of the manifestations, e.g. tachycardia, arrhythmias, raised BP, tremor, hyperglycaemia are mediated, at least partly, by sensitization of adrenergic receptors to catecholamines. Induction of adenylyl cyclase, proliferation of β adrenoceptors and a better coupling between these two has also been demonstrated.

Apart from the nuclear T_3 receptor, other sites of thyroid hormone action have been defined It acts on cell membrane to enhance ammoacid and glucose entry and on mitochondria to increase oxygen consumption On these sites T_4 appears to be equipotent to T_3, while at the nuclear receptor T_4 is largely mactive and has 10 times lower affinity The physiological significance of extranuclear actions of thyroid hormones is not clearly defined

Relation between T_4 and T_3

- Thyroid secretes more T_4 than T_3, but in iodine deficient state this difference is reduced.
- T_4 is the major circulating hormone because it is 15 times more tightly bound to plasma proteins.
- T_3 is 5 times more potent than T_4 and acts faster. Peak effect of T_3 comes in 1–2 days while that of T_4 takes 6–8 days.
- In some *in vitro* models T_4 is inactive while T_3 is active.
- T_3 is more avidly bound to the nuclear receptor than T_4 and the T_4-receptor complex is unable to activate/derepress gene transcription.
- About ⅓ of T_4 is converted to T_3 in peripheral tissues.

On the basis of above, it is believed that T_3 is the active hormone and T_4 is only the transport form. The low potency and delayed action of T_4 are due to low concentration of its free form, its lower affinity for the nuclear receptor and inability of T_4-receptor complex to affect gene function. While T_4 itself may produce some nongenomic actions, physiologically it largely functions as a prohormone of T_3.

Preparations

1-thyroxine sod (the 1-isomer is 10–40 times more potent than d-isomer) ELTROXIN, ROXIN 100 ug tab THYRONORM, THYROX 25 μg,

50 μg, 100 μg tabs Triiodothyronine (Liothyronine) 5, 25 μg tab—25 μg is equivalent to 100 μg 1-thyroxine not freely available in India

Absorption of 1-thyroxine is incomplete, varies from 50–70%. For most purposes 1-thyroxine is superior to liothyronine because of longer duration of action. The only specific indication for the latter is myxoedema coma where a quick response is essential.

Uses

The most important uses of thyroid hormone are as *replacement therapy* in deficiency states:

1. Cretinism It is due to failure of thyroid development /a defect in hormone synthesis (sporadic cretinism) or due to extreme iodine deficiency (endemic cretinism). It is usually detected during infancy or childhood. Treatment with thyroxine 12.5–50 μg (6–8 μg/kg) daily should be started as early as possible, because mental retardation that has already ensued is only partially reversible. Response is dramatic: physical growth and development are restored and further mental retardation is prevented.

2. Adult hypothyroidism It develops as a consequence of thyroiditis, thyroidectomy, treatment with goitrogens or ^{131}I; may accompany simple goiter if iodine deficiency is severe, or may be idiopathic. Treatment with T_4 is most gratifying. It is often wise to start with a low dose—50 μg of 1-thyroxine daily and increase every 2–3 weeks to an optimum of 100–200 μg/day (adjusted by clinical response and serum TSH levels). It has been observed that if pretreatment TSH level is markedly raised—higher maintenance dose of T_4 is generally required. Individualization of proper dose is critical, aiming at normalization of serum TSH levels. Increase in dose is mostly needed during pregnancy.

Subclinical hypothyroidism characterized by euthyroid status and raised TSH level should be treated with T_4 if other cardiovascular risk factors are present; otherwise replacement therapy is optional.

3. Myxoedema coma It is an emergency; Liothyronine 100 μg i.v. followed by 25 μg 6 hourly is preferred over thyroxine due to its prompt action. Alternatively, thyroxine 500 μg i.v. followed by maintenance doses can be used. Concurrently existing adrenal insufficiency may be unmasked by restoration of thyroid status — corticosteroids may be given prophylactically.

4. Nontoxic goiter It may be endemic or sporadic. Endemic is due to iodine deficiency which may be accentuated by factors present in water (excess calcium), food or milk (goitrin, thiocyanates). A defect in hormone synthesis may be responsible for sporadic cases. In both, deficient production of thyroid hormone leads to excess TSH → thyroid enlarges, more efficient trapping of iodide occurs and probably greater proportion of T_3 is synthesized → enough hormone to meet peripheral demands is produced. Thus, treatment with T_4 is in fact replacement therapy in this condition also, despite no overt hypothyroidism. Full maintenance doses must be given. Most cases of recent diffuse enlargement of thyroid regress. Long standing goiters with degenerative and fibrotic changes and nodular goiter respond poorly or not at all. Therapy may be withdrawn after a year or so in some cases if adequate iodine intake is ensured. Others need life long therapy.

Endemic goiter and cretinism due to iodine deficiency in pregnant mother is preventable by ensuring daily ingestion of 150-200 μg of iodine. This is best achieved by iodizing edible salt In India lodization of table salt (100 μg iodine/g salt) is required under the National Programme, but recently mandatory lodization rule has been withdrawn

5. Thyroid nodule Certain benign functioning nodules regress when TSH is suppressed by T_4 therapy. Nonfunctional nodules and those non-responsive to TSH (that are associated with low TSH levels) do not respond. T_4 therapy should be stopped if the nodule does not decrease in size within 6 months and when it stops regressing.

6. Papillary carcinoma of thyroid It is often responsive to TSH. In nonresectable cases, full doses of T_4 suppress TSH production and may induce temporary regression.

7. Empirical uses T_4 has been sometimes used in the following conditions without any rationale, response is unpredictable.

Refractory anaemias

Menstrual disorders, infertility not corrected by usual treatment

Chronic/non healing ulcers

Obstinate constipation

Thyroxine is no longer recommended for obesity and as a hypocholesterolemic agent d-Thyroxine received brief trial because of its selective action on cholesterol metabolism It was, however, found to actually increase cardiovascular mortality and morbidity, and has been discontinued.

THYROID INHIBITORS

These are drugs used to lower the functional capacity of the hyperactive thyroid gland.

Thyrotoxicosis is due to excessive secretion of thyroid hormones. The two main causes are *Grave's disease* and *toxic nodular goiter.* Grave's disease is an autoimmune disorder: IgG class of antibodies (LATS) to the TSH receptor are detected in blood. They bind to and stimulate thyroid cells, and produce other TSH like effects. Due to feedback inhibition, TSH levels are low. The accompanying exophthalmos is due to autoimmune inflammation of periorbital tissues.

Toxic nodular goiter, which produces thyroid hormone independent of TSH, mostly supervenes on old nontoxic goiters. It is more common in the elderly; ocular changes are generally absent.

CLASSIFICATION

1. *Inhibit hormone synthesis (Antithyroid drugs)*
   Propylthiouracil, Methimazole, Carbimazole
2. *Inhibit iodide trapping (Ionic inhibitors)*
   Thiocyanates (-SCN), Perchlorates (-ClO_4), Nitrates (-NO_3)
3. *Inhibit hormone release*
   Iodine, Iodides of Na and K, Organic iodide.
4. *Destroy thyroid tissue*
   Radioactive iodine (^{131}I, ^{125}I, ^{123}I).

Compounds in groups 1 and 2 may be collectively called *goitrogens.*

In addition certain drugs used in high doses for prolonged periods cause hypothyroidism/goiter as a side effect:

- Lithium inhibits thyroid hormone release.
- Amiodarone inhibits peripheral conversion of T_4 to T_3, also probably interferes with thyroid hormone action.
- Sulfonamides, paraaminosahcylic acid inhibit thyro-globulin lodmation and coupling reaction.
- Phenobarbitone, phenytoin, carbamazepine, rifampin induce metabolic degradation of T_4/T_3.

Goitrin—found m plants (cabbage, turnip, mustard etc), is the cause of goiter in cattle who feed on these plants May contribute to endemic goiter in certain iodine deficient regions.

ANTITHYROID DRUGS

By convention, only the synthesis inhibitors are called antithyroid drugs, though this term has also been applied to all thyroid inhibitors.

Thiourea derivatives were found to produce goiter and hypothyroidism in rats in the 1940s. Open chain compounds were found to be toxic. Subsequently, methyl and propyl thiouracil and thioimidazole derivatives methimazole and carbimazole were found to be safe and effective.

Antithyroid drugs bind to thyroid peroxidase and prevent oxidation of iodide/iodotyrosyl residues, thereby:

(i) Inhibit iodination of tyrosine residues in thyroglobulin.

(ii) Inhibit coupling of iodotyrosine residues to form T_3 and T_4.

Action (ii) has been observed at lower concentration of antithyroid drugs than action (i). Thyroid colloid is depleted over time and blood levels of T_3/T_4 are reduced.

They do not interfere with trapping of iodide and do not modify the action of T_3 and T_4 on peripheral tissues or on pituitary. Goiter is not the result of potentiation of TSH action on thyroid, but is due to increased TSH release as a consequence of reduction in feed back inhibition. No goiter occurs if antithyroid drugs are given to hypophysectomised animals or if T_4 is given along with them. Antithyroid drugs donot affect release of T_3 and T_4—their effects are not apparent till thyroid is depleted of its hormone content.

Propylthiouracil also inhibits peripheral conversion of T_4 to T_3: this may partly contribute to its effects. Methimazole and carbimazole do not have this action and may even antagonize that of propylthiouracil.

Pharmacokinetics All antithyroid drugs are quickly absorbed orally, widely distributed in the body, enter milk and cross placenta, are metabolized in liver and excreted in urine primarily as metabolites. All are concentrated in thyroid: intrathyroid t½ is longer: effect of a single dose lasts longer than would be expected from the plasma t½. Carbimazole acts largely by getting converted to methimazole in the body.

Adverse effects Hypothyroidism due to over-treatment is common but reversible on stopping the drug. It is indicated by enlargement of thyroid, and is due to excess TSH production. Goiter does not develop with appropriate doses which restore T_4 concentration to normal so that feed back TSH inhibition is maintained.

Important side effects are: g.i. intolerance, skin rashes and joint pain.

Loss or graying of hair, loss of taste, fever and liver damage are rare.

A less common but serious adverse effect is agra-nulocytosis (1 in 500 to 1000 cases); It is mostly reversible. There is no cross reactivity between propylthiouracil and carbimazole.

Preparations and Dose:

Propylthiouracil 50–150 mg TDS followed by 25–50 mg BD-TDS for maintenance PTU 50 mg tab.

Methimazole 5–10 mg TDS initially, maintenance dose 5–15 mg daily in 1–2 divided doses.

Carbimazole 5–15 mg TDS initially, maintenance dose 2 5–10 mg daily in 1–2 divided doses, NEO MERCAZOLE, THYROZOLE, ANTITHYROX 5 mg tab.

Carbimazole is more commonly used in India. Propylthiouracil (600–900 mg/day) may be prefered in thyroid storm for its inhibitory action on peripheral conversion of T_4 to more active T_3. It is also used in patients developing adverse effects with carbimazole.

Table 5.1

Differences between propylthiouracil and carbimazole

Propylthiouracil	*Carbimazole*
1. Dose to dose less potent	About 3 × more potent
2. Highly plasma protein bound	Less bound
3.Less transferred across placenta and in milk	Larger amounts cross to foetus and in milk
4. Plasma t½ 1–2 hours	6–10 hours
5. Single dose acts for 4–8 hours	12–24 hours
6. No active metabolite	Produces active metabolite—methimazole
7. Multiple (2–3) daily doses needed	Mostly single daily dose
8. Inhibits peripheral conversion of T_4 to T_3	Does not inhibit T_4 to T_3 conversion

Use Antithyroid drugs control thyrotoxicosis in both Grave's disease and toxic nodular goiter Clinical improvement starts after 1-2 weeks or more (depending on hormone content of thyroid gland) Iodide loaded patients are less responsive Maintenance doses are titrated on the basis of clinical status of the patient The following strategies are adopted.

(i) *Definitive therapy* (a) Remission may occur in upto half of the patients of Grave's disease after 1–2 years of treatment the drug can then be withdrawn If symptoms recur—treatment is reinstituted This is preferred in young patient with a short history of Grave's disease and a small goiter; (b) Remissions are rare in toxic nodular goiter surgery (or ^{131}I) is preferred However, in frail elderly patient with multinodular goiter who may be less responsive to ^{131}I, permanent maintenance therapy with antithyroid drugs can be employed

(ii) *Preoperatively* Surgery in thyrotoxic patients is risky Young patients with florid hyperthy-roidism and substantial goiter are rendered euthyroid with carbimazole before performing partial thyroidectomy.

(iii) *Along with^{131}I* Initial control with antithyroid drug—1–2 weeks gap—radioiodine—resume antithyroid drug after 5–7 days and gradually withdraw over 3 months as the response to ^{131}I develops. This approach is preferred in older patients who are to be treated with ^{131}I, but require prompt control of severe hyperthyroidism This will also prevent initial hyperthyroidism following ^{131}I due to release of stored T_4 Advantages of antithyroid drugs over surgery/ ^{131}I are:

(a) No surgical risk, scar or chances of injury to parathyroids or recurrent laryngeal nerve.

(b) Hypothyroidism, if induced, is reversible.

(c) Canbe used even in children and young adults.

Disadvantages are:

(a) Prolonged (often life long) treatment is needed because relapse rate is high.

(b) Not practicable in uncooperative/unintelligent patient.

(c) Drugtoxicity.

During pregnancy thyroidectomy and ^{131}I are contramdicated With antithyroid drugs risk of foetal hypothyroidism and goiter is there However, low doses of propylthiouracil are preferred its greater protein binding allows less transfer to the foetus For the same reason it is to be preferred in the nursing mother However, some reports of safety of methimazole during pregnancy have appeared recently.

IONIC INHIBITORS

Certain monovalent anions inhibit iodide trapping by the thyroid probably because of similar hydrated ionic size—T_4/T_3 cannot be syn-

thesized Thiocyanate also inhibits Iodination at high doses Their relative inhibitory potency is—

SCN 1:CLO_4 10:NO_3 1/30

They are toxic and not used now.

Thiocyanates can cause liver kidney, bone marrow and brain toxicity.

Perchlorates produce rashes, fever, aplastic anaemia agranulocytosis.

Nitrates are weak drugs, can induce methemoglobinaemia and vascular effects.

IODINE AND IODIDES

Though iodine is a constituent of thyroid hormones, it is the fastest acting thyroid inhibitor It is reduced in the intestines to iodide and the response to iodine or iodides is identical The gland, if enlarged, shrinks, becomes firm and less vascular The thyroid status starts returning to normal at a rate commensurate with complete stoppage of hormone release from the gland The gland itself involutes and colloid is restored With daily administration, peak effects are seen in 10–15 days, after which 'thyroid escape' occurs and thyrotoxicosis may return with greater vengence Worsening of hyperthyroidism specially occurs in multinodular goiter.

All facets of thyroid function seem to be affected, but the most important action is inhibition of hormone release—'thyroid constipation' Endo-cytosis of colloid and proteolysis of thyroglobulin comes to a halt The mechanism of action is not clear It appears to be a direct action on thyroid cells, though attenuation of TSH and cAMP induced thyroid stimulation has been demonstrated. Excess iodide inhibits its own transport in thyroid cells and may alter the redox potential of cells thus interfering with iodination → reduced T_3/T_4 synthesis (Wolff-Chaikoff effect).

Preparations and dose Lugol's solution (5% iodine 10% Pot iodide solution) LUGOL'S SOLUTION, COLLOID IODINE 10% 5–10 drops/day COLLOSOL 8mg iodine/5 ml liq.

Iodide (Sod /Pot) 100–300 mg/day — therapeutic, 5–10 mg/day prophylactic for endemic goiter.

USES

1. *Preoperative preparation* for thyroidectomy: generally given for 10 days just preceding surgery. The aim is to make the gland firm, less

vascular and easier to operate on. Though iodide itself will lower the thyroid status, it cannot be relied upon to attain euthyroidism which is done by use of carbimazole before starting iodide. Propranolol may be given additionally for rapid control of symptoms.

2. *Thyroid storm* Sod./Pot. iodide is given i.v. or orally to stop any further release of T_3/T_4 from the thyroid.

3. *Prophylaxis of endemic goiter* It is generally used as "iodized salt".

4. *Expectorant:* See Ch. DRUGS FOR COUGH AND BRONCHIAL ASTHMA.

5. *Antiseptic:* As tincture iodine, etc.

Adverse effects

1. *Acute reaction* It occurs in sensitive individuals only—swelling of lips, eyelids, angioedema of larynx (may be dangerous), fever, joint pain, petechial haemorrhages, thrombocytopenia, lymphadenopathy.

2. *Chronic overdose (iodism)* Inflammation of mucous membranes, salivation, rhinorrhoea, sneezing, lacrymation, swelling of eyelids, burn-ing sensation in mouth, headache, rashes, g.i. symptoms etc. The symptoms regress on stopping iodide ingestion.

Long term use of high doses can cause hypo-thyroidism and goiter.

Iodide may cause flaring of acne in adolescents. Given to pregnant or nursing mothers, it may be responsible for foetal/infantile goiter and hypothyroidism.

RADIOACTIVE IODINE

The stable isotope of iodine is ^{127}I. Its radioactive isotopes of medicinal importance are:

^{131}I: physical half life 8 days—most commonly used.

^{123}I: physical half life 13 hours—only rarely used diagnostically.

^{125}I: physical half life 60 days.

Their chemical behaviour is similar to the stable isotope.

^{131}I emits X-rays as well as β particles. The former are useful in tracer studies, as they traverse the tissues and can be monitored by a counter, while the latter are utilized for their destructive effect on thyroid cells. ^{131}I is concentrated by thyroid, incorporated in colloid—emits radiation from within the follicles. The β particles penetrate only 0.5–2 mm of tissue. The thyroid follicular cells are affected from

within, undergo pyknosis and necrosis followed by fibrosis when a sufficiently large dose has been administered, without damage to neighbouring tissues. With carefully selected doses it is possible to achieve partial ablation of thyroid.

It is used as sodium salt of ^{131}I dissolved in water and taken orally.

Diagnostic 25–100 μ curie is given; counting or scanning is done at intervals. No damage to thyroid cells occurs at this dose.

Therapeutic The most common indication is *hyperthyroidism* due to Graves' disease or toxic nodular goiter. The average therapeutic dose is 3–6 m curie—calculated on the basis of previous tracer studies and thyroid size. Higher doses are generally required for toxic multinodular goiter than for Graves' disease. The response is slow—starts after 2 weeks and gradually increases, reaching peak at 3 months or so. Thyroid status is evaluated after 3 months, and a repeat dose, if needed, is given. About 20–40% patients require one or more repeat doses.

Advantages

1. Treatment is simple, conveniently given on outpatient basis and inexpensive.
2. No surgical risk, scar or injury to parathyroids/recurrent laryngeal nerves.
3. Once hyperthyroidism is controlled, cure is permanent.

Disadvantages

1. Hypothyroidism: About 5–10% patients of Graves' disease treated with ^{131}I become hypothyroid every year (upto 50% or more patients may ultimately require supplemental thyroxine treatment). This probably reflects the natural history of Graves' disease, because only few patients of toxic nodular goiter treated with ^{131}I develop hypothyroidism and eventual hypothyroidism is a complication of subtotal thyroidectomy/prolonged carbimazole therapy as well.
2. Long latent period of response.
4. Contraindicated during pregnancy—foetal thyroid will also be destroyed—cretinism, other abnormalities if given during first trimester.
5. Not suitable for young patients: they are more likely to develop hypothyroidism later and would then require life long T_4 treatment. Genetic damage/cancer is also feared, though there is no evidence for it.

^{131}I is the treatment of choice after 35 years of age and if CHF, angina or any other contraindication to surgery is present. In some centres, the cutoff age has now been reduced to 25 years.

Metastatic carcinoma of thyroid (specially papillary or those cases of follicular which concentrate iodine), ^{131}I may be used as palliative therapy after thyroidectomy. Much higher doses are required and prior stimulation with TSH is recommended.

β ADRENERGIC BLOCKERS

Propranolol (and other nonselective β blockers) have emerged as an important form of therapy to rapidly alleviated manifestations of thyrotoxicosis that are due to sympathetic overactivity: palpitation, tremor, nervousness, severe myo-pathy, sweating. They have little effect on thyroid function and the hypermetabolic state. They are used—

(i) during thyrotoxic crisis (thyroid storm)—β blockers are valuable due to quick symptomatic relief; are used along with propylthiouracil, glucocorticoids (all three reduce peripheral T_4 to T_3 conversion; propylthiouracil, also reduces hormone synthesis and glucocorticoids help tide over crisis), rehydration and appropriate antibiotics. Dilitiazem may be used to supplement propranolol in suppressing tachyarrhythmias.

(ii) while awaiting response to carbimazole or ^{131}I.

(iii) along with iodide for preoperative preparation before subtotal thyroidectomy.

INSULIN, ORAL HYPOGLYCAEMIC DRUGS AND GLUCAGON

Diabetes mellitus (DM) It is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipemia, negative nitrogen balance and sometimes ketonemia. A wide-spread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular insufficiency.

Enhanced nonenzymatic glycosylation of tissue proteins due to persistent exposure to high glucose concentrations and the accumulation of larger quantities of sorbitol (a reduced product of glucose) in tissues are believed to be causative in the pathological changes of diabetes. The concentration of glycosylated haemoglobin (Hb A_{lc}) is taken as an index of protein glycosylation: it reflects the state of glycaemia over the preceding 2–3 months.

Two major types of diabetes mellitus are:

Type I Insulin dependent diabetes mellitus (IDDM), juvenile onset diabetes mellitus: There is β cell destruction in pancreatic islets; majority of cases are autoimmune (type 1A) antibodies that destroy β cells are detectable in blood, but some are idiopathic (type IB)—no β cell antibody is found. In all type 1 cases circulating insulin levels are low or very low, and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition.

Approaches to Drug Therapy in type 2 DM

Improve Insulin Availability	Overcome Insulin Resistance
Exogenous insulin	Biguanides
Sulfonylureas	Thiazolidinediones
Meglitinide analogues	α glucosidase inhibitors
Major Limitations	*Major Limitations*
Hypoglycaemic episodes	Inability to achieve normoglycaemia
Weight gain	by themselves in many patients,
Concern about premature atherosclerosis due to hyperinsulinemia	especially moderate to severe cases

Type II Non insulin dependent diabetes mellitus (NIDDM), maturity onset diabetes mellitus: There is no loss or moderate reduction in β

cell mass; insulin in circulation is low, normal or even high, no anti-β-cell antibody is demonstrable; has a high degree of genetic predisposition; generally has a late onset (past middle age). Over 90% cases are type 2 DM. Causes may be:

- Abnormality in glucoreceptor of β cells so that they respond at higher glucose concentration.
- Reduced sensitivity of peripheral tissues to insulin: reduction in number of insulin receptors, 'down regulation' of insulin receptors. Many hypertensives are hyperinsulinemic but normoglycaemic; exhibit insulin resistance. Hyperinsulinemia *per se* has been implicated in causing angiopathy.
- Excess of hyperglycemic hormones (glucagon etc.)/obesity: cause relative insulin deficiency—the β cells lag behind.

INSULIN

Insulin was discovered in 1921 by Banting and Best who demonstrated the hypoglycaemic action of an extract of pancreas prepared after degeneration of the exocrine part due to ligation of pancreatic duct. It was first obtained in pure crystalline form in 1926 and the chemical structure was fully worked out in 1956 by Sanger. Insulin is a two chain polypeptide having 51 amino acids and MW about 6000. The A-chain has 21 while B-chain has 30 amino acids. There are minor differences between human, pork and beef insulins—

Specks	*A-chain*		*B-chain*
	8th AA	*10th AA*	*30th AA*
Human	THR	ILEU	THR
Pork	THR	ILEU	ALA
Beef	ALA	VAL	ALA

Thus, pork insulin is more homologous to human insulin than is beef insulin. The A and B chains are held together by two disulfide bonds.

Insulin is synthesized in the β cells of pancreatic islets as a single chain peptide *Preproinsulin* (110 AA) from which 24 AAs are first removed to produce *Proinsulin*. The connecting or 'C' peptide (35 AA) is split off by proteolysis in Golgi apparatus; both insulin and C peptide are stored in granules within the cell. The C peptide is secreted in the blood along with insulin.

Assay Insulin is bioassayed by measuring blood sugar depression in rabbits (1 U reduces blood glucose of a fasting rabbit to 45 mg/dl) or by its potency to induce hypoglycaemic convulsions in mice. 1 mg of the International Standard of insulin = 24 units. With the availability of pure preparations, it can now be assayed chemically also. Plasma insulin can be measured by radio-immunoassay or enzyme immunoassay.

Regulation of Insulin Secretion

Under basal condition ~1U insulin is secreted per hour by human pancreas. Much larger quantity is secreted after every meal. Secretion of insulin from β cells is regulated by chemical, hormonal and neural mechanisms.

Chemical The β cells have a glucose sensing mechanism dependent on entry of glucose into β cells (through the aegis of a glucose transporter GLUT2) and its phosphorylation by*glucokinase.*

Activation of the glucoceptor indirectly causes partial depolarization of the β cells and increases intracellular Ca^{2+} availability (due to increased influx, decreased efflux and release from intracellular stores) → exocytotic release of insulin. Other nutrients that can evoke insulin release are—aminoacids, fatty acids and ketone bodies, but glucose is the principal regulator and it stimulates synthesis of insulin as well. Glucose induces a brief pulse of insulin output within 2 min *(first phase)* followed by a delayed but more sustained *second phase* of insulin release. Glucose entry into the β cells indirectly inhibits the ATP sensitive K^+ channel resulting in depolarization of the membrane triggering Ca^{2+} mediated exocytosis of insulin storing granules.

Glucose and other nutrients are more effective in invoking insulin release when given orally than i.v. They generate chemical signals 'incretins' from the gut which act on β cells in the pancreas to cause anticipatory release of insulin. The incretins involved are gutglucagon, secretin, gastrin, gastric inhibitory polypeptide (GIP), vasoactive intestinal peptide (VIP), pancreozymin-cholecys-tokinin etc.; but different incretin may mediate signal from different nutrient. Glucagon and some of these peptides enhance insulin release by increasing cAMP formation in the β cells.

Hormonal A number of hormones, e.g. growth hormone, corticosteroids, thyroxine modify insulin release in response to glucose. PGE has been shown to inhibit insulin release. More important are the intra-islet paracrine interactions between the hormones produced by dif-

ferent types of islet cells. The β cells constitute the core of the islets and are the most abundant cell type. The α cells, comprising 25% of the islet cell mass, surround the core and secrete glucagon. The D cells (about 10%) elaborating somatostatin are interspersed between the α cells. There are some PP (or F) cells (pancreatic polypeptide containing) also.

Somatostatin inhibits release of both insulin and glucagon.

Glucagon evokes release of insulin as well as somatostatin.

Insulin inhibits glucagon secretion.

The three hormones released from closely situated cells influence each other's secretion and appear to provide fine tuning of their output in response to metabolic needs.

Neural The islets are richly supplied by sympathetic and vagal nerves.

- Adrenergic α_2 receptor activation decreases insulin release (predominant) by inhibiting β cell adenylyl cyclase.
- Adrenergic β_2 stimulation increases insulin release (less prominent) by stimulating β cell adenylyl cyclase.
- Cholinergic—muscarinic activation by ACh or vagal stimulation causes insulin secretion through IP_3/DAG-increased intracellular Ca^{2+} in the β cells.

These neural influences appear to govern both basal as well as evoked insulin secretion, because the respective blocking agents have effects opposite to that mentioned above. The primary central site of regulation of insulin secretion is in the hypothalamus: stimulation of ventrolateralnuclei evokes insulin release, whereas stimulation of ventromedial nuclei has the opposite effect.

ACTIONS OF INSULIN

The overall effects of insulin are to favour storage of fuel. The actions of insulin and the results of its deficiency can be summarized as:

1. Insulin facilitates glucose transport across cell membrane; skeletal muscle and fat are highly sensitive. The availability of glucose intracellu-larly is the limiting factor for its utilization in these and some other tissues. However, glucose entry in liver, brain, RBC, WBC and renal medullary cells is largely independent of insulin. Ketoacidosis interferes with glucose utilization by brain → diabetic coma. Muscular activity induces glucose entry in muscle cells without the need for insulin. As such, exercise has insulin sparing effect.

The intracellular pool of vesicles containing glucose transporter glycoproteins GLUT4 and GLUT1 is in dynamic equilibrium with the GLUT vesicles inserted into the membrane. This equilibrium is regulated by insulin to favour translocation to the membrane. Moreover, on a long term basis, synthesis of GLUT4 is upregulated by insulin.

2. The first step in intracellular utilization of glucose is its phosphorylation to form glucose-6-phosphate. This is enhanced by insulin through increased production of glucokinase. Insulin facilitates glycogen synthesis from glucose in liver, muscle and fat by stimulating the enzyme glycogen synthetase. It also inhibits phosphorylase → decreased glycogenolysis in liver.

3. Insulin inhibits gluconeogenesis (from protein, FFA and glycerol) in liver by gene mediated decreased synthesis of phosphoenol pyruvate carboxykinase. In insulin deficiency, proteins and aminoacids are funneled from peripheral tissues to liver where these are converted to carbohydrate and urea. Thus, in diabetes there is underutilization and over production of glucose → hyperglycaemia → glycosuria.

4. Insulin inhibits lipolysis in adipose tissue and favours triglyceride synthesis. In diabetes increased amount of fat is broken down due to unchecked action of lipolytic hormones (gluca-gon, Adr, thyroxine etc.) → increased FFA and glycerol in blood → taken up by liver to produce acetyl-CoA. Normally acetyl-CoA is resynthe-sized to fatty acids and triglycerides, but this process is reduced in diabetics and acetyl CoA is diverted to produce ketone bodies (acetone, acetoacetate, β-hydroxy-butyrate). The ketone bodies are released in blood — partly used up by muscle and heart as energy source, but when their capacity is exceeded, ketonemia and ketonuria result.

5. Insulin stimulates transcription of vascular endothelial lipoprotein lipase and thus increases clearance of VLDL and chylomicrons.

6. Insulin facilitates AA entry and their synthesis into proteins and inhibits protein breakdown in muscle and most other cells. Insulin deficiency leads to protein breakdown → AAs are released in blood → taken up by liver and converted to pyruvate, glucose and urea. The excess urea produced is excreted in urine resulting in negative nitrogen balance. Thus, catabolism takes the upper hand over anabolism in the diabetic state.

Actions of Insulin producing hypoglycaemia		
Liver	Muscle	Adipose tissue
▲ Increases glucose uptake and glycogen synthesis	▲ Increases glucose uptake and utilization	▲ Increases glucose uptake and storage as fat and glycogen
▲ Inhibits glycogenolysis and glucose output	▲ Inhibits proteolysis and release of amino acids, pyruvate, lactate into blood which form substrate for gluconeogenesis in liver	▲ Inhibits lipolysis and release of FFA + glycerol which form substrate for gluconeogenesis in liver
▲ Inhibits gluconeogenesis from protein, pyruvate, FFA and glycerol		

Most of the above metabolic actions of insulin are exerted within seconds or minutes and are called the *rapid actions.* Others involving DNA mediated synthesis of glucose transporter and some enzymes of amino acid metabolism have a latency of few hours—the *intermediate* actions. In addition insulin exerts major *long term* effects on multiplication and differentiation of cells.

Mechanism of action Insulin acts on specific receptors located on the cell membrane of practically all cells, but their density depends on the cell type: liver and fat cells are very rich. The insulin receptor has been isolated and found to be a heterotetrameric glycoprotein consisting of 2 extracellular α and 2 transmembrane β subunits linked together by disulfide bonds. The α subunits carry insulin binding sites while the β subunits have tyrosine protein kinase activity.

Binding of insulin to α subunits induces aggregation and internalization of the receptor along with the bound insulin molecules. This activates tyrosine kinase activity of the β subunits → tyrosine residues of the β subunits get autophosphorylated so that the activity of this subunit to phosphorylate tyrosine residues of Insulin Receptor Substrate proteins (IRS1, IRS2) is increased. In turn a cascade of phosphorylation and dephosphorylation reactions is set into motion resulting in stimulation or inhibition of enzymes involved in the rapid metabolic actions of insulin.

Certain second messengers like phosphatidyl inositol glycan (PIG) and DAG which are generated through activation of a specific phospholipase C also mediate the action of insulin on metabolic enzymes.

Insulin stimulates glucose transport across cell membrane by ATP dependent translocation of glucose transporters GLUT4 and GLUT1 to the plasma membrane as well as by increasing their activity. Over a period of time it also promotes expression of the genes directing synthesis of GLUT. Genes for a large number of enzymes and carriers have been shown to be regulated by insulin primarily through MAP kinases.

The internalized receptor-insulin complex is either degraded intracellularly or returned back to the surface from where the insulin is released extracellularly. The relative preponderance of these two processes differs among different tissues: maximum degradation occurs in liver, least in vascular endothelium.

Table 6.1

Conventional (standard) preparations of insulin

Type	*Appearance*	*Onset (hr)*	*Peak (hr)*	*Duration (hr)*	*Can be mixed with*
Short Acting					
Regular (soluble) Insulin	Clear	0 5–1	2–4	6–8	All preparations
Prompt Insulin Zinc Suspension (amorphous) or semilente	Cloudy	1	3–6	12–16	Regular, Lente preparations
Intermediate Acting					
Insulin Zinc Suspension or Lente (Ultra Semi 7:3)	Cloudy	1–2	8–10	20–24	Regular, Semilente
Neutral Protamine Hagedorn (NPH) or Isophane Insulin	Cloudy	1–2	8–10	20–24	Regular
Long Acting					
Extended Insulin Zinc Suspension (Crystalline) or Ultralente	Cloudy	4–6	14–18	24–36	Regular, Semilente
Protamine Zinc Insulin (PZI)	Cloudy	4–6	14–20	24–36	Regular

Fate of insulin Insulin is distributed only extracellularly. It is a peptide—degraded in the g.i.t. if given orally. Injected insulin or that

released from pancreas is metabolized primarily in liver and to a smaller extent in kidney and muscles. Nearly half of the insulin entering portal vein from pancreas is inactivated in the first passage through liver. Thus, normally liver is exposed to a much higher concentration (4–8 fold) of insulin than are other tissues As noted above, degradation of insulin after receptor mediated internalization occurs to variable extent in most targetcells. During biotransformation the disulfide bonds are reduced—A and B chains are separated. These are further broken down to the constituent amino acids. The plasma t½ is 5–9 min.

Conventional Preparations of Insulin

The conventional commercial preparations of insulin are derived from beef and pork pancreas. Monospecies beef or pork insulin are also available. Regular insulin has to be injected 2–3 times daily. It has been modified by adding zinc with or without protamine to yield slowly absorbed and longer acting 'modified' or 'retard' preparations. These are tabulated in Table 6.1. All are available in 40 U/ml strength. Regular insulin is also available in 100 U/ml and 500 U/ml strength. Regular, lente and isophane insulins are the most commonly used preparations now. Protamine zinc insulin is rarely used.

All preparations of insulin are given s.c. Only regular insulin can be injected i.v. or i.m. also.

Highly Purified Insulin Preparations

The conventional or standard preparations of insulin contain 1% (10,000 ppm) or more of other proteins (proinsulin, other polypeptides, pancreatic proteins, insulin derivatives etc.) which are potentially antigenic. In the 1970s improved purification techniques were applied which resulted in the availability of highly purified and practically nonantigenic preparations. Single species insulins from pork or beef have been made available: pork insulin, being more homologous to human insulin, is less immunogenic. These can then be modified like the conventional preparations into longer acting forms (lente, ultralente, isophane).

According to the purification method used the preparations can be categorized into:

1. *Single peak insulins* Purified by gel filtration and repeated crystallization, they contain 50–200 ppm proinsulin.

ACTRAPID, RAPIDICA. Highly purified pork regular insulin, 40 U/ml.

LENTARD, ZINULIN Highly purified pork lente insulin, 40 U/ml.

ACTRAPHANE, RAPIMIX, MIXTARD Highly purified pork regular insulin (30%) and isophane insulin (70%) 40 U/ml, 1SLETIN-N Highly purified bovine-porcine isophane insulin 40 U/ml

2. *Monocomponent (MC) insulins* After gel filtration it is further purified by ion exchange chromatography; the content of proinsulin is reduced to < 20ppm.

ACTRAPID MC Monocomponent pork regular insulin, 40 U/ml, 100 U/ml.

MONOTRAD MC Monocomponent pork lente insulin, 40 U/ml.

The immunogenicity of pork MC insulins is similar to that of human insulins, while the single peak preparations still have significant immunogenicity. These preparations are more expensive, but offer the advantage of greater stability, less allergic reactions, less insulin resistance and less lipodystrophy.

Human insulins In the 1980s the human insulins were produced by recombinant DNA technology in *Escherichia coli*—'proinsulin recombinant bacterial' (prb) and in yeast—'precursor yeast recombinant' (pyr), or by 'enzymatic modification of porcine insulin (emp).

HUMAN ACTRAPID Human regular insulin, 40 U/ml, 100 U/ml, ACTRAPID HM PENFIL 100 U/ml pen inj. HUMAN MONOTRAD Human lente insulin, 40 U/ml, 100 U/ml.

HUMAN INSULATARD, HUMINSULIN-N Human isophane insulin 40 U/ml.

HUMAN ACTRAPHANE, HUMINSULIN 30/70, HUMAN MIXTARD Human soluble insulin (30%) and isophane insulin (70%), 40U/ml.

ACTRAPHANE HM PENFIL Human soluble insulin 30% + isophane insulin 70% 100 U/ml pen injecter.

In developed countries the use of human insulins has rapidly overtaken that of conventional and purified animal insulins: in Britain now > 75% diabetics who use insulin are taking human insulins. Human insulin is more water soluble as well as hydrophobic than porcine or bovine insulin. It has a more rapid s.c. absorption, earlier and more defined peak and slightly shorter duration of action.

Soon after introduction of human insulins, several reports appeared describing changes in hypoglycaemic symptoms experienced by patients when they switched over from animal to human insulin Human insulin was alleged to Produce *hypoglycaemic unawareness,* exposing

the patients to risk of severe hypoglycaemia However, after prolonged treatment, irrespective of the type of insulin, many diabetics develop relative hypoglycaemic unawareness/change in symptoms, because of autonomic neuropathy, change in perception/attitude and other factors There is no evidence that human insulin causes more hypoglycaemic unaware-ness than pork/beef insulin The cost of human insulin now is the same as that of pork MC insulin.

Superiority of human insulin over pork MC insulin has not been demonstrated Though new pabents may be started on human insulins, the only indication for transfer from purified pork to human insulin is allergy to pork insulin It is unwise to transfer stabilized patients from one to another species insulin without good reason.

Though it is desirable to employ human/ highly purified pork insulin in all diabetics, in developing countries conventional insulin preparations are still routinely used for economic reasons. Human/highly purified insulins are specially indicated in the following situations:

1. Insulin resistance: specially when due to large amounts of insulin binding antibodies.
2. Allergy to conventional preparations.
3. Injection site lipodystrophy; changeover causes resolution of the lesions.
4. Short term use of insulin in diabetics who are otherwise stabilized on diet and exercise with/without oral hypoglycaemics, e.g. to tideover surgery, trauma, infections, ketoacidosis etc.
5. During pregnancy.

REACTIONS TO INSULIN

1. Hypoglycaemia This is the most frequent and potentially the most serious reaction. It is commonly seen in patients of 'labile' diabetes in whom insulin requirement fluctuates unpredic-tably. Hypoglycaemia can occur in any diabetic following inadvertent injection of large doses, by missing a meal or by performing vigorous exercise. The symptoms can be divided into those due to counter regulatory sympathetic stimulation—sweating, anxiety, palpitation, tremor; and those due to deprivation of brain of its essential nutrient—glucose (neuroglucopenic symptoms)—dizziness, headache, behavioural changes, visual disturbances, hunger, fatigue, weakness, muscular in-

coordination and some times fall in BP. Generally, the reflex sympathetic symptoms occur before the neuroglucopenic, but the warning symptoms of hypoglycaemia differ from patient to patient and also depend on the rate of fall in blood glucose level. After long term treatment about 30% patients lose adrenergic symptoms. Diabetic neuropathy can abolish the autonomic symptoms.

Finally, when blood glucose falls further (to < 40 mg/dl) mental confusion, seizures and coma occur. Irreversible neurological deficits are sequelae of prolonged hypoglycaemia.

Treatment Glucose must be given orally or i.v. (for severe cases)—reverses the symptoms rapidly. Glucagon 0.5–1 mg i.v. or Adr 0.2 mg s.c. (less preferable) may be given as an expedient measure in patients who are not able to take sugar orally and injectable glucose is not available.

2. Local reactions Swelling, erythema and stinging sometimes occur specially in the beginning. *Lipodystrophy* occurs at injection sites after long usage. This is not seen with newer preparations — which may even facilitate reversal of lipoatrophy when injected at the same sites.

3. Allergy This is infrequent; is due to contaminating proteins; very rare with human/highly purified insulins.

Urticaria, angioedema and anaphylaxis are the manifestations.

4. Edema Some patients develop short lived dependent edema (due to Na^+ retention) when insulin therapy is started.

Drug Interactions:

1. β adrenergic blockers prolong hypoglycaemia by inhibiting compensatory mechanisms operating through β_2 receptors (β_1 selective agents are less liable). Warning signs of hypoglycaemia like palpitation, tremor and anxiety are masked. Rise in BP can occur due to unopposed α action of released Adr.

2. Thiazides, furosemide, corticosteroids, oral contraceptives, salbutamol, nifedipine tend to raise blood sugar and reduce effectiveness insulin.

3. Acute ingestion of alcohol can precipitate hypoglycaemia by depleting hepatic glycogen.

4. Salicylates, lithium and theophylline may also accentuate hypoglycaemia by enhancing insulin secretion and peripheral glucose utilization.

USES OF INSULIN

Diabetes mellitus The purpose of therapy in diabetes mellitus is to restore metabolism to normal, avoid symptoms due to hyperglycaemia and glucosuria, prevent short term complications (infection, ketoacidosis etc.) and long term sequelae (cardiovascular, retinal, neurological, renal etc.)

Insulin is effective in all forms of diabetes mellitus and is a must for type 1 cases. Many type 2 cases can be controlled by diet, reduction in body weight and appropriate exercise. Insulin is needed by such cases when—

(i) Not controlled by diet and exercise or when these are not practicable.

(ii) Primary or secondary failure of oral hypo-glycaemics or when these drugs are not tolerated.

(iii) Underweightpatients.

(iv) Temporarily to tide over infections, trauma, surgery, pregnancy. In the perioperative period and during labour, monitored i.v. insulin infusion is preferable.

(v) Any complication of diabetes, e.g. ketoacidosis, gangrene of extremities.

When instituted, insulin therapy is generally started with regular insulin given s.c. before each major meal. The requirement is assessed by testing urine or blood glucose levels (glucose oxidase impregnated sticks and spot tests are available for instant measurements). Most type 1 patients require 0.4–0.8 U/kg/day. In type 2 patients, insulin dose varies (0.2–1.6 U/kg/day) with the severity of diabetes and body weight: obese patients require proportionately higher doses due to relative insulin resistance. A suitable regimen for each patient is then devised by including modified insulin preparations.

Any satisfactory regimen should provide basal control by inhibiting hepatic glucose output, as well as supply extra amount to meet postprandial needs for disposal of absorbed glucose and amino acids. Often mixtures of regular and lente/isophane insulins are used, but a single daily injection (before breakfast) hardly ever satisfies both the above needs. The total daily dose of a 30:70 mixture of regular and NPH insulin is usually split into two (split-mixed regimen) and injected s.c. before breakfast and before dinner. Several variables *viz.* site and depth of s.c. injection, posture, regional muscular activity, injected volume, type of insulin can alter the rate of absorption of s.c.

injected insulin and can create mismatch between the actual requirement (high after meals, low at night) and the attained insulin levels.

Many complex regimens of 2–4 daily injections of mixtures of regular and intermediate/long acting preparations or insulin pumps are being employed with the objective of achieving round the clock euglycaemia. The large multicentric diabetes control and complications trial (DCCT) among type 1 patients has established that intensive insulin therapy markedly reduces the occurrence of primary diabetic retinopathy, neuropathy, nephropathy and slows progression of these complications in those who already have them in comparison to conventional regimens which attain only intermittent euglycaemia. Thus, the risk of macrovascular disease appears to be related to the glycaemia control. The recently concluded UK prospective diabetes study (UK PDS, 1998) has extended these observations to type 2 DM patients as well. Since the basis of pathological changes in both type 1 and type 2 DM is accumulation of glycosylated proteins and sorbitol in tissues as a result of exposure to high glucose concentrations, tight glycaemia control can delay end-organ damage in all diabetic subjects.

However, regimens attempting near normoglycaemia are associated with higher incidence of severe hypogly-caemic episodes. Moreover, injected insulin fails to reproduce the normal pattern of increased insulin secretion in response to each meal, and liver is exposed to the same concentration of insulin as other tissues while normally liver receives much higher concentration. As such, the overall desirability and practicability of intensive insulin therapy has to be determined in individual patients. Intensive insulin therapy is best avoided in young children (risk of hypoglycaemic brain damage) and in elderly (more prone to hypoglycaemia and its serious consequences).

Diabetic Ketoacidosis (Diabetic coma) Ketoacidosis of different grades generally occurs in insulin dependent diabetics. It is infrequent in type 2 DM. The most common precipitating cause is infection; others are trauma, stroke, pancreatitis, stressful conditions and inadequate doses of insulin.

The development of cardinal features of diabetic ketoacidosis is outlined in Fig. 18.4. Patients may present with varying severity. Typically they are dehydrated, hyperventilating and have impaired consciousness. The principles of treatment remain the same, irrespective of severity, only the vigour with which therapy is instituted is varied.

1. *Insulin* Regular insulin is used to rapidly correct the metabolic abnormalities. A bolus dose of 0.1–0.2 U/kg i.v. is followed by 0.1 U/kg/hr infusion; rate is doubled if no significant fall in blood glucose occurs in 2 hr. Fall in blood glucose level by 10% per hour can be considered adequate response.

Usually, within 4–6 hours blood glucose reaches 300 mg/dl. Then rate of infusion is reduced to 2–3 U/hr. This is maintained till the patient becomes fully conscious and routine therapy with s.c. insulin is instituted. The massive dose regimen (1 U/kg i.v. + 1 U/kg s.c. followed by 1 U/kg s.c. every 2 hr) is obsolete.

2. *Intravenous fluids* It is vital to correct dehydration. Normal saline is infused i.v., initially at the rate of 1 L/hr, reducing progressively to 0.5 L/4 hours depending on the volume status. Once BP and heart rate have stabilized and adequate renal perfusion is assured change over to ½N saline. After blood sugar has reached 300 mg/dl, 5% glucose in ½N saline is the most appropriate solution because blood glucose falls before ketones are fully cleared from the circulation. Also glucose is needed to restore the depleted hepatic glycogen.

3. *KCI* Though upto 400 mEq of K^+may be lost in urine during ketoacidosis, serum K^+ is usually normal due to exchange with intracellular stores. When insulin therapy is instituted ketosis subsides and K^+ is driven intracellularly—dangerous hypokalemia can occur. After 4 hours it is appropriate to add 10–20 mEq/hr KCI to the i.v. fluid. Further rate of infusion is guided by serum K^+ measurements and ECG.

4. *Sodium bicarbonate* It is not routinely needed. Acidosis subsides as ketosis is controlled.

However, if arterial blood pH is < 7.1, acidosis i not corrected spontaneously or hyperventilation is exhausting, 50 mEq of sod. bicarbonate is added to the i.v. fluid.

Bicarbonate infusion is continued slowly till blood pH rises above 7.2.

5. *Phosphate* When serum PO_4 is in the low-normal range, 5–10 m mol/hr of sod./pot. phosphate infusion is advocated. However, routine use of PO_4 in all cases is still controversial.

6.*Antibiotics* and other supportive measures and treatment of precipitating cause must be instituted simultaneously.

Hyperosmolar (nonketotic hyperglycaemic) coma This usually occurs in elderly type 2 cases. Its cause is obscure, but appears to be

precipitated by the same factors as ketoacidosis. Uncontrolled glycosuria of DM produces diuresis resulting in dehydration and haemoconcen-tration over several days → urine output is finally reduced and glucose accumulates in blood rapidly to > 800 mg/dl, plasma osmolarity is > 350 m osm/L → coma, and death can occur if not vigourously treated.

The general principles of treatment are same as for ketoacidotic coma, except that faster fluid replacement is to be instituted and alkali is usually not required. These patients are prone to thrombosis (due to hyperviscosity and sluggish circulation), prophylactic heparin therapy is recommended.

Despite intensive therapy, mortality in hyperosmolar coma remains high. Treatment of precipitating factor and associated illness is vital.

Insulin Resistance

When insulin requirement is increased (conventionally > 200 U/day, but physiologically >100 U/day), insulin resistance is said to have developed. However, it may be of different grades.

1. *Acute* It develops rapidly and is usually a short term problem. Causes are—

(a) Infection, trauma, surgery, emotional stress; corticosteroids and other hyperglycaemic hormo-nes may be produced in excess as a reaction to the stress →oppose insulin action.

(b) Ketoaddosis—ketone bodies and FFA inhibit glucose uptake by brain and muscle. Also insulin binding may increase. Treatment is to overcome the precipitating cause and to give high doses of regular insulin. The insulin requirement comes back to normal once the condition has been controlled.

2. *Chronic* This is generally seen in patients treated for years with conventional preparations of beef or pork insulins. Antibodies to homologous contaminating proteins are produced which also bind insulin. Very high grades of insulin resistance may be produced in this way. It is more common in type 2 DM.

Development of such insulin resistance is an indication for switching over to the more purified newer preparations. Some patients may be selectively resistant to beef insulin and respond well to pork or human insulin. After instituting highly pure preparations, insulin requirement gradually declines over weeks and months, and majority of patients stabilize at ~ 60 U/day.

Pregnancy and oral contraceptives often induce relatively low grade and reversible insulin resistance Other rare causes are—acromegaly, Cushmg's syndrome, pheochromocytoma, lipo-atrophic diabetes mellitus. Hypertension is often accompanied with relative insulin resistance.

Newer insulin delivery devices A number of innovations have been made to improve ease and accuracy of insulin administration as well as to achieve tight glycaemia control These are:

1. *Insulin syringes* Prefilled disposible syringes contain specific types or mixtures of regular and modified insulins.

2. *Pen devices* Fountain pen like use insulin cartridges for s.c. injection through a needle Preset amounts (in 2 U increments) are propelled by pushing a plunger or trigger, convenient in carrying and injecting.

3. *Jet injectors* Deliver insulin subcutaneously without using a needle Absorption is more rapid due to greater dispersion Although initial pain is minimal, delayed pain and bleeding can occur.

4. *Insulin pumps* Portable infusion devices connected to a subcutaneously placed cannula provide 'continuous subcutaneous insulin infusion' (CSII) Only regular insulin is used They can be programmed to deliver insulin at a low basal rate (approx 1 U/hr) and premeal boluses (4-is times the basal rate) to control post prandial glycaemia. Though theoretically more appealing, no definite advantage of CSII over multidose s.c. injection has been demonstrated Moreover, cost, strict adherence to diet, exercise, care of the device and cannula, risk of pump failure, site infection, are too demanding on the patient.

5. *Implantable pumps* Consist of an electromechanical mechanism which regulates insulin delivery from a percu-taneously refillable reservoir. Mechanical pumps, fluoro-carbon propellant and osmotic pumps are being developed.

6. *External artificial pancreas* This is a microprocessor controlled device connected through i.v. lines, which measures blood glucose and then infuses appropriate amounts of insulin in a continuous feed back manner Its size, cost and other problems limit use to only research situations.

7. *Other routes of insulin delivery* Intrapentoneal, oral (by complexing insulin into liposomes or coating it with impermeable polymer) and rectal routes are being tried. These have the advantage of providing higher concentrations in the portal circulation, which is more physiological.

Intranasal application with a surfactant to promote dispersion and absorption is a promising approach, but the short duration of action and local side effects of the surfactant are the limitations.

ORAL HYPOGLYCAEMIC DRUGS

These drugs lower blood glucose levels and are effective orally. The chief draw back of insulin is—it must be given by injection. Orally active drugs Have always been searched. The early sulfonamides tested in 1940s produced hypoglycaemia as side effect. Taking this lead, the first clinically acceptable sulfonylurea *tolbutamide* was introduced in 1957. Others followed soon after. In the 1970s many so called 'second generation' sulfonylureas have been developed which are 20–100 times more potent. A diguanidine *synthalin* was found to be hypoglycaemic in the 1920s, but was toxic.

SULFONYLUREAS

First generation	*Second generation*
Tolbutamide	Gilbenclamide
Chlorpropamide	(Glyburide)
	Glipizide
	Gliclazide
	Glimepiride
BIGUANIDES	
Phenformin	Metformin
MEGLITINIDE ANALOGUES	
Repaglinide	Nateglinide
THIAZOLIDINEDIONES	
Rosiglitazone	Pioglitazone
α GLUCOSIDASE INHIBITORS	
Acarbose	Miglitol

Clinically useful biguanide *phenformin* was developed parallel to sulfonylureas in 1957. Recently 3 newer classes of drugs, *viz. α glucosidase inhibitors, meglitinide analogues* and *thiazolidinediones* have been inducted.

SULFONYLUREAS

All have similar pharmacological profile—sole significant action being lowering of blood glucose level in normal subjects and in type 2 diabetics, but not in type 1 diabetics.

Mechanism of action Single doses provoke a brisk release of insulin from pancreas. They act on the so called 'sulfonylurea receptors' on the pancreatic β cell membrane—cause depolarization by reducing conductance of ATP sensitive K^+ channels. This enhances Ca^{2+} influx → degranulation. The rate of insulin secretion at any glucose concentration is increased. In type 2 DM the kinetics of insulin release in response to glucose or meals is delayed and subdued. The sulfonylureas primarily augment the 2nd phase insulin secretion with little effect on the 1st phase. That they do not cause hypoglycaemia in pancreatectomised animals and in type 1 diabetics (presence of at least 30% functional β cells is essential for their action) confirms their indirect action through pancreas.

A minor action reducing glucagon and increasing somatostatin release has been demonstrated. Hepatic degradation of insulin may be slowed.

Extrapancreatic action After chronic administration, the insulinemic action of sulfonylureas declines probably due to down regulation of sulfonylurea receptors on β cells, but improvement in glucose tolerance is maintained. In this phase, they sensitize the target tissues (specially liver) to the action of insulin. This is due to increase in number of insulin receptors and/or a postreceptor action—improving translation of receptor activation. It is hypothesized that long term improvement in carbohydrate tolerance leads to a decreased insulin concentration in blood which reverses the down regulation of insulin receptors — apparent increase in their number. A direct extrapancreatic action of sulfonylureas to increase insulin receptors on target cells and to inhibit gluconeogenesis in liver has been suggested, but not proven.

Pharmacokinetics All are well absorbed orally, and are 90% or more bound to plasma proteins: have low volumes of distribution (0.2–0.4 L/kg). Some are primarily metabolized—may produce active metabolite; others are mainly excreted unchanged in urine. Accordingly they should be used cautiously in patients with liver or kidney dysfunction.

The distinctive features of different sulfonylureas are given in Table 6.2.

Interactions

Drugs that enhance sulfonylurea action (may precipitate hypoglycaemia) are—

(a) *Displace from protein binding:* Phenylbutazone, sulfinpyrazone, salicylates, clofibrate, sulfonamides, PAS.

(b) *Inhibit metabolism/excretion:* Phenylbutazone, sulfinpyrazone, cimetidine, sulfonamides, warfarin, chloramphenicol, acute alcohol intake (also synergises by causing hypoglycaemia).

(c) *Synergise with or prolong pharmacodynamic action:* Salicylates, propranolol (cardioselective β_1 blockers less liable), sympatholytic antihypertensives, lithium, theophylline, alcohol (by inhibiting gluconeogenesis).

Drugs that decrease sulfonylurea action (vitiate diabetes control) are—

(a) *Induce metabolism:* Phenobarbitone, phenytoin, rifampicin, chronic alcoholism.

(b) *Opposite action/suppress insulin release:* Cortico-steroids, diazoxide, thiazides, furosemide, oral contraceptives.

Adverse effects Incidence of adverse effects is quite low (3–7%).

1. *Hypoglycaemia* It is the commonest problem, may occasionally be severe and rarely fatal. It is more common in elderly, liver and kidney disease patients and when potentiating drugs are added. Chlorpropamide is a frequent culprit due to its long action. Tolbutamide carries lowest risk due to its low potency and short duration of action. Lower incidence is also reported with glipizide, glibenclamide, glimepiride.

Treatment—give glucose, may be for few days because hypoglycaemia may recur.

2. *Nonspecific side effects* Nausea, vomiting, flatulence, diarrhoea or constipation, headache, paresthesias and weight gain.

3. *Hypersensitivity* Rashes, photosensitivity, purpura, transient leukopenia, rarely agranulocytosis.

Chlorpropamide in addition causes cholestatic jaundice, dilutional hyponatremia (sensitises the kidney to ADH action), intolerance to alcohol (flushing and a disulfiram like reaction); other sulfonylureas are less prone to this interaction.

Tolbutamide reduces iodide uptake by thyroid but hypothyroidism does not occur.

Safety of sulfonylureas during pregnancy is not established—change over to insulin. They are secreted in milk: should not be given to nursing mothers.

BIGUANIDES

They differ markedly from sulfonylureas: cause little or no hypoglycaemia in nondiabetic subjects and do not stimulate pancreatic β cells. The two biguanides have similar actions; potency differs due to pharmacokinetic differences. Metformin has been reported to improve lipid profile as well in type 2 diabetics.

Mechanism of action It is not clearly understood. They do not cause insulin release, but presence of some insulin is essential for their action. Explanations offered for their hypogly-caemic action are—

(i) Suppress hepatic gluconeogenesis and glucose output from liver: the major action.

(ii) Enhance insulin mediated glucose disposal in muscle and fat. Though they do not alter translocation of GLUT4 (the major glucose transporter in skeletal muscle), they enhance GLUT1 transport from intracellular site to plasma membrane. The effect thus differs from that of insulin.

(iii) Interfere with mitochondrial respiratory chain—promote peripheral glucose utilization by enhancing anaerobic glycolysis. Metformin binds less avidly to mitochondrial membrane and has weaker inhibitory effect on oxidative phosphorylation than phenformin.

(iv) Inhibit intestinal absorption of glucose, other hexoses, amino acids and vit B_{12}.

Actions (iii) and (iv) contribute little to the therapeutic effect.

Pharmacokinetics The important features are given in Table 6.2. Phenformin is incompletely but adequately absorbed. Clearance of metformin approximates g.f.r.

Adverse effects Abdominal pain, anorexia, nausea, metallic taste, mild diarrhoea and tiredness are the frequent side effects. Metformin does not cause hypoglycaemia except in overdose.

Lactic acidosis is the most serious complication. It is more common with phenformin. Though small increase in blood lactate is common with metformin, lactic acidosis is rare (<1 per 10,000 patient years). Alcohol ingestion can precipitate severe lactic acidosis.

Vit B_{12} deficiency due to interference with its absorption can occur—specially with high dose of metformin.

In addition to general restrictions for use of oral hypoglycaemics *(see* below), biguanides are contraindicated in hypotensive states, cardiovascular, respiratory, hepatic and renal disease and in alcoholics because of increased risk of lactic acidosis.

MEGLITINIDE ANALOGUES

These are recently developed quick and short acting insulin releases.

Repaglinide It is the first member of a new class of oral hypoglycaemics designed to normalise meal time glucose excursions. Though not a sulfonylurea, it acts in an analogous manner by binding to sulfonylurea receptor as well as to other distinct receptors → closure of ATP dependent K^+ channels → depolarisation → insulin release.

Repaglinide induces rapid onset short lasting insulin release. It is administered before each major meal to control postprandial hyper-

glycaemia; the dose may be omited if a meal is missed. Because of short lasting action it may have a lower risk of serious hypoglycaemia. Side effects are mild headache, dyspepsia, arthralgia and weight gain.

Repaglinide is indicated only in type 2 DM as an alternative to sulfonylureas, or to supplement metformin/long acting insulin. It should be avoided in liver disease.

Nateglinide Another nonsulfonylurea drug which principally stimulates the 1st phase insulin secretion resulting in rapid onset and shorter duration of hypoglycaemic action than repag-linide. Ingested 10–30 min before meal, it limits postprandial hyperglycaemia in type 2 diabetics without producing late phase hypoglycaemia. There is little effect on fasting blood glucose level. Episodes of hypoglycaemia are less frequent than with sulfonylureas. Side effects are dizziness, nausea, flu like symptoms and joint pain. It is used in type 2 DM along with other antidiabetics, to control postprandial rise in blood glucose.

THIAZOLIDINEDIONES

Two thiazolidinediones *Rosiglitazone* and *Pioglitazone* have recently become available, while the first member *Thiaglitazone* has been withdrawn globally due to reports of serious liver toxicity.

This novel class of oral antidiabetic drugs are selective agonists for the nuclear *peroxisome proliferator-activated receptor γ* (PPARγ) which enhances the transcription of several insulin responsive genes. They tend to reverse insulin resistance by stimulating GLUT4 expression and translocation: entry of glucose into muscle and fat is improved. Hepatic gluconeogenesis is also suppressed. Activation of genes regulating fatty acid metabolism and lipogenesis in adipose tissue may contribute to the insulin sensitizing action. Improved glycaemic control results in lowering of circulating insulin levels in type 2 DM patients.

Pioglitazone lowers serum triglyceride level and raises HDL level without much change in LDL level. The effect of rosiglitazone on lipid profile is inconsistent.

Both pioglitazone and rosiglitazone are well tolerated; adverse effects are plasma volume expansion, edema, weight gain, headache, myalgia and mild anaemia. Monotherapy with glitazones is not associated with hypoglycaemic episodes. Few cases of hepatic dysfunction and some cardiovascular events have been reported. Monitoring of liver function is advised. They are contraindicated in liver disease and in CHF.

Table 6.2

Important features of oral hypoglycaemics

Drug	*Preparations*	*Plasma t1/2 (hr)*	*Duration of action (hr)*	*Clearance route**	*Daily dose*	*No. of doses per day*	*Remarks*
SULFONYLURFAS							
1. Tolbutamide	RASTINON, 0.5 g tab	6-8	6-8	L	0.5-3 g	2–3	Weaker, shorter acting, flexible dosage, safer in those prone to hypoglycaemia
2. Chlorpropamide	DIABINESE, 0.1, 0.25 g tab	30–36	36-48	K,L	0.1-0.5 g	1	Longest acting, can cause prolonged hypoglycaemia, potentiates ADH action, more cholestatic jaundice, alcohol flush
3. Glibenclamide (Glybunde)	DAONIL, EUGLUCON, BETANASE, 25, 5 mg tab	4–6	18-24	L	5-15 mg	1–2	Potent but slow acting, marked initial insulinemic action, ay work when others fail, metabolite excreted in urine as ell as bile, single daily dose possible despite short t½
4. Glipizide	GLYNASE, GLIDE MINIDIAB, 5 mg tab	3–5	12-18	L	5-20 mg	1–2	Fast acting, insulinemic action persists even after prolonged use, can be given once daily despite short t½, weight gain less likely
5. Gliclazide	DIAMICRON 80 mg tab DIAZIDE 20, 80 mg tab GLIZID 30, 40, 80 mg tab	8–20	12-24	L	40-240 mg	1–2	Has antiplatelet action, reduces free radicals, may delay diabetic retinopathy, less weight gain
6. Glimepiride	AMARYL, GLYPRIDE GUMER 1, 2 mg tab	5–7	24	L	1-6 mg	1	Stronger extrapancreatic action, less hyper-insulinemia Divide in two if daily dose ≥ 4 mg
BIGUANIDES							
1. Phenformin	DBI 25 mg tab DBI-TD 50 mg tab	3–10	8–12	L,K	25-150 mg	1–3	Lactic acidosis more common, withdrawn in many countries
2. Metformin	GLYCIPHAGE GLYCOMET 05, 085 g tab	15–3	6–8	K	0 5-2 g	2–4	Not metabolized at all, lactic acidosis less common
MEGLITINIDE ANALOGUES							
1. Repaglinide	EUREPA, RAPLIN 05, 1, 2 mg tab	≤ 1	2–3	L	15-8 mg	3–4	Given ½ hr before each meal for limiting p.p hyperglycaemia
2. Nateglinide	GLINATE 60, 120 mg tab	1.5	2–3	L	180-480 mg	3–4	Stimulates 1st phase insulin secretion, less likely to cause delayed hypoglycaemia
THIAZOLIDINEDIONES							
1. Rosightazone	REGLIT, ROSINORM ROSS, 2, 4,8 mg tab	4	12–24	L	4-8 mg	1–2	Reverses insulin resistance No hypoglycaemia, C/I in liver and heart disease
2. Pioglitazone	PIONORM, PIOREST, PIOZONE 15, 30 mg tab	3–5	24	L	15-45 mg	1	-do-, May improve lipid profile

*L—Metabolized in liver, K—Excreted unchanged by kidney, pp —postprandial

Rosiglitazone is metabolized by CYP2C8 while pioglitazone is metabolized by both CYP2C8 and CYP3A4. Failure of oral contraception may occur during pioglitazone therapy. Ketoconazole inhibits metabolism of pioglitazone.

The thiazolidinediones are indicated in type 2 DM, but not in type 1 DM. They reduce blood glucose and Hb A_{1c} without increasing circulating insulin. Some patients may not respond (non-responders), especially those with low baseline insulin levels. They are primarily used to supplement sulfonylureas /metformin and in case of insulin resistance. They may also be used as monotherapy (along with diet and exercise) in mild cases, and to supplement insulin in advanced cases, but firm evidence of benefit of such use is yet to be obtained.

Status of Oral Hypoglycaemics in Diabetes Mellitus

After 8 years of prospective study involving large number of patients, the University Group Diabetes Programme (UGDP) of USA (1970) presented findings that cardiovascular mortality was higher in patients treated with oral hypoglycaemics than in those treated with diet and exercise alone or with insulin. A decline in their use followed. Subsequent studies have both refuted and supported these conclusions.

The controversy has now been settled; UK PDS found that both sulfonylureas and metformin did not increase cardiovascular mortality over > 10 years observation period. Related to degree of glycaemia control, both insulin and sulfonylureas reduced microvascular complications in type 2 DM, but did not have significant effect on macrovascular complications. Metformin, however, could reduce macrovascular complications as well; it decreased risk of death and other diabetes related endpoints in overweight patients. This may be related to the fact that both sulfonylureas and exogenous insulin improve glycaemic control by increasing insulin supply rather than by reducing insulin resistance, while metformin can lower insulin resistance. The recently introduced thiazolidinediones are another class of drugs which reverse insulin resistance. All oral hypoglycaemics do however control symptoms that are due to hyperglycaemia and glycosuria, and are much more convenient than insulin.

Oral hypoglycaemics are indicated only in type 2 diabetes, when not controlled by diet and exercise. They are best used in patients with—

1. Age above 40 years at onset of disease.
2. Obesity at the time of presentation.
3. Duration of disease < 5 years when starting treatment.
4. Fasting blood sugar < 200 mg / dl.
5. Insulin requirement < 40 U/day.
6. No ketoacidosis or a history of it, or any other complication.

Introduced in the prediabetic 'impaired glucose tolerance phase', sulfonylurea + dietary regulation has been shown to postpone manifest type 2 DM. This may be due to the fact that hyperglycaemia is a self perpetuating condition.

Oral hypoglycaemics should be used to supplement dietary management and not to replace it. Sulfonylureas are generally preferred over biguanides which do reduce fasting blood glucose and glycosylated Hb, but effect may be less marked than that of sulfonylureas and g.i. tolerance of metformin is poorer. Metformin is preferred in obese type 2 patients: its anorectic action aids weight reduction. It can also be used to supplement sulfonylureas in patients not adequately controlled by the latter alone. Most diabetic clinics have stopped prescribing phen-formin because metformin rarely causes lactic acidosis.

There is no difference in the clinical efficacy of different sulfonylureas. This however does not signify that choice of drug is irrelevant. Differences between them are mainly in dose, onset and duration of action which governs flexibility of regimens. The second generation drugs are dose to dose more potent and commonly used, but no spectacular features have emerged.

Chlorpropamide is not recommended because of long duration of action, greater risk of hypogtycaemia and other adverse effects. *Tolbutamide* is less popular due to low potency, but may be employed in the elderly to avoid hypoglycaemia. *Glibenclamide* and *glyclazide* are suitable for most patients. *Glipizide* is preferred when a faster and shorter acting drug is required. *Glimepiride* is a newer sulfonylurea, claimed to have stronger extrapancreatic action by enhancing GLUT4 translocation to the plasma membrane, thus causing lesser hyperinsulinemia. It is suitable for once daily dosing due to gradual release from tissue binding.

Even in properly selected patients, sulfonyl-ureas may fail from the beginning (primary failure 5–28%) or become ineffective after a few months or years of satisfactory control (secondary failure 5–10%

per year): may be due to progression of the disease, continuing insulin resistance, drug and dietary noncompliance or desensitization of receptors. If one sulfonylurea proves ineffective in a patient, another one (especially a second generation) may still work. Combined use of a sulfonylurea and a biguanide may be tried if either is not effective alone and the glitazones are now available as add on/ alternative drugs. Patients with marked/only posprandial hyperglycaemia may be treated with repaglinide/nateglinide. Upto 50% patients of type 2 DM initially treated with oral hypoglycaemics ultimately need insulin. Despite their limitations, oral hypoglycaemics are suitable therapy for majority of type 2 DM patients. However, when a diabetic on oral hypoglycaemics presents with infection, severe trauma or stress, pregnancy, ketoacidosis or any other complication or has to be operated upon—switch over to insulin.

α GLUCOSIDASE INHIBITORS

Acarbose It is a complex oligosaccharide which reversibly inhibits α-glucosidases, the final enzymes in the digestion of carbohydrates in the brush border of small intestine mucosa. It slows down and decreases digestion and absorption of polysaccharides and sucrose: postprandial glycaemia is reduced without increasing insulin levels. Regular use tends to lower Hb A_{lc}, body weight and serum triglyceride. These beneficial effects, though modest, have been confirmed in several studies.

Acarbose is a mild antihyperglycaemic and not a hypoglycaemic: may be used as an adjuvant to diet (with or without a sulfonylurea) in obese diabetics. Dose 50–100 mg TDS taken at the beginning of each major meal. It is minimally absorbed, but produces flatulence and loose stool in about 50% patients due to fermentation of unabsorbed carbohydrates.

GLUCOBAY 50, 100 mg tabs, ASUCROSE, GLUCAR 50 mg tabs.

Miglitol is similar to acarbose.

Guargum It is a dietary fibre (polysaccharide) from Indian cluster beans (Guar), which forms a viscous gel on contact with water. Administered just before or mixed with food, it slows gastric emptying, intestinal transit and carbohydrate absorption: postprandial glycaemia is suppressed but overall lowering of blood glucose is marginal. It also reduces serum cholesterol by about 10%. Guargum can be used to

supplement diet and to lower sulfonylurea dose, and as a hypocholesterolemic. Absorption of other drugs administered with guargum may be reduced—give 2–3 hr gap. It is not absorbed but fermented in the colon. Side effects are flatulence, feeling of fullness, loss of appetite (can improve ability to stick to reducing diet), nausea, gastric discomfort and diarrhoea. Start with a low dose (2.5g/day) and gradually increase to 5 g TDS. DIATAID, CARBOTARD 5 g sachet

Other uses of oral hypoglycaemics

1. *Diagnosis of insulinoma* Tolbutamide 1 g i.v. causes marked fall in blood sugar in patients with insulin secreting tumour.

2. *Diabetes insipidus* Chlorpropamide potentiates ADH action on renal tubules. It is effective in disease of pituitary origin but not when the cause is renal. Seldom used due to attending hypoglycaemia.

GLUCAGON

A hyperglycaemic principle was demonstrated to be present in the pancreatic islets just two years after the discovery of insulin in 1921. It was named 'glucagon'. Glucagon is a single chain polypeptide containing 29 aminoacids, MW 3500. Beef and pork glucagon are identical to human glucagon. It is secreted by the a cells of the islets of Langerhans.

Regulation of Secretion Like insulin, glucagon is also derived by cleavage of a larger peptide prohormone Its secretion is regulated by glucose levels, other nutrients, paracrine hormones and nervous system. Glucose has opposite effects on insulin and glucagon release, i.e. high glucose level inhibits glucagon secretion and it is more sensitive to orally administered glucose: suggesting that the same gastrointestinal incretins which evoke insulin release may be inhibiting glucagon secretion. FFA and ketone bodies also inhibit glucagon release. Aminoacids, however, induce both insulin and glucagon secretion. Both insulin and somatostatin, elaborated by the neighbouring β and D cells respectively, inhibit glucagon secretion. Sympathetic stimulation consistently and parasympathetic stimulation under certain conditions evokes glucagon release.

Actions Glucagon is hyperglycemic; most of its actions are opposite to that of insulin. Glucagon causes hyperglycaemia primarily by enhancing glycogenolysis and gluconeogenesis in liver; suppression of glucose utilization in muscle and fat contributes modestly. It is considered to be the hormone of fuel mobilization. Its secretion is in-

creased during fasting: this serves to maintain energy supply by mobilizing stored fat and carbohydrate as well as by promoting gluconeogenesis in liver. It plays an essential role in the development of diabetic ketoacidosis. Increased secretion of glucagon has been shown to attend all forms of severe tissue injury (trauma, surgery, burns, infections, myocardial infarction). It is believed to be called in under these conditions to enhance glucose supply to the injured tissue.

Glucagon increases the force and rate of cardiac contraction and this is not antagonized by β blockers. It has a relaxant action on the gut and inhibits gastric acid production.

Mechanism of action Glucagon, through its own receptor and coupling Gs protein activates adenylyl cyclase and increases cAMP in liver, fat cells, heart and other tissues; most of its actions are mediated through this cyclic nucleotide.

Glucagon is inactive orally; that released from pancreas is broken down in liver, kidney, plasma and other tissues. Its t½ is 3–6 min.

Uses

1. *Hypoglycaemia* due to insulin or oral hypoglycaemics, use of glucagon is secondary to that of glucose, only an expedient measure It may not work if hepatic glycogen is already depleted 0.5–1 mg i.v. or i.m.

2. *Cardiogenic shock* to stimulate the heart in β adrenergic blocker treated patients. However, action is not very marked.

3. *Diagnosis of pheochromocytoma* 1 mg i.v. causes release of catecholamines from the tumour and markedly raises BP. Phentolamine should be at hand to counter excessive rise in BP.

4. The relaxant action of glucagon has been exploited for X-ray examination of gut, biliary colic, diverticulitis etc GLUCAGON 1 mg inj.

Other hyperglycaemics

Diazoxide It inhibits insulin release from β cells and causes hyperglycaemia lasting 4–8 hours Its action on ATP sensitive K^+ channels is opposite to that of sulfonylureas. Other actions which may contribute to hyperglycaemia are decreased peripheral utilization of glucose and release of catecholamines It has been used to prevent hypoglycaemia in insulinomas.

Thiazide diuretics and *phenytoin* These are also mild hyperglycaemics.

Somatostatin It causes hyperglycaemia primarily by inhibiting insulin release.

Streptozocin It is obtained from *Streptomyces achromo-genes* Causes selective damage to insulin secreting β cells It has been used to produce experimental diabetes in animals and to treat insulin secreting tumours of pancreas.

Future Trends

A number of innovations in insulin therapy are currently under trial. Attempts are continuing to make alternative routes of insulin delivery (nasal, oral) practicable. Liposome encapsulated insulin is being tried Analogues of insulin with differing pharmacokinetic profile have been synthesized.

Lispro insulin produced by reversing lysine and proline at 28th and 29th position in insulin β chain, has an onset of action within 15 mm after s.c. injection. The action peaks at 30–90 min and lasts only 3–4 hours. The reason is rapid disaggregation into monomers at the s.c. injection site. Greater flexibility in timing of insulin injection before meals and reduced late-postprandial hypoglycaemic episodes are the advantages.

Insulin aspart is another analogue with faster and shorter lasting action.

Glargine insulin This substituted insulin congener is supplied at acidic pH (4 0). Neutralized by higher pH at s.c. injection site, it gets deposited as microprecipitates from which absorption occurs slowly and uniformly. An almost peakless action starting at 2–5 hours and lasting 24 hr is obtained Its advantages are uniform basal action and reduction in symptomatic and nocturnal hypoglycaemia after single daily dose.

Other drugs being tried in DM are amylin analogues like:

Pramlintide which delay gastric emptying and suppress glucagon secretion.

β-cell transplants and incorporation of insulin gene in non-β cell lines (fibroblasts) is likely to provide a long lasting endogenous source of insulin to the diabetic patient.

DRUGS AFFECTING CALCIUM BALANCE

CALCIUM

After C, O, H and N, Calcium is the most abundant body constituent, making up about 2% of body weight: 1–1.5 kg in an adult. Over 99% of this is stored in bones, the rest being distributed in plasma and all tissues and cells.

Physiological roles

1. Calcium controls excitability of nerves and muscles and regulates permeability of cell membranes. It also maintains integrity of cell membranes and regulates cell adhesion.

2. Ca^{2+} ions are essential for excitation-contraction coupling in all types of muscle and excitation-secretion coupling in exocrine and endocrine glands, release of transmitters from nerve ending and other release reactions.

3. Intracellular messenger for hormones, auta-coids and transmitters.

4. Impulse generation in heart—determines level of automaticity and A-V conduction.

5. Coagulation of blood.

Plasma calcium level It is precisely regulated by 3 hormones almost exclusively devoted to this function viz. *parathormone* (PTH), *calcitonin* and *calcitriol* (active form of vit D).

Normal plasma calcium is 9–11 mg/dl. Of this about 40% is bound to plasma proteins—chiefly albumin; 10% is complexed with citrate, phosphate and carbonate in an undissociable form; the remaining (about 50%) is ionized and physiologically important. For example, in hypoalbu-minemia, total plasma calcium may be low but the concentration of Ca^{2+} ion is usually normal. Acidosis favours and alkalosis disfavours ioniza-tion of calcium: hyperventilation precipitates tetany and laryngospasm in calcium deficiency by reducing ionization.

Influences affecting bone turnover

↑ *Resorption*	↓ *Resorption*
Corticosteroids	Androgens /Estrogens
Parathormone	Calcitonin
Thyroxine (excess)	*Growth hormone*
Hypervitaminosis D	Bisphosphonates
Prostaglandin E_2	Fluoride
Interleukin 1 & 6	Gallium nitrate
Alcoholism	Mithramycin
Loop diuretics	Thiazide diuretics

Calcium turnover Major fraction of calcium in the bone is stored as crystalline hydroxyapatite deposited on the organic bone matrix *osteoid,* while a small labile pool is in dynamic equilibrium with plasma. Even the fully laid down parts of the bone undergo constant *remodeling* by way of two closely coupled but directionally opposite processes of resorption and new bone formation. Millions of tiny remodeling units are working on the surface of bone trabeculae and Haversian canals to dig micropits by osteoclastic activity and then repair by osteoblastic activity in which first collagen and other proteins (osteoid) are deposited followed by mineralization; the full cycle taking 4–6 months. Diet, exercise, several hormones and drugs regulate the number and efficiency of bone remodeling units at any given time. Remodeling deficits accumulate over life time to account for age related bone loss, the pace of which can be retarded or accelerated by modulating the above listed influences. Estrogen lack after menopause mainly causes loss of trabecular bone, particularly affecting vertebrae, wrist bones and femoral neck. Minimal trauma/compression fractures are most common at these sites.

Absorption and excretion Calcium is absorbed by facilitated diffusion from the entire small intestine as well as from duodenum by a carrier mediated active transport under the influence of vit D. Phytates, phosphates, oxalates and tetracyclines complex Ca^{2+} in an insoluble form in the intestines and interfere with absorption. Glucocorticoids and phenytoin also reduce calcium absorption.

All ionized calcium is filtered at the glomerulus and most of it is reabsorbed in the tubules.

Vit D increases and calcitonin decreases proximal tubular reabsorption, while PTH increases distal tubular reabsorption of Ca^{2+}. About 300 mg of endogenous calcium is excreted daily: half in urine and half in faeces. To maintain calcium balance the same amount has to be absorbed in the small intestine from diet. Because normally only ⅓ of ingested calcium is absorbed, the dietary allowance for calcium is 0.8–1.5 g per day. However, calcium deficiency and low dietary calcium increases fractional calcium absorption. Thiazide diuretics impede calcium excretion by facilitating tubular reabsorption.

Preparations

1. Calcium chloride (27% Ca): is freely water soluble but highly irritating—tissue necrosis occurs if it is injected i.m. or extravasation takes place during i.v. injection. Orally also the solution irritates.

2. Calcium gluconate (9% Ca): is available as 0.5 g and 1 g tablets and 10% injection (5 ml amp.) It is nonirritating to g.i.t. and the vascular endothelium—a sense of warmth is produced at i.v. injection: extravasation should be guarded. It is the preferred injectable salt.

3. Calcium lactate (13% Ca): is given orally, nonirritating and well tolerated.

4. Calcium dibasic phosphate (23% Ca): is insoluble, reacts with HC1 to form soluble chloride in the stomach. It is bland; used orally as antacid and to supplement calcium.

5. Calcium carbonate (40% Ca) insoluble tasteless and nonirritating It has been used as an antacid—reacts with HCl to form chloride which may be absorbed from the intestines.

Side effects Calcium supplements are usually well tolerated, only g 1 side effects like constipation, bloating and excess gas (specially with cal carbonate) have been reported

Some combined formulations

CALCINOL-RB: Cal. carb 0.375 g, Cal. Phos 75 mg + vit D_3 250 IU tab

CALCIUM-SANDOZ: Cal glucobionate 137.5 mg/ml inj 10 ml amp also tabs containing cal carbonate 650mg

KALZANA: Cal dibasic phos 430 mg + Vit C and D_3 200 IU tab also syrup: Cal. gluconate 300 mg, Cal. lactobionate 1.1 g, Cal. phos 75 mg per 5 ml containing Vit A, C, niacmamide and D_3 200 IU.

OSTOCALCIUM: Cal. phos 380 mg + Vit D3 400 IU tab, also syrup: Cal. phos 240 mg per 5 ml containing Vit D_3 200 IU and B_{12}.

SHELCAL: Cal. carb 625 mg (eq 250 mg elemental cal), Vit D_3 125 IU tab and per 5 ml syr.

MACALVIT: Cal. carb 1.25 g, cholecalciferol 250 IU tab, Cal. gluconate 1.18 g, Cal. lactobionate 260 mg + Vit D_3 100 IU per 5 ml syr.

CALCIMAX: Cal. carb (150 mg cal), dibasic cal. phos. (23.3 mg cal) with magnesium, zinc and vit D_3 200 IU tab, also syrup cal. carb (150 mg cal) with magnesium, zinc and vit D_3 200 IU per 5 ml syrup.

Use

1. *Tetany* For immediate treatment of severe cases 5–10 ml of Cal. gluconate is injected i.v. followed by slow 1 v infusion A total of 0.45–0.9 g calcium (50 to 100 ml of cal. gluconate solution) over 6 hours is needed for completely reversing the muscle spasms Long term oral

treatment to provide 1–1.5 g of calcium daily is instituted along with vit D Milder cases need oral therapy only

2. *As dietary supplement* specially in growing children, pregnant, lactating and menopausal women The dietary allowance recommended by National Institute of Health (1994) is—

- Children 1–10 yr : 0 8 1 2 g
- Young adult 11–24 yr pregnant and lactating women : 1.2–1.5 g
- Men 25 65 yr, women 25 50 yr and 51–65 yr if taking HRT: 1.0 g
- Women 51 65 yr not taking HRT every one > 65 yr : 1.5 g

Calcium supplement is often given to fracture patients, but if diet is adequate this does not accelerate healing

3. *Osteoporosis* In the prevention and treatment of osteoporosis with HRT/raloxifene/ alendronate, it is important to ensure that calcium deficiency does not occur. Medicinal calcium given alone appears to be only marginally effective in reducing the incidence of fracture among menopausal women/elderly males, though rate of cortical bone loss is reported to be reduced Calcium + vit D_3 has adjuvant role to HRT/raloxifene in prevention and treatment of osteoporosis.

4. Empirically, Cal. gluconate i.v. has been used in dermatoses, paresthesias, weakness and other vague complaints. Any benefit is probably psychological due to warmth and other subjective effects produced by the injection.

5. As antacid.

PARATHYROID HORMONE (Parathormone)

Vassale and Generali (1900) were the first to perform selective parathyroidectomy (without removing thyroids) and found that it produced tetany and death. MacCallum and Voegtlin in 1909 established this to be due to decrease in plasma calcium levels, parathormone (PTH) was isolated in 1925.

PTH is a single chain 84 amino acid poly-peptide, MW 9500 It is synthesized as prepro-PTH, the excess amino acids are split off in two steps and it is then stored in intracellular vesicles. Secretion of PTH is regulated by plasma Ca^{2+} concentration; there is no trophic hormone for it Fall in plasma Ca^{2+} induces PTH release and rise inhibits secretion probably by decreasing cAMP in the parathyroid cells. Agents that increase cAMP cause PTH release, but direct activation of protein

kinase C by fall in Ca^{2+} concentration is more important physiologically. Prolonged hypocalcaemia causes hypertrophy and hyperplasia of parathyroids, while sustained hypercalcaemia has the opposite effect. Changes in phosphate concentration in plasma affect PTH secretion indirectlyby altering Ca^{2+} concentration. The active form of vit. D calcitriol inhibits expression of PTH gene in parathyroid cells. PTH is rapidly degraded in liver and kidney; its plasma t½ is 2–5 min.

Actions

PTH increases plasma calcium levels by:

1. ***Bone*** PTH promptly increases resorption of calcium from bone. This is the most important action of PTH—exerted by increasing the number of bone remodeling units and inhibiting osteoblasts.

2. ***Kidney*** PTH increases calcium reabsorption in the distal tubule and provides moment to moment regulation of calcium excretion. It also promotes phosphate excretion which tends to supplement the hypercalcaemic effect. However, grossly increased plasma calcium level occurring in hyperparathyroidism overrides the direct action on tubules and calcium excretion in urine is actually increased. The converse occurs in hypoparathyroidism.

3. ***Intestines*** PTH has no direct effect on calcium absorption but increases it indirectly by enhancing the formation of calcitriol (active form of vit D) in the kidney by activating 1α-hydroxylase.

4. ***PTH*** decreases calcium levels in milk, saliva and ocular lens—may be responsible for development of cataract in hypoparathyroidism.

Mechanism of action The PTH receptor is a G protein coupled receptor which on activation increases cAMP formation and intracellular Ca^{2+} in target cells. In bone the target cell appears to be the osteoblast because PTH receptors are not expressed on the surface of osteoclasts. It has been proposed that PTH-osteoblast complex somehow increases the activity of osteoclasts as well as the birth rate of bone remodeling units in which osteoclast precursors are recruited. Bone forming activity of osteoblasts is inhibited though their number increases due to increase in population of remodeling units.

Hypoparathyroidism Manifestations are: Low plasma calcium levels, tetany, convulsions, laryngospasm, paresthesias, cataract and psychiatric changes. Pseudohypoparathyroidism occurs due to reduced sensitivity of target cells to PTH caused by a mutant G protein that couples PTH receptor activation to cAMP generation in target cells.

Hyperparathyroidism It is mostly due to parathyroid tumour. It produces—Hypercalcaemia, decalcification of bone—deformities and fractures (osteitis fibrosa generalisata), metastatic calcification, renal stones, muscle weakness, constipation and anorexia.

Treatment is surgical removal of the parathyroid tumour. When this is not possible—low calcium, high phosphate diet with plenty of fluids is advised.

Preparation PTH is not available commercially. A preparation (Tenparatide) containing the 1–34 amino acid residues of human PTH has been synthesized for investigational purposes.

Use PTH is not used therapeutically because plasma calcium can be elevated and kept in the normal range more conveniently by vit D therapy PTH has to be given parenterally while vit D can be given orally. Vit D is cheap.

Diagnostic use To differentiate pseudo from true hypoparathyroidism. 200 U of teriparatide is given i.v. if plasma calcium level fails to rise, then it is pseudohypoparathyroidism

CALCITONIN

Calcitonin is the hypocalcaemic hormone discovered by Copp in 1962. It is a 32 amino acid single chain polypeptide (MW 3600) produced by parafollicular 'C cells of thyroid. Parathyroids, thymus and cells of medullary carcinoma of thyroid also contain calcitonin.

Synthesis and secretion of calcitonin is regulated by plasma Ca^{2+} concentration itself: rise in plasma Ca^{2+} increases while fall in plasma Ca^{2+} decreases calcitonin release. However, the physiological role of calcitonin in regulating plasma Ca^{2+} appears to be minor. The plasma t½ of calcitonin is 10 min, but its action lasts for several hours.

Actions

The actions of calcitonin are generally opposite to that of PTH.

It inhibits bone resorption by direct action on osteoclasts—decreasing their ruffled surface which forms contact with the resorptive pit. It is doubtful whether it also promotes calcium deposition by osteoblasts. The hypocalcemic action of calcitonin lasts ~8 hours.

Calcitonin inhibits proximal tubular calcium and phosphate reabsorption by direct action on kidney. However, hypocalcaemia which occurs overrides the direct action by decreasing the total calcium filtered at the glomerulus—urinary Ca^{2+} is actually reduced.

The actions of calcitonin are probably mediated through increase in cAMP formation, but its target cells are different from that of PTH.

Preparation and unitage Synthetic salmon calcitonin is used clinically, because it is more potent due to slower metabolism Human calcitonin has also been produced

1 IU = 4 ug of standard preparation

CALSYNAR, ZYCALCIT Synthetic salmon calcitonin 100 IU/ml amp for i.m. or s.c. injection Adverse effects experienced are nausea, flushing, tingling of fingers, bad taste and allergic reaction. By lowering plasma Ca^{2+} calcitonin may interfere with action of digoxin

Uses

1. *Hypercalcaemic states* Hyperparathyroidism, hyper-vitaminosis D, osteolytic bony metastasis etc 4–8 U/kg BD It acts rapidly, but refractoriness develops over time and other measures to reduce plasma calcium are more convenient

2. *Postmenopausal osteoporosis* 100 IU s.c. or i.m. daily along with calcium and vit D supplements.

A nasal spray formulation (MIACALCIN) delivering 200 IU per actuation has become available in some countries One spray in one nostril daily has been shown to increase bone mineral density in menopausal women effect becoming perceptable after 6 month therapy, and is maintained thereafter It is indicated when estrogens cannot be given and the women is menopausal for at least 5 years with definite evidence of osteoporosis. Rhinitis, epistaxis, nasal ulceration and headache are the side effects.

3. *Paget's disease* 100 U daily or on alternate days produces improvement for few months. Later, resistance usually develops due to production of antibodies. Human calcitonin may prove better in this regard.

VITAMIN D

Vitamin D is the collective name given to antirachitic substances synthesized in the body and found in foods activated by UV radiation.

D3: cholecalciferol — synthesized in skin under the influence of UV rays.

D2: calciferol—present in irradiated food—yeasts, fungi, bread, milk.

Dl: mixture of antirachitic substances found in food—only of historic interest.

In 1919 it was established that rickets was due to deficiency of a dietary factor as well as lack of exposure to sunlight. McCollum (1922) showed that this fat soluble dietary factor was different from vit A and its structure was determined in 1935. The interrelation between calciferol and cholecalciferol and their activation in the body has been fully understood only in the 1970s.

Activation of Vit D takes place in the following manner—

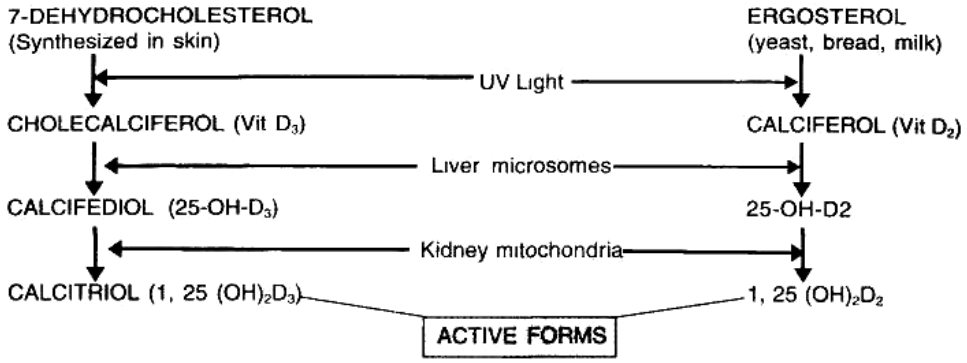
Ergosterol differs from 7-dehydrocholesterol in having an extra double bond between C22-23 and a methyl group at C24. In man vit D_2 and D_3 are equally active and *calcitriol* (active form of D_3) is more important physiologically; 25-OH D_3 is released in blood from liver and binds loosely to a specific vit D binding globulin. The final hydroxylation in kidney is rate limiting and controlled by many factors. This step is activated or induced by calcium/vit D deficiency and by PTH, estrogens and prolactin, while calcitriol inhibits it in a feed back manner.

Thus vit D should be considered a hormone because—

(a) It is synthesized in skin: a specific tissue (under ideal conditions it is not required in diet).

(b) It is transported by blood, activated and then acts on specific receptors in target tissues.

(c) Feed back regulation of vit D activation occurs by plasma Ca^{2+} level and by the active form itself.



Actions

1. Calcitriol enhances absorption of calcium and phosphate from *intestine.* This is brought about probably by increasing synthesis of a carrier protein for Ca^{2+} called 'calcium binding protein' (Ca BP) or *Calbindin.* The action of calcitriol is analogous to that of steroid hormones which bind to a cytoplasmic receptor → translocate to the nucleus → increase synthesis of specific mRNA → regulation of protein

synthesis. Another line of evidence suggests that activation of vit D receptor promotes endocytotic capture of calcium and its transport across duodenal mucosal cell in vesicular form. At least part of vit D action is quick (within minutes) and therefore appears to be exerted by mechanisms not involving gene regulation.

2. Calcitriol enhances resorption of calcium and phosphate from *bone* by promoting recruitment and differentiation of osteoclast precursors in the bone remodeling units, but mature osteoclasts lack vit D receptor. Though osteoblastic cells express vit D receptor and respond to it, calcitriol appears to help bone mineralization indirectly by maintaining normal plasma calcium and phosphate concentration. Its action is independent of but facilitated by PTH.

3. It enhances proximal tubular reabsorption of both calcium and phosphate in *kidney* but the action is less marked than that of PTH. However, in hypervitaminosis D, influence of hypercalcaemia overrides the direct action and more calcium is excreted in urine.

4. *Other actions* Actions of calcitriol on immu-nological cells, lymphokine production, proliferation and differentiation of epidermal and certain malignant cells, neuronal and skeletal muscle function have also been demonstrated.

Vit D deficiency Plasma calcium and phosphate tend to fall due to inadequate intestinal absorption. As a consequence, PTH is secreted → calcium is mobilized from bone in order to restore plasma Ca^{2+}. The bone fails to mineralize normally in the newly laid area, becomes soft → rickets in children and osteomalacia in adults. However, in contrast to *osteoporosis,* the organic matrix (osteoid) is normal in these conditions.

Hypervitaminosis D It may occur due to chronic ingestion of large doses (~50,000 IU/day) or due to increased sensitivity of tissues to vit D. Manifestations are due to elevated plasma calcium and its ectopic deposition.

Hypercalcaemia, weakness, fatigue, vomiting, diarrhoea, sluggishness, polyuria, albuminuria, ectopic Ca^{2+} deposition (in soft tissues, blood vessels, parenchymal organs), renal stones or nephrocalcinosis, hypertension, growth retardation in children. Even coma has been reported. *Treatment:* consists of withholding the vitamin, low calcium diet, plenty of fluid and cortico-steroids. Recovery may be incomplete in many cases.

Pharmacokinetics

Vit D is well absorbed from intestines in the presence of bile salts. Absorption of D_3 form is somewhat better than that of D_2. Malabsorption and steatorrhoea interfere with its absorption.

In the circulation, it is bound to a specific a globulin and is stored in the body, mostly in adipose tissues, for many months. It is hydroxy-lated in liver to active and inactive metabolites. The t½ of different forms varies from 1–18 days: 25-OHD_3, having the longest t½, constitutes the primary circulating form. Metabolites of vit D are excreted mainly in bile.

Unitage and Preparations

1 μg of cholecalciferol = 40 IU of Vit D The daily requirement varies, depending on exposure to sunlight It is estimated that if no Vit D_3 is synthesized in the body, a dietary allowance of 400 IU/day will prevent deficiency symptoms The forms in which Vit D is supplied are—

1. Calciferol (Ergocalciferol, Vit D2) As solution in oil, filled in gelatin capsules 25,000 and 50,000 IU caps

2. Cholecalciferol (Vit D3) As granules for oral ingestion and oily solution for i.m. injection.

ARACHITOL 300,000 IU (7.5 mg) and 600,000 IU (15 mg) per ml inj.

CALCIROL 60,000 IU in 1 g granules—given at 3-4 weeks intervals followed by every 2–6 months

3. Calcitriol 0.25–1 μg orally daily or on alternate days, CALTROL, ROLSICAL, ROCALTROL 0.25 μg cap.

4. Alfacalcidol It is 1 α-OHD_3—a prodrug that is rapidly hydroxylated in the liver to 1, 25 $(OH)_2$ D3 or calcitriol Therefore, it does not require hydroxylation at position 1 which is the limiting step in the generation of the active form of vit D, and which takes place in the kidney As such, it is effective in renal bone disease, Vit D dependent rickets, vit D resistant rickets, hypoparathyroidism etc.—indications for which calcitriol is needed. It is also being used in osteoporosis.

Alfacalcidol is orally active and clinically equally effective on long term basis to calcitriol. Its metabolic activation in liver does not pose a problem even in severe liver disease.

Dose: 1–2 μg/day, children < 20 kg 0.5 fig/day. Repeated serum calcium measurements are essential for regulation of maintenance dose. Hypercalcaemia should be watched for and therapy promptly interrupted for few days when it develops.

ONE ALPHA, ALPHA D_3, ALPHADOL 0.25 and 1 μg caps, ALFACAL 0.25, 0.5 μg caps

5. Dihydrotachysterol (DHT) A synthetic analogue of vit D_2—less active in antirachitic tests but directly mobilizes calcium from bone: does not require PTH dependent activation in the kidney—particularly useful in hypoparathyroidism and renal bone disease.

Dose: 0.25–0.5 mg/day.

Use

1. Prophylaxis (400 IU/day) and treatment (3000–4000 IU/day) of *nutritional vit D deficiency.* Alternatively 300,000–600,000 IU can be given orally or i.m. once in 2–6 months. Prophylactic treatment may be given in obstructive jaundice, steatorrhoea and other conditions which predispose to vit D deficiency.

2. Metabolic rickets These are a group of conditions in which tissues do not respond to normal doses of vit D.

(a) *Vit D resistant rickets:* X-linked hereditary disease in which vit D metabolism is normal but calcium and phosphate metabolism is deranged. Administration of phosphate with high dose of calcitriol or alfacalcidol is beneficial.

(b) *Vit D dependent rickets:* Another genetic disorder due to deficiency of renal hydroxylating mechanism which converts 25-OHD_3 into calcitriol. Administration of calcitriol or alfacalcidol is effective in normal doses.

(c) *Renal rickets:* Conversion of 25-OHD_3 into calcitriol does not occur due to chronic renal disease. Calcitriol/alfacalcidol or dihydrotachysterol are needed in usual doses.

3. Senile or postmenopausal osteoporosis Age related decrease in calcium absorption from gut has been noted. Vit D_3 + calcium has been shown to improve calcium balance in osteoporotic females and elderly males. It can improve bone mineral density and reduce fracture incidence in the elderly population. Active therapy with calcitriol/alfacalcidol has been recommended by some investigators in patients with established osteoporosis, because is suppresses parathyroids and reduces bone remodeling. Though bone mineral density may be improved, it carries the risk of hypercalcemia, calcium stones and metastatic calcification.

4. Hypoparathyroidism Dihydrotachysterol or calcitriol/alfacalcidol are more effective than vit D_2 or D_3 because they act quickly and directly

without the need for hydroxylation in kidney which needs PTH. However, these are expensive and may be given initially allowing time for the conventional forms to act; 50,000–200,000 IU of vit D_3 may be needed daily.

5. Fanconi syndrome Vit D can raise the lowered phosphate levels that occur in this condition.

6. A nonhypercalcaemic analogue of vit D *Calcipotriol* (DAIVONEX 0.005% oint) is used locally in plaque type psoriasis, and has yielded good results. Systemically it has been tried in skin cancer and immunological disorders.

Interactions

1. Cholestyramine and chronic use of liquid paraffine can reduce vit D absorption.

2. Phenytoin and phenobarbitone reduce the responsiveness of target tissues to calcitriol; their prolonged use (for epilepsy) can cause rickets/osteomalacia. It was believed earlier that these drugs enhance degradation of vit D. However, now it has been shown that plasma level of calcitriol is normal, but its effect on intestine and bone is diminished.

BISPHOSPHONATES

Currently three bisphosphonates (BPNs) *Etidronate, Pamidronate* and *Alendronate* are available in India. They are analogues of pyrophosphate: carbon atom replacing oxygen in P-O-P skeleton. They inhibit bone resorption and have recently attracted considerable attention because of their ability to prevent osteoporosis in addition to their usefulness in metabolic bone diseases and hypercalcemia.

The mechanism of action of BPNs is not fully understood, but two facets of action have been delineated:

(a) BPNs have strong affinity for calcium phosphate: have selective action in calcified tissue. The two main components of bone are protein matrix and the solid mineral phase (hydroxyapatite). On the surface of resorptive pits the mineral phase is solubilized in the clear acidic zone created at the ruffled border of osteoclasts, followed by resorption of protein matrix in this area by acid hydrolases secreted from osteoclasts. BPNs localise in the acidic zone under osteoclasts due to their high affinity for Ca^{2+} ions. When Ca^{2+} ions are released from bone surface due to high acidity, the BPNs are also released and are internalized into osteoclasts by endocytosis. This results in:

• Accelerated apoptosis of osteoclasts reducing their number.

• Disruption of cytoskeleton and ruffled border of osteoclasts.In addition BPNs appear to affect osteoclast precursors and inhibit their differentiation by suppressing IL-6.

(b) It has been shown recently that BPNs, specially the second generation potent amino-derivatives like alendronate, have important metabolic effects in the mevalonate pathway for isoprenoid lipid synthesis. They inhibit prenylation of certain GTP-binding proteins involved in cytoskeletal organization, membrane ruffling and vesicle movement. The net result is inactivation of osteoclasts, impaired vesicle fusion and enhanced apoptosis.

The BPNs are useful in conditions characterized by enhanced bone turnover.

1. *Osteoporosis* The second generation BPNs are effective in preventing and treating post-menopausal osteoporosis in women as well as idiopathic and steroid induced osteoporosis in both men and women. Alendronate has been found as effective as HRT or raloxifene in conserving bone mineral density and has reduced the risk of vertebral or hip fracture by 47–56%.

2. *Paget's disease* This disease due to abnormal osteoclast function producing disordered bone architecture is benefited by BPNs. They arrest osteolytic lesions, reduce bone pain and improve secondary symptoms. Long lasting remissions may be induced. They are more convenient and cheaper than calcitonin. Combined use of BPNs and calcitonin is more effective.

3. *Osteolytic bone metastasis* Parenteral pamidronate arrests osteolytic lesions and reduces bone pain.

4. *Hypercalcemia of malignancy* Pamidronate and etidronate injected i.v. normalise plasma Ca^{2+} level, but oral BPNs have limited efficacy.

Etidronate This is the first BPN to be used clinically, employed in hypercalcemia and Paget's disease. However, it also interferes with bone mineralization: continuous therapy produces osteomalacia. It should be given intermittently with 3 month gap between courses. Etidronate is administered both orally and i.v., but is not preferred now. Adverse effects are gastric irritation, bone pain, headache, metallic taste, pyrexia and hypersensitivity.

Dose: 5–7.5 mg/kg/day; DRONATE-OS 200 mg tab, 300 mg inj; DISONATE 200 mg tab.

Pamidronate A more potent BPN which is administered only by i.v. infusion in a dose of 30–90 mg over 4–12 hours once a day to once in 2 months depending on the condition. It is used in Paget's disease, hypercalcemia of malignancy and in bony metastasis. Adverse effects are thromboflebitis of injected vein, bone pain, fever and leukopenia.

AREDIA 15, 30, 60 mg inj; AREDRONET 30, 90 mg inj.

Alendronate This potent orally effective second generation amino-BPN is used primarily for prevention and treatment of osteoporosis both in women and men. It is to be taken on empty stomach in the morning with a full glass of water and patient is instructed not to lie down or take food for at least 30 min. These measures are needed to prevent contact with esophageal mucosa which results in esophagitis. Calcium, iron, antacids, mineral water, tea, coffee, fruit juice interfere with alendronate absorption. NSAIDs accentuate gastric irritation caused by alendronate. Other adverse effects are gastric erosion, retrosternal pain, flatulence, headache, bodyache and initial fall in serum Ca^{2+} level.

Dose: 5–10 mg OD; OSTEOPHOS, DENFOS 5, 10 mg tab, RESTOFOS, DRONAL 10 mg tab.

Only a small fraction of orally taken BPN is absorbed. A fraction of the drug entering the body is sequestrated in bone while rest is excreted unchanged mainly by the kidney. The terminal elimination t½ of alendronate has been measured as 10.5 years.

Other second/third generation BPNs are *Tiludronate, Risedronate, Zolendronate* and *Ibandronate,* not yet marketed in India.

DRUGS USED IN MENTAL ILLNESS: ANTIPSYCHOTIC AND ANTIANXIETY DRUGS

The psychopharmacological agents or psychotropic drugs are those having primary effects on *psyche* (mental processes) and are used for treatment of psychiatric disorders.

During the past 50 years psychiatric treatment has witnessed major changes due to advent of drugs which can have specific salutary effect in mental illnesses. The trend has turned from custodial care towards restoring the individual patient to his place in the community. All that could be done before 1952 was to dope and quieten agitated and violent patients. The introduction of *chlorpromazine* in that year has transformed the lives of schizophrenics; most can now be rehabilitated to productive life. *Reserpine* was discovered soon after; though it is a powerful pharmacological tool to study monoaminergic systems in brain and periphery, its clinical use in psychiatry lasted only few years. Next came the *tricyclic* and MAO *inhibitor antidepressants* in 1957–58 and covered another group of psychiatric patients. Many novel antipsychotics and anti-depressants have been introduced since the 1980s. Meprobamate (1954) aroused the hope that anxiety could be tackled without producing marked sedation. This goal has been realised more completely by the development of *Chlordiazepoxide* (1957) and other *benzodiazepines* in the 1960s. *Buspirone* is a significant recent addition.

Little attention was paid to Cade's report in 1949 that *Lithium* could be used for excitement and mania: its effective use started in the 1960s and now it has a unique place in psychiatry. Interestingly some antiepileptics like carbamazepine and valproate have shown promise in mania and bipolar disorders.

Psychiatric diagnostic categories are often imprecise. The criteria adopted overlap in individual patients. Nevertheless, broad divisions have to be made, primarily on the basis of predominant manifestations, to guide the use of drugs. It is important to make an attempt to characterise the primary abnormality, because specific drugs are now available for most categories. Principal types are: **Psychoses** These are severe psychiatric illness with serious distortion of thought, behaviour, capacity to recognise reality and of perception (delusions and hallucinations). There is inexplicable misperception and misevaluation; patient is unable to meet the ordinary demands of life.

(a) *Acute and chronic organic brain syndromes (cognitive disorders)* Such as delirium and dementia; some toxic or pathological basis can often be defined; prominent features are confusion, disorientation, defective memory and disorganized behaviour.

(b) *Functional disorders* No underlying cause can be defined; memory and orientation are mostly retained but emotion, thought and behaviour are seriously altered.

(i) *Schizophrenia* (split mind) i.e. splitting of perception and interpretation from reality—hallucinations, inability to think coherently.

(ii) *Paranoid states* with marked persecutory or other kinds of fixed delusions (false beliefs) and loss of insight into the abnormality.

Affective disorders The primary symptom is change in mood state; may manifest as:

Mania—elation, hyperactivity, uncontrollable thought and speech, may be associated with violent behaviour, or

Depression—sadness, guilt, physical and mental slowing, melancholia, self destructive ideation. It may be bipolar (manic-depressive) with cyclically alternating manic and depressive phases or unipolar (mania or depression) with waxing and waning course.

Neuroses These are less serious; ability to comprehend reality is not lost, though patient may undergo extreme suffering. Depending on the predominant feature, it may be labelled as:

(a) *Anxiety* An unpleasant emotional state associated with uneasiness and concern for the future.

(b) *Phobic states* Fear of the unknown or of some specific objects, person or situations.

(c) *Obsessive, compulsive* Limited abnormality of thought or behaviour (ritual like) which the patient is not able to overcome even on voluntary effort.

(d) *Reactive depression* due to physical illness, loss, blow to self esteem or bereavement, but is excessive or disproportionate.

(e)*Post-traumatic stress disorder* Varied symptoms following distressing experiences like war, riots, earthquakes, etc.

(f) *Hysterical* Dramatic symptoms resembling serious physical illness, but situational, and always in the presence of others; the patient does not feign but actually undergoes the symptoms, though the basis is only psychic and not physical.

Pathophysiology of mental illness is not clear, though some ideas have been formed, e.g. dopa-minergic overactivity in the limbic system may be involved in schizophrenia and mania, and monoaminergic (NA, 5-HT) deficit may underlie depression. Treatment is empirical, symptom oriented and not disease specific. However, it is highly effective in many situations. Depending on the primary use, the psychotropic drugs may be grouped into—

1. *Antipsychotic* (neuroleptic, ataractic, major tranquillizer) useful in all types of psychosis, specially schizophrenia.
2. *Antianxiety* (anxiolytic-sedative, minor tranquillizer) used for anxiety and phobic states.
3. *Antidepressants* used for minor as well as major depressive illness, phobic states, obsessive compulsive behaviour, and certain anxeity disorders.
4. *Antimanic* (mood stabiliser) used to control mania and to break into cyclic affective disorders.

Antidepressants and antimanic drugs are sometimes collectively referred as *'Drugs for Affective Disorders'.*

5. *Psychotomimetic* (psychedelic, psychodysleptic, hallucinogen). These are seldom used therapeutically but produce psychosis like states, majority are drugs of abuse.

Tranquillizer It is an old term meaning "a drug which reduces mental tension and produces calmness without inducing sleep or depressing mental faculties." It was used to describe the effects of reserpine. However, it has been interpreted differently by different people; some extended it to cover both reserpine like and antianxiety drugs, others felt that it should be restricted to the antianxiety drugs only. Their division into *major* and *minor* tranquillizers is not justified, because the 'minor tranquillizers' are not less important drugs: they are more frequently prescribed and carry higher abuse liability than the 'major tranquillizers'. The term tranquillizer is, therefore, best avoided.

ANTIPSYCHOTIC DRUGS

These are drugs having a salutary therapeutic effect in psychoses.

Many more drugs have been marketed in other countries but do not deserve special mention. Pharmacology of chlorpromazine (CPZ) will be described as prototype; others only as they differ from it.

CLASSIFICATION

1. Phenothiazines	
Aliphatic side chain:	Chlorpromazine
	Triflupromazine
Piperidine side chain:	Thioridazine
Piperazine side chain:	Trifluoperazine
	Fluphenazine
2. Butyrophenones	Haloperidol
	Trifluperidol
	Droperidol
	Penfluridol
3. Thioxanthenes	Thiothixene
	Flupenthixol
4. Other heterocyclics	Pimozide,
	Loxapine
	Reserpine
5. Atypical neuroleptics	Clozapine
	Risperidone
	Olanzapine

PHARMACOLOGICAL ACTIONS

1. CNS Effects differ in normal and psychotic individuals.

In normal individuals It produces indifference to surroundings, paucity of thought, psychomotor slowing, emotional quietening, reduction in initiative and tendency to go off to sleep from which the subject is easily arousable. Spontaneous movements are minimized but slurring of speech, ataxia or motor incoordination does not occur. This has been referred to as the 'neuroleptic syndrome' and is quite different from the sedative action of barbiturates and other similar drugs. The effects are appreciated as 'neutral' or 'unpleasant' by most normal individuals.

In a psychotic It reduces irrational behaviour, agitation and aggressiveness and controls psychotic symptomatology. Disturbed thought and behaviour are gradually normalised, anxiety is relieved. Hyperactivity, hallucinations and delusions are suppressed.

All phenothiazines, thioxanthenes and butyrophenones have the same antipsychotic efficacy, but potency differs in terms of equieffective doses.

The aliphatic and piperidine side chain phenothiazines (CPZ, triflupromazine, thioridazine) have low potency, produce more sedation and cause greater potentiation of hypnotics, opioids etc. The sedative effect is produced irnmediately while antipsychotic effect takes weeks to develop. Moreover, tolerance develops to the sedative but not to the antipsychotic effect. Thus, the two appear to be independent actions.

Performance and intelligence are relatively unaffected but vigilance is impaired. Extrapyramidal motor disturbances *(see* adverse effects) are intimately linked to the antipsychotic effect but are more prominent in the high potency compounds and least in thioridazine. A predominance of lower frequency waves occurs in EEG and arousal response is dampened. However, no consistent effect on sleep architecture has been noted. The disturbed sleep pattern in a psychotic is normalised.

Chlorpromazine lowers seizure threshold and can precipitate fits in untreated epileptics. The piperazine side chain compounds have a lower propensity for this action. Temperature control is knocked off at relatively higher doses rendering the individual poikilothermic—body temperature falls if surroundings are cold. The medullary respiratory and other vital centres are not affected, except at very high doses. It is very difficult to produce coma with these drugs. Neuroleptics, except thioridazine, have potent antiemetic action exerted through the CTZ. However, they are ineffective in motion sickness.

In animals, neuroleptics selectively inhibit *'conditioned avoidance response'* (CAR) without blocking the unconditioned response to a noxious stimulus. This action has shown good correlation with the antipsychotic potency of different compounds, though it may be based on a different facet of action. In animals, a state of rigidity and immobility (catalepsy) is produced which resembles the bradykinesia seen clinically.

Mechanism of action All antipsychotics clozapine like) have potent dopamine receptor blocking action; antipsychotic potency has shown good correlation with their capacity to bind to D2 receptor. Phenothiazines and thioxanthines also block Dl, D3 and D4 receptors (see p. 383 for subtypes of DA receptors). Blockade of dopaminergic projections to the temporal and prefrontal areas constituting the 'limbic system' and in mesocortical areas is probably responsible for the antipsychotic action. This along with the observation that drugs which increase DA activity (amphetamines) induce or exacerbate schizo-

phrenia has given rise to the *'Dopamine theory of Schizophrenia'* envisaging DA overactivity in limbic area to be responsible for the condition. As an adaptive change to blockade of D2 receptors the firing of DA neurones and DA turnover increases initially. However, over a period of time this subsides and gives way to diminished activity, specially in the basal ganglia—corresponds to emergence of parkinsonian side effect. Tolerance to DA turnover enhancing effect of antipsychotics is not prominent in the limbic area—may account for the continued antipsychotic effect.

The above model fails to explain the anti-psychotic activity of clozapine which has weak D2 blocking action. However, it has significant 5-HT_2 and α blocking action, and is relatively selective for D4 receptors. Thus, antipsychotic action may depend on a specific profile of action of the drugs on several neurotransmitter receptors. Recent positron emission tomography (PET) studies of D2 and other receptor occupancy in brains of antipsychotic treated patients have strengthened this concept.

Dopaminergic blockade in the basal ganglia appears to cause the extrapyramidal symptoms, while that in CTZ is responsible for antiemetic action.

2. ANS Neuroleptics have varying degrees of α adrenergic blocking activity which may be graded as—

CPZ = triflupromazine > thioridazine > fluphenazine > haloperidol > trifluoperazine > clozapine > pimozide, i.e. more potent compounds have lesser α blocking activity.

Anticholinergic property of neuroleptics is weak and may be graded as—

thioridazine > chlorpromazine > triflupromazine > trifluoperazine = haloperidol. The phenothiazines have weak H_1-antihistaminic and anti-5-HT actions as well.

3. Local anaesthetic Chlorpromazine is as potent a local anaesthetic as procaine. However, it is not used for this purpose because of its irritant action. Others have weaker membrane stabilizing action.

4. CVS Neuroleptics produce hypotension (primarily postural) by a central as well as peripheral action on sympathetic tone. The hypotensive action is more marked after parenteral administration and roughly parallels the α adrenergic blocking potency. This is not prominent in psychotic patients and is accentuated by hypovolemia.

Partial tolerance develops after chronic use. Reflex tachycardia accompanies hypotension.

High doses of CPZ directly depress the heart and produce ECG changes. (Q-T prolongation and suppression of T wave). CPZ exerts some antiarrhythmic action, probably due to membrane stabilization. Arrhythmia may occur in overdose, specially with thioridazine.

5. Skeletal muscle Neuroleptics have no effect on muscle fibres or neuromuscular transmission. They reduce certain types of spasticity: the site of action being in the basal ganglia or medulla oblongata. Spinal reflexes are not affected.

6. Endocrine Neuroleptics consistently increase prolactin release by blocking the inhibitory action of DA on pituitary lactotropes. This may result in galactorrhoea and gynaecomastia.

They reduce gonadotropin secretion but amenorrhoea and infertility occur only occasionally. ACTH release in response to stress is diminished—corticosteroid levels fail to increase under such circumstances. Release of GH is also reduced but this is not sufficient to cause growth retardation in children or to be beneficial in acromegaly. Decreased release of ADH may result in an increase in urine volume. A direct action on kidney tubules may add to it, but Na^+ excretion is not affected.

TOLERANCE AND DEPENDENCE

Tolerance to the sedative and hypotensive actions develops within days or weeks, but maintenance doses in most psychotics remain fairly unchanged over years, despite increased DA turnover in the brain. The antipsychotic, extrapyramidal and other actions based on DA antagonism do not display tolerance.

Neuroleptics are hedonically (pleasurably) bland drugs. Physical dependence is probably absent, though some manifestations on discontinuation have been considered to be withdrawal phenomena. No drug seeking behaviour has been exhibited.

PHARMACOKINETICS

Oral absorption of CPZ is somewhat unpredictable and bioavailability is low. More consistent effects are produced after i.m. or i.v. administration. It is highly bound to plasma as well as tissue proteins—brain concentration is higher than plasma concentration. Vol-

ume of distribution, therefore, is large (20 L/kg). It is metabolized in liver into a number of metabolites.

The acute effects of a single dose generally last 6–8 hours. The elimination t½ is variable, but is in the range of 18–30 hours. The drug cumulates on chronic administration and it is possible to give the total maintenance dose once a day. Some metabolites are probably active. The intensity of antipsychotic action is poorly correlated with plasma concentration. Nevertheless, therapeutic effect may be seen at 30–200 ng/ ml. The metabolites are excreted in urine and bile for months after discontinuing the drug.

The broad features of pharmacokinetics of other neuroleptics are similar.

DISTINCTIVE FEATURES OF INDIVIDUAL NEUROLEPTICS

Antipsychotic drugs differ in potency and in their propensity to produce different effects. This is summarized in a comparative manner in Table 30.1.

1. Trifluprom azine An aliphatic side chain phenothiazine somewhat more potent than CPZ. It frequently produces acute muscle dystonias in children, specially when injected as antiemetic.

2. Thioridazine A low potency phenothiazine having marked central anticholinergic action. Incidence of extrapyramidal side effects is very low. Cardiac arrhythmias and interference with male sexual function are more common. Risk of eye damage limits long term use.

3. Trifluoperazine, fluphenazine These are high potency piperazine side chain phenothiazines. They have minimum autonomic actions; hypotension and sedation are not significant. They are less likely to cause jaundice and hypersensitivity reactions. However, extrapyramidal side effects are marked. They are less likely to precipitate seizure in epileptics.

Fluphenazine decanoate can be given as a depot i.m. injection every 2–4 weeks. ANATENSOL DECANOATE, PROLINATE 25 mg/ml inj.

4. Haloperidol It is a potent antipsychotic with pharmacological profile resembling that of piperazine substituted phenothiazines. It produces few autonomic effects, is less epileptogenic, does not cause weight gain, jaundice is rare. It is the preferred drug for acute schizophrenia, Huntington's disease and Gilles de la Tourette's syndrome.

5. Trifluperidol It is similar to but slightly more potent than haloperidol.

6. Droperidol A short acting potent neuroleptic, occasionally used in anaesthesia *(see* Ch. GENERAL ANAESTHETICS).

DROPEROL 2.5 mg/ml inj.

7. Penfluridol An exceptionally long acting neuroleptic, recommended for chronic schizophrenia, affective withdrawal and social maladjustment.

Dose: 20–60 mg (max 120 mg) once weekly; SEMAP, FLUMAP, PENFLUR 20 mg tab.

8. Flupenthixol It is less sedating than CPZ; indicated in schizophrenia and other psychoses, particularly in withdrawn and apathetic patients, but not in those with psychomotor agitation or mania. At relatively lower doses (1–3 mg/day) it is also useful in depression; generally used for short periods only.

9. Pimozide It is a specific DA antagonist with little a adrenergic or cholinergic blocking activity. Because of long duration of action (several days) after a single oral dose, it is considered good for maintenance therapy but not when psychomotor agitation is prominent. Incidence of dystonic reactions is low, but it tends to prolong myocardial APD and carries risk of arrhythmias. It has been particularly used in Gilles de la Tourett's syndrome.

10. Loxapine A dibenzoxazepine having CPZ like DA blocking and antipsychotic activity. The actions are quick and last upto 12 hrs. Sedation is less marked but neurological and cardiac toxicity is prominent in overdose. No clear cut advantage over other antipsychotics has emerged.

11. Clozapine An atypical or second generation antipsychotic: pharmacologically distinct from others in that it has only weak D2 blocking action, produces few extrapyramidal symptoms; tardive dyskinesia is rare and prolactin level does not rise. It suppresses both positive and negative symptoms of schizophrenia and many patients refractory to typical neuroleptics respond. The differing pharmacological profile may be due to its relative selectivity for D4 receptors (which are sparse in basal ganglia) and additional 5-HT_2 as well as a blockade. Moderately potent anticholinergic, but paradoxically induces hypersalivation. Significant H_1 blocking property is present.

The major limitation of clozapine is higher incidence of agranulocytosis (0.8%) and other blood dyscrasias: weekly monitoring of leucocyte count is required. High dose can induce seizures even in nonepileptics. Other side effects are sedation, unstable BP, tachycardia,

urinary incontinence and weight gain. Few cases of myocarditis have been reported which start like flu but may progress to death.

Clozapine is used only as a reserve drug in resistant schizophrenia.

12. Risperidone Another compound whose antipsychotic activity has been ascribed to a combination of D2 + 5-HT_2 receptor blockade. In addition it has high affinity for α_1, α_2 and H_1 receptors: blockade of these may contribute to efficacy as well as side effects like postural hypotension. Risperidone is more potent D2 blocker than clozapine; extrapyramidal side effects are less only at low doses (<6 mg/day). Prolactin levels rise during risperidone therapy, but it is less epileptogenic than clozapine, though frequently causes agitation.

13. Olanzapine A new atypical antipsychotic; resembles clozapine in blocking multiple monoaminergic (D2, 5-HT_2, α_1, α_2) as well as muscarinic and H_1 receptors. The antipsychotic effect has been ascribed to a combination of D2 and 5-HT_2 blockade. Both positive and negative symptoms of schizophrenia appear to be benefited. A broader spectrum of efficacy covering schizo-affective disorders has been claimed. It may be combined with lithium/valproate for mania/bipolar disorder.

Olanzapine is a potent antimuscarinic, produces dry mouth and constipation. Weaker D2 blockade results in few extrapyramidal side effects and little rise in prolactin levels, but is more epileptogenic than high potency pheno-thiazines and causes weight gain. Agranulocytosis has not been reported with olanzapine. Olanzapine is metabolized by CYP1A2 and glucuronyl transferase. The t½ is 24–30 hours.

14. Reserpine It is now only of historical importance in psychiatry. It is a low efficacy antipsychotic; acts by depleting brain DA, NA and 5-HT.

Mental depression, suicidal tendency and other adverse effects are prominent at antipsychotic doses.

ADVERSE EFFECTS

Neuroleptics are very safe drugs in single or infrequent doses: deaths from overdose are almost unknown. However, side effects are common.

I. Based on pharmacological actions (dose related)

1. CNS Drowsiness, lethargy, mental confusion: more with low potency agents; tolerance develops; increased appetite and weight gain (not with haloperidol); aggravation of seizures in epileptics; even nonepileptics may develop seizures with high doses of some antipsychotics like clozapine.

2. α adrenergic blockade Postural hypotension, palpitation, inhibition of ejaculation (specially with thioridazine) are more common with low potency phenothiazenes.

3. Anticholinergic Dry mouth, blurring of vision, constipation, urinary hesitancy in elderly males (thioridazine has the highest propensity); absent in high potency agents. Some like clozapine induce hypersalivation despite anticholinergic property, probably due to central action.

4. Endocrine Amenorrhoea, infertility, gynaecomastia, galactorrhoea—due to hyperprolactinemia and low levels of gonadotropins; occurs infrequently after prolonged use.

5. Extrapyramidal disturbances These are the major dose limiting side effects; more prominent with high potency drugs like fluphenazine, haloperidol, pimozide, etc. least with thioridazine, clozapine, olanzapine and low doses of risperidone. These are of following types.

(a) *Parkinsonism* with typical manifestations—rigidity, tremor, hypokinesia, mask like facies, shuffling gait; appears between 1–4 weeks of therapy and persists unless dose is reduced. If that is not possible, one of the anticholinergic antiparkinsonian drugs may be given concurrently. Though quite effective, routine combination of the anticholinergic from the start of therapy in all cases is not justified. Levodopa is not effective, but amantadine may help.

A rare form of extrapyramidal side effect is perioral tremors 'rabbit syndrome' that generally occurs after years of therapy. It often responds to central anticholinergic drugs.

(b) *Acute muscular dystonias* Bizarre muscle spasms, mostly involving linguofacial muscles—grimacing, torticollis, locked jaw; occurs within few hours of a single dose or at the most in the first week of therapy. It is more common in children below 10 years and in girls, particularly after parenteral administration; overall incidence is 2%. It lasts one to few hours and then resolves spontaneously. One of the central anticholinergics, promethazine or hydroxyzine injected i.m. clears the reaction within 10–15 min.

(c) *Akathisia* Restlessness, feeling of discomfort, apparent agitation manifested as a compelling desire to move about but without anxiety is seen in some patients between 1–8 weeks of therapy: upto 20% incidence. It may be mistaken for exacerbation of psychosis. Mechanism of this complication is not understood; no specific antidote is available. A central anticholinergic may reduce the intensity in some cases; propranolol

is more effective, but most cases require reduction of dose or an alternative neuroleptic. Addition of diazepam may help.

(d) *Malignant neuroleptic syndrome* It occurs rarely with high doses of potent agents; patient develops marked rigidity, immobility, tremor, fever, semiconsciousness, fluctuating BP and heart rate, myoglobin may be present in blood—lasts 5–10 days after drug withdrawal and may be fatal. The neuroleptic must be stopped promptly and symptomatic treatment given. Though antidopaminergic action of the neuroleptic may be involved in the causation of this syndrome; anticholinergics are of no help. Intravenous dantrolene may benefit. Bromocrip-tine in large doses has been found to be useful.

(e) *Tardive dyskinesia* It occurs late in therapy, sometimes even after withdrawal of the neuroleptic: manifests as purposeless involuntary facial and limb movements like constant chewing, pouting, puffing of cheeks, lip licking, choreoathetoid movements. It is more common in elderly women; probably a manifestation of progressive neuronal degeneration along with supersensitivity to DA. It is accentuated by anticholinergics and temporarily suppressed by high doses of the neuroleptic (this should not be tried except in exceptional circumstances). An incidence of 10–20% has been reported after long term treatment; uncommon with clozapine, olanzapine and risperidone. The dyskinesia may subside months or years after withdrawal of therapy or may be lifelong. There is no satisfactory solution of the problem.

6. Miscellaneous *Weight gain* often occurs with long term antipsychotic therapy; blood sugar and lipids may tend to rise. *Blue pigmentation* of exposed skin, *corneal and lenticular opacities, retinal degeneration* (more with thioridazine) occur rarely after long term use of high doses of phenothiazines.

Cardiac arrhythmia is another rare toxicity. Few cases of myocarditis have occurred with clozapine.

II. Hypersensitivity reactions These are not dose related.

1. *Cholestatic jaundice* with portal infiltration; 2-4% incidence; occurs between 2–4 weeks of starting therapy. It calls for withdrawal of the drug—resolves slowly. More common with low potency phenothiazines; rare with haloperidol.

2. *Skin rashes, urticaria, contact dermatitis, photosensitivity* (more with CPZ): occur in about 5% patients.

3. *Agranulocytosis* is rare; more common with clozapine.

INTERACTIONS

1. Neuroleptics potentiate all CNS depressants—hypnotics, anxiolytics, alcohol, opioids, arttihistaminics and analgesics. Overdose symptoms may occur.
2. They block the actions of levodopa and direct DA agonists in parkinsonism.
3. CPZ and few others abolish the antihypertensive action of guanethidine by blocking its active transport into the adrenergic terminal. Antihypertensive action of clonidine and methyldopa is also reduced, may be due to central α_2 adrenergic blockade.
4. Phenothiazines and others are poor enzyme inducers—no significant pharmacokinetic interactions. Enzyme inducers (barbiturates, anticonvulsants) can reduce blood levels of neuroleptics.

USES

1. Psychoses

Schizophrenia The neuroleptics are used primarily in functional psychoses: have indefinable but definite therapeutic effect in all forms: produce wide range of symptom relief. They control positive symptoms (hallucinations, delusions, disorganized thought, restlessness, insomnia, anxiety, fighting, aggression) better than negative symptoms (apathy, loss of insight and volition, affective flattening, poverty of speech, social withdrawal). However, they tend to restore cognitive, affective and motor disturbances and help upto 90% patients to lead a near normal life in the society. But, some patients donot respond, and vertually none responds completely. They are only symptomatic treatment, do not remove the cause of illness; long term (even life long) treatment is required. They cause little improvement in judgement, memory and orientation. Patients with recent onset of illness respond better.

Choice of drug is largely empirical, guided by the presenting symptoms (it is the target symptoms which respond rather than the illness as a whole), associated features and mood state, and on the type of side effect that is more acceptable in a particular patient. Individual patients differ in their response to different antipsychotics; there is no way to predict which patient will respond better to which drug. The following may help drug selection:

- Agitated, combative and violent—CPZ, triflupromazine, haloperidol.
- Withdrawn and apathetic—trifluoperazine, fluphenazine.
- Patient with mainly negative symptoms and resistant cases—clozapine, olanzapine.
- Patient with mood elevation, hypomania—haloperidol, fluphenazine.
- If extrapyramidal side effects must be avoided—thioridazine, clozapine, olanzapine.
- Elderly patients who are more prone to sedation, mental confusion and hypotension—one of the more potent drugs.

Overall, the high potency drugs are more commonly used and the trend is to avoid older low potency drugs.

Mania Antipsychotics are required for rapid control, may be given i.m.—takes 1–3 days; lithium or carbamazepine may be started simultaneously or after the acute phase. After 1–3 weeks when lithium has taken effect, neuroleptic may be withdrawn gradually.

Organic brain syndromes Neuroleptics are used on a short term basis—one of the potent drugs is preferred to avoid mental confusion, hypotension and precipitation of seizures.

Dose of antipsychotic drugs should be individualized by titration with the symptoms and kept at minimum. In chronic schizophrenia maximal therapeutic effect is seen after 2–4 months therapy. However, injected neuroleptics control aggressive symptoms of acute schizophrenia over hours or a few days. Combination of 2 or more neuroleptics is not advantageous.

However, a patient on maintenance therapy with a nonsedative drug may be given additional CPZ or triflupromazine by i.m. injection to control exacerbations or violent behaviour.

In a depressed psychotic a tricyclic antidepressant may be combined.

Benzodiazepines may be added for brief periods in the beginning. Low dose maintenance or intermittent regimens have been tried in relapsing cases. Depot injections, e.g. fluphenazine/ haloperidol decanoate given at 2-4 week intervals are preferable in many cases.

2. Anxiety Neuroleptics relieve anxiety but should not be used for simple anxiety because of autonomic and extrapyramidal side effects: benzodiazepines are preferable. However, those not responding or having a psychotic basis for anxiety may be treated with these drugs.

3. As antiemetic Neuroleptics are potent antiemetics—control a wide range of drug and disease induced vomiting at doses much lower than those needed in psychosis. However, they should not be given unless the cause of vomiting has been identified. They are effective in morning sickness but should not be used for this purpose. They are ineffective in motion sickness: probably because dopaminergic pathway through the CTZ is not involved in this condition.

4. Other uses

(a) *To potentiate hypnotics, analgesics and anaesthetics* Justified only in anaesthetic practice.

(b) *Intractable hiccough* may respond to parenteral CPZ.

(c) *Tetanus* CPZ is a secondary drug to achieve skeletal muscle relaxation.

(d) *Alcoholic hallucinosis, Huntington's disease and Gilles de la Tourette's syndrome* are rare indications.

ANTIANXIETY DRUGS

Anxiety It is an emotional state, unpleasant in nature, associated with uneasiness, discomfort and concern or fear about some defined or undefined future threat. Some degree of anxiety is a part of normal life. Treatment is needed when it is disproportionate to the situation and excessive. Some psychotics also exhibit pathological anxiety.

Cardiac neurosis (unfounded fear of heart disease—palpitation, functional precordial pain); g.i. neurosis (fixation on bowel movement, distention, eructation, reflux, acidity); social anxiety (fear of being observed and evaluated by others); obsessive-compulsive disorder (OCD), post-traumatic stress disorder and various forms of phobias are some specific types of anxiety disorders.

Antianxiety drugs These are an ill-defined group of drugs, mostly mild CNS depressants which are aimed to control the symptoms of anxiety, produce a restful state of mind without interfering with normal mental or physical functions. The anxiolytic-sedative drugs differ markedly from antipsychotics, and more closely resemble sedative-hypnotics. They—

1. Have no therapeutic effect to control thought disorder of schizophrenia.
2. Do not produce extrapyramidal side effects.
3. Have anticonvulsant property.

4. Produce physical dependence and carry abuse liability.
5. Do not selectively block conditioned avoidance response in animals.

CLASSIFICATION

1. *Benzodiazepines*	Diazepam
	Chlordiazepoxide
	Oxazepam
	Lorazepam,
	Alprazolam
2. *Azapirones*	Buspirone,
	Gepirone,
	Ispapirone
3. *Sedative antihistaminic*	Hydroxyzine
4. β *blocker*	Propranolol

In addition to above drugs, antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs) are effective in obsessive compulsive disorder (OCD), phobias, panic and many types of severe generalized anxiety disorders.

BENZODIAZEPINES

The pharmacology of benzodiazepines as a class is described in Ch. SEDATIVE-HYPNOTICS.

Some members have a slow and prolonged action, relieve anxiety at low doses without producing global CNS depression. They have a selective taming effect on aggressive animals and suppress induced aggression. They also suppress the performance impairing effect of punishment. In contrast to barbiturates, they are more selective for limbic system and have proven clinically better in both quality and quantity of improvement in anxiety and stress related symptoms.

At antianxiety doses, cardiovascular and respiratory depression is minor.

Because anxiety is a common complaint and is a part of most physical and mental illness, and because these drugs—

(i) have little effect on other body systems,

(ii) have lower dependence producing liability: withdrawal syndrome is milder and delayed due to their long half lives,

(iii) are relatively safe even in gross overdosage, they are presently one of the most widely used class of drugs. Potent BZDs like loraze-

pam and alprazolam injected i.m. have adjuvant role in the management of acutely psychotic and manic patients.

They act primarily by facilitating inhibitory GABAergic transmission, but other additional mechanisms of action have been suggested. Higher doses induce sleep and impair performance.

Adverse effects of BZDs noted in their use as hypnotics are described in Ch. SEDATIVE-HYPNOTICS. Side effects that occur in their use to relieve anxiety are-sedation, lightheadedness, psychomotor and cognitive impairment, vertigo, confusional state (especially in elderly), increased appetite and weight gain, alterations in sexual function. Rashes are uncommon. Some women fail to ovulate while on regular use of BZDs. The major constraint in their long term use for anxiety disorders is their potential to produce dependence.

Differences between individual BZDs recommended for anxiety are primarily pharmacokinetic: choice of one over the other is largely empirical.

1. Chlordiazepoxide It was the first BZD to be used clinically. Oral absorption is slow: produces a smooth long lasting effect; preferred in chronic anxiety states; often combined with other drugs in psychosomatic diseases. Its t½ is 5–15 hours but active metabolites are produced which extend the duration of action. It has poor anticonvulsant action.

Daily dose: 20–100 mg; LIBRIUM 10, 25 mg tabs; EQUILIBRIUM 10 mg tab.

2.Diazepam It is quickly absorbed; produces a brief initial phase of strong action followed by prolonged milder effect due to a two phase plasma concentration decay curve (distributive phase t½ 1 hr, elimination phase t½ 20–30 hours). The biological effect t½ is still longer due to production of active metabolites. It is preferred in acute panic states and anxiety associated with organic disease.

Daily dose: 5–30 mg; VALIUM, PLACIDOX 2,5,10 mg tabs; CALMPOSE 5, 10 mg tab, 2 mg/5 ml Syr.

3. Oxazepam It is slowly absorbed; being relatively polar, its penetration in brain is also slow. The plasma t½ is about 10 hours; no active metabolite is produced—duration of action is relatively shorter. It may be preferred in the elderly and in those with liver disease, because its hepatic metabolism is not significant and duration of action is short. It has been used mainly in short lasting anxiety states.

Daily dose: 30-60 mg in 2-3 divided portions; SEREPAX 15, 30 mg tab.

4. Lorazepam Has slow oral absorption; being less lipid soluble than diazepam, its rate of entry in brain is slower. It has a relatively shorter t½ (10–20 hours); no active metabolite is produced. However, it is quite sedative and capable of producing marked amnesia when given i.v. Injection site complications are few—is the only BZD recommended for i.m. use. It has been preferred for shortlived anxiety states, obsessive-compulsive neurosis and tension syndromes, as well as psychosomatic diseases.

Daily dose: 1–6 mg; LARPOSE, ATIVAN 1, 2 mg tab. CALMESE 1,2 mg tabs, 4 mg/2 ml inj.

5.Alprazolam A high potency anxiolytic BZD which in addition has some mood elevating action in mild depression: is particularly useful in anxiety associated with depression. Good response has been obtained in panic disorders with severe anxiety and autonomic symptoms. Its plasma t½is about 12 hours, but an active metabolite is produced. Alprazolam is claimed to cause less drowsiness, but some patients experience anxiety in between doses.

Dose: 0.25–1.0 mg TDS; upto 6 mg/day in panic disorder; ALPRAX, 0.25, 0.5, 1.0 mg tabs., 0.5, 1.0, 1.5 mg SR tabs; ALZOLAM 0.25, 0.5, 1.0 mg tabs; 1.5 mg SR tab, ALPROCONTIN 0.5, 1.0, 1.5 mg CR tabs.

OTHER ANTIANXIETY DRUGS

Buspirone It is the first azapirone, a new class of antianxiety drugs, distinctly different from BZDs.

- Does not produce significant sedation or cognitive/functional impairment.
- Does not interact with BZD receptor or modify GABAergic transmission.
- Does not produce tolerance or physical dependence.
- Does not suppress BZD or barbiturate withdrawal syndrome.
- Has no muscle relaxant or anticonvulsant activity.

Buspirone relieves mild to moderate generalized anxiety, but is ineffective in severe cases, in those showing panic reaction and in OCD. The therapeutic effect develops slowly: maximum benefit may be delayed upto 2 weeks. The mechanism of anxiolytic action is not clearly

known, but may be dependent on its selective partial agonistic action on 5-HT_{1A} receptors. By stimulating presynaptic 5-HT_{1A} autoreceptors it reduces activity of dorsal raphe serotonergic neurones. Antagonism at certain postsynaptic 5-HT_{1A} receptors has also been demonstrated. After chronic treatment adaptive reduction in cortical 5-HT_2 receptors may occur. Buspirone has weak dopamine D2 blocking action but no antipsychotic or extrapyramidal effects. A mild mood elevating action has been noted occasionally—may be due to facilitation of central nor-adrenergic system.

Buspirone is rapidly absorbed; undergoes extensive first pass metabolism; (bioavailability <5%), one metabolite is active and excretion occurs both in urine and faeces; t½ is 2–3.5 hrs. Side effects are minor: dizziness, nausea, headache, light headedness, rarely excitement. It may cause rise in BP in patients on MAO inhibitors, but does not potentiate CNS depressants. Though most patients on buspirone remain alert, those operating machinery/motor vehicles should be cautioned.

Dose: 5–15 mg OD-TDS: ANXIPAR, BUSPIN, BUSCALM 5, 10 mg tab.

Hydroxyzine A H_1 antihistaminic with sedative, anti-emetic, antimuscarinic and spasmolytic properties. It is claimed to have selective anxiolytic action, but accompanying sedation is quite marked; may be used in reactive anxiety or that associated with marked autonomic symptoms. Due to antihistaminic and sedative property, it is effective in pruritus and urticaria. Daily dose 100–200 mg; ATARAX 10, 25 mg tab, 10 mg/5 ml syr, 25 mg/2 ml inj.

β Blockers

Many symptoms of anxiety (palpitation, rise in BP, shaking, tremor, gastrointestinal hurrying etc.) are due to sympathetic overactivity and these symptoms reinforce anxiety. Propranolol and other nonselective β blockers help anxious patients troubled by these symptoms, by cutting the vicious cycle and provide symptomatic relief. They do not affect psychological symptoms such as worry, tension and fear, but are valuable in acutely stressful situations (examination fear, unaccustomed public appearance etc.). They be used for performance/situational anxiety or as adjuvant to BZDs.

TREATMENT OF ANXIETY

Anxiety is a universal phenomenon and to experience it in appropriate circumstances is the normal response. However, if anxiety

symptoms are frequent and persist in a severe form, they are a cause of distress and markedly impair performance. It should be treated with drugs only when excessive and disabling in its own right.

The established drugs are BZDs which should be used in the smallest possible dose. The dose has to be found out for each patient by titration with symptoms of anxiety. Acute anxiety states generally respond better. The drug should be withdrawn as soon as it is no longer required. But when large doses have been used for longer periods—withdrawal should be gradual. Long term use of BZDs is of questionable value.

The usual practice is to give ½ to ⅔ of the daily dose at bed time to ensure good nightly rest; the remaining is divided in 2-3 doses given at day time. Though the t½ of BZDs used in anxiety are longer, divided day time doses are required to avoid high peaks.

Buspirone is a nonsedating alternative to BZDs for less severe forms of generalized anxiety. The tricyclic and SSRI antidepressants are now being increasingly used in many forms of severe anxiety disorders. They produce a delayed but often gratifying response and can be combined with BZDs. The SSRIs are now drugs of choice for social anxiety in which BZDs though effective, carry abuse potential on long term use.

Patients with hypertension, peptic ulcer, ulcerative colitis, irritable bowel, gastroeso-phageal reflux, thyrotoxicosis, angina pectoris are often given low doses of BZD in addition to specific therapy, though anxiety may not be a prominent manifestation.

Fixed dose combination of tranquillizers with vitamins has been banned.

HALLUCINOGENS (Psychotomimetics, Psychedelics, Psychodysleptics, Psychotogens)

These are drugs which alter mood, behaviour, thought and perception in a manner similar to that seen in psychosis. Many natural products having hallucinogenic property have been discovered and used by man since prehistoric times. A number of synthetic compounds have also been produced. The important ones are briefly described below.

INDOLE AMINES

1. Lysergic acid diethylamide (LSD) Synthesized by Hofmann (1938) who was working on chemistry of ergot alkaloids, and himself experienced its hallucinogenic effect. It is the most potent psychedelic, 25–50 μg produces all the effects. In addition to the mental ef-

fects, it produces pronounced central sympathetic stimulation. Its action appears to involve serotonergic neuronal systems in brain.

2. Lysergic acid amide A close relative of LSD but 10 times less potent; found in morning glory *(Ipomoea violace)* seeds.

3. Psilocybin Found in a Mexican mushroom *Psilocybe mexicana;* it has been used by Red Indian tribals during religious rituals.

4. Harmine It is present in a vine *Banisteriopsis caapi,* found in the Amazon region. The Brazilian natives have used it as a snuff.

5. Bufotenin Isolated from skin of a toad *(Bufo marinus).* It is also found in 'Cohaba Snuff and in the mushroom *Amanita muscaria.*

The above are all *Indolealkylamines* related chemically to 5-HT. A number of other synthetic derivatives like Dimethyltryptamine (DMT) are also hallucinogenic.

PHENYLALKYL AMINES

Mescaline From Mexican 'Peyote cactus' *Lophophora williamsi.* It is a low potency hallucinogen used by natives during rituals. It is a phenylalkylamine but does not have marked sympathomimetic effects. Other synthetic phenylalkylamines with hallucinogenic property are—Dimethoxymethyl amphetamine (DOM) and Dimethoxyamphetamine (DMA). High doses and repeated use of amphetamine can also cause psychosis.

ARYLCYCLOHEXYL AMINES

Phencyclidine It is an anticholinergic, which activates σ receptors in brain causing disorientation, distortion of body image, hallucinations and an anaesthetic like state: ketamine is a closely related compound with lower hallucinogenic potential and is used in anaesthesia.

CANNABINOIDS

$^{9}\Delta$ Tetrahydrocannabinol ($^{9}\Delta$ THC) It is the active principle of *Cannabis indica* (Marijuana). It has been the most popular recreational and ritualistic intoxicant used for millennia. Its use has spread world wide. The following are the various forms in which it is used.

Bhang the dried leaves—is generally taken by oral route, acts slowly.

Ganja the dried female inflorescence—is more potent and is smoked: effects are produced almost instantaneously.

Charas is the dried resinous extract from the flowering tops and leaves—most potent, smoked with tobacco; also called 'hashish'. Cannabis is the drug of abuse having lowest acute toxicity.

Considerable insight has been obtained recently in cannabinoid pharmacology. Since 1990 two *cannabinoid receptors CB1* (in CNS) and *CB2* (in peripheral tissues) have been identified and cloned. A host of endogenous ligands for the cannabinoid receptors have also been isolated. *Anandamide* the ethanolamide of arachidonic acid is the principal endocannabinoid synthesized in the brain. Endocannabinoids are released by macrophages during haemorrhagic shock and cause fall in BP. However, all actions of cannabis are nor mimicked by anandamide.

Cannabis produces potent analgesic, antiemetic, anti-inflammatory and many other pharmacological actions. The crude herb, its active constituents and some synthetic analogues have been tried in a variety of conditions and many potential clinical applications are proposed.

- To ameliorate muscle spasm and pain in multiple sclerosis, and certain dystonias.
- Cancer chemotherapy induced vomiting: the synthetic cannabinoids nabilone and dronabinol are licenced for this use.
- As a neuronal protective after head injury and cerebral ischaemia.
- To relieve anxiety; migraine.
- To reduce i.o.t. in glaucoma.
- As appetite stimulant.
- As bronchodilator in asthma.

However, the hallucinogenic and psychomotor effects are a limitation; nonhallucinogenic congeners are being investigated.

The hallucinogens, in general, produce a dream like state with disorientation, loss of contact with reality, field of vision may appear to sway and objects distorted like images in a curved mirror, faces may appear grotesque. On closing the eyes an unending series of colourful, very realistic and fantastic images appear to surge; time sense is altered, music appears tangible. Ability to concentrate is impaired, one can read but does not know what he is reading; however, ataxia is not prominent. Many feel relaxed and supremely happy, may laugh uncontrollably or may become sad and weep. With higher doses—panic reactions and sinking sensation are common.

Some degree of tolerance occurs, but *reverse tolerance* is not unusual.

Psychological dependence may be mild (occasional trips) to marked (compulsive abuse), but physical dependence does not occur. All are drugs of abuse.

Hallucinogens have been rarely used in psychiatry to facilitate conversation and for opening up the inner self in case of withdrawn patients.

DIURETICS

These are drugs which cause a net loss of Na^+ and water in urine.

Calomel (mercurous chloride) had been used as a diuretic from the time of Paracelsus and it was one of the constituents of the famous 'Guy's Hospital Pill'. Organomercurials given by injection were introduced in the 1920s and dominated for nearly 40 years. The CAse inhibitors were developed in the 1950s from the observation that early sulfonamides caused acidosis and mild diuresis. The first modern orally active diuretic *chlorothiazide* was discovered in 1957, and by early 1960s its congeners (thiazide diuretics) were already in common use. Availability of *furosemide* and *ethacrynic acid* by mid 1960s revolutionized the pattern of diuretic use. The K^+ sparing diuretics *spironolactone* and *triamterene* were developed in parallel to these.

Diuretics are among the most widely prescribed drugs. Application of diuretics to the management of hypertension has outstripped their use in edema. Availability of diuretics has also had a major impact on the understanding of renal physiology.

CLASSIFICATION

1. *High efficacy diuretics (Inhibitors of Na^+-K^+-2Cl^- cotransport)*

(a) *Sulphamoyl derivatives:* Furosemide, Bumetanide,

(b) *Phenoxyacetic acid derivative:* Ethacrynic acid.

(c) *Organomercurials:* Mersalyl.

2. *Medium efficacy diuretics (Inhibitors of Na^+-Cl^- symport)*

(a) *Benzothiadiazines (thiazides):* Chlorothiazide, Hydrochlorothiazide, Benzthiazide, Hydroflumethiazide, Clopamide

(b) *Thiazide like (related heterocyclics):* Chlorthalidone, Metolazone, Xipamide, Indapamide.

3. *Weak or adjunctive diuretics*

(a) *Carbonic anhydrase inhibitors:* Acetazolamide

(b) *Potassium sparing diuretics*

(i) *Aldostewne antagonist:* Spironolactone

(ii) *Directly acting (Inhibitors of renal epithelial Na^+ channel):* Triamterene, Amiloride.

(c) *Osmotic diuretics:* Mannitol, Isosorbide, Glycerol

(d) *Xanthines:* Theophylline

HIGH CEILING (LOOP) DIURETICS(Inhibitors of Na^+-K^+-2Cl^- Cotransport)

Furosemide (Frusemide) Prototype drug The development of this orally and rapidly acting highly efficacious diuretic was a breakthrough. Its maximal natriuretic effect is much greater than that of other classes. The diuretic response goes on increasing with increasing dose: upto 10 L of urine may be produced in a day. It is active even in patients with relatively severe renal failure. The onset of action is prompt (i.v. 2–5 min., i.m. 10–20 min., oral 20–40 min.) and duration short (3–6 hours).

The major site of action is the thick AscLH (site II) where furosemide inhibits Na^+-K^+-2C1$^-$cotransport. A minor component of action on PT has also been indicated. It is secreted in PT by organic anion transport and reaches Asc LH where it acts from luminal side of the membrane. It abolishes the cortico-medullary osmotic gradient and blocks positive as well as negative free water clearance. K^+ excretion is increased mainly due to high Na^+ load reaching DT. However, at equinatriuretic doses, K^+ loss is less than that with thiazides.

Furosemide has weak CAse inhibitory action and increase HCO_3^- excretion as well; urinary pH may rise but the predominant urinary anion is Cl^-; acidosis does not develop. Its action is independent of acid-base balance of the body and it causes little distortion of the same; mild alkalosis occurs at high doses.

In addition to its prominent tubular action, furosemide causes acute changes in renal and systemic haemodynamics. After 5 min of i.v. injection, renal blood flow is transiently increased and there is redistribution of blood flow from outer to midcortical zone; g.f.r. generally remains unaltered due to compensatory mechanisms despite increased renal blood flow. Pressure relationship between vascular, interstitial and tubular compartments is altered, the net result of which is decreased PT reabsorption. The intrarenal haemodynamic changes are brought about by increased local PG synthesis.

Intravenous furosemide causes prompt increase in systemic venous capacitance and decreases left ventricular filling pressure, even before the saluretic response is apparent. This is responsible for the quick relief it affords in LVF and pulmonary edema. This action may be PG mediated.

Furosemide increases Ca^{2+} excretion (contrast thiazides which reduce it) as well as Mg^{2+} excretion. It tends to raise blood uric acid level by decreasing its renal excretion. This is due both to interference with tubular secretion of uric acid and increased reabsorption in PT

which is a consequence of reduced e.c.f. volume. The magnitude of hyperuricaemia is lower than that with thiazides. Hyperglycaemic action of furosemide is also less marked than thiazides.

Molecular mechanism of action: A glycoprotein with 12 membrane spanning domains has been found to function as the Na^+-K^+-$2Cl^-$ cotransporter in many epithelia performing secretory/ absorbing function, including AscLH. Recently, *distinct absorptive* or *secretory* isoforms of Na^+-K^+-$2Cl^-$ cotransporter have been isolated. The former is exclusively expressed at the luminal membrane of thick AscLH—furosemide attaches to the Cl^- binding site of this protein to inhibit its transport function. The secretory form is expressed on the basolateral membrane of most glandular and epithelial cells.

Pharmacokinetics Furosemide is rapidly absorbed orally but bioavailability is about 60%. In severe CHF oral bioavailability may be markedly reduced. Lipid solubility is low, and it is highly bound to plasma proteins. It is partly conjugated with glucuronic acid and mainly excreted unchanged by glomerular filtration as well as tubular secretion. Some excretion in bile and directly in intestine also occurs. Plasma t½ averages 1–2 hour but is prolonged in patients with pulmonary edema, renal and hepatic insufficiency.

Dose Usually 20–80 mg once daily in the morning. In renal insufficiency, upto 200 mg 6 hourly has been given by i.m. /i.v. route. In pulmonary edema 40–80 mg may be given i.v.

LASIX, 40 mg tab., 20 mg/2 ml inj. LASIX HIGH DOSE 500 mg tab, 250 mg/25 ml inj; (solution degrades spontaneously on exposure to light), SALINEX 40 mg tab, FRUSENEX 40, 100 mg tab.

Bumetanide It is similar to furosemide in all respects, but is 40 times more potent; oral dose ranges from 1–5 mg; i.v./i.m. 2–4 mg (max. 15 mg in renal failure). It induces very rapid diuresis and is highly effective in pulmonary edema. However, the site of action, ceiling effect, renal haemodynamic changes and duration of action are similar to furosemide. A secondary action in PT has also been demonstrated. It may act in some cases not responding to furosemide. Hyperuricaemia, K^+ loss, glucose intolerance and ototoxicity are claimed to be less than with furosemide. However, it may rarely cause myopathy.

Bumetanide is more lipid soluble, 80-100% bioavailable orally, extensively bound to plasma proteins, partly metabolized and partly

excreted unchanged in urine. Its accumulation in tubular fluid is less dependent on active secretion. Plasma t½ ~60 min, gets prolonged in renal and hepatic insufficiency.

BUMET, 1 mg tab., 0.25 mg/ml inj.

Ethacrynic Acid

It was synthesized as a -SH reactive agent; has actions similar to mercurials; acts by inhibiting Na^+-K^+-$2Cl^-$cotransport in AscLH. It is chemically different from furosemide but ceiling effect is similar. It does not inhibit CAse, there is no increase in HCO_3^- excretion, the predominant urinary anion is Cl^-. Loss of K^+ is less marked but chances of hypochloremic alkalosis are greater.

The dose response curve of ethacrynic acid is steeper than that of furosemide and, in general, it is less manageable; dose range is 50-150 mg. It is an irritant, oral administration frequently produces diarrhoea; g.i. bleeding may occur at higher dose. Chances of hearing loss are greater with ethacrynic acid and hepatotoxicity is reported. Because of these reasons it has practically gone out of use.

Mercurial Diuretics

The organomercurial diuretics were in vogue from 1920—1960. They are strong diuretics, primarily inhibit Na^+-K^+-2C1$^-$ cotransport in Asc LH and produce acidic urine. Their action probably involves interaction with sulfhydryl enzymes in the kidney tubule. They had to be given by injection; were toxic and accentuated kidney damage. They could be used only intermittently since regular administration caused alkalosis and refractoriness. They have been replaced now by better drugs.

Use of high ceiling diuretics

Edema Diuretics are used irrespective of etiology of edema—cardiac, hepatic or renal. The high ceiling diuretics are preferred initially in CHF for rapid mobilization of edema fluid *(see* Ch. Cardiac Glycosides and Drugs for C.H.F.). Thiazides are considered more appropriate for maintenance, but when they prove ineffective, high ceiling drugs are called in. They are the diuretic of choice for nephrotic and other forms of resistant edema. In chronic nephrotic failure massive doses have to be used, but they continue to be effective while thiazides just do not produce any action.

1. *Acute pulmonary edema (acute LVF, following Ml):* Intravenous administration of furosemide or its congeners produces prompt relief.

This is due to vasodilator action that precedes the saluretic action. Subsequently, decrease in blood volume and venous return is responsible for the improvement.

2. *Cerebral edema* Though osmotic diuretics are preferred, furosemide may be employed by i.m. route.

3. *Forced diuresis* In hypnotic or other poisonings; again they may be used in place of mannitol because they can be more conveniently administered.

4. *Hypertension* High ceiling diuretics are indicated only in presence of renal insufficiency, CHF, in resistant cases or hypertensive emergencies; otherwise thiazides are preferred.

5. Along with blood transfusion in severe anaemia, to prevent vascular overload.

6. Hypercalcaemia and renal calcium stones: because they increase calcium excretion and urine flow; excess salt that is lost must be replaced.

THIAZIDE AND RELATED DIURETICS (Inhibitors of Na^+-Cl^- symport).

Chlorothiazide was synthesized as a CAse inhibitor variant which produced urine that was rich in Cl^-, and diuresis occurred in alkalosis as well as acidosis. A large number of congeners were developed subsequently and the thiadiazine ring was replaced by other heterocyclic rings, but the type of activity remained the same. The important features of agents marketed in India are presented in Table 19.1.

The primary site of action of these diuretics is cortical diluting segment or the early DT (Site III). Here they inhibit Na^+-Cl^- symport at the luminal membrane. They do not affect the corticomedullary osmotic gradient indicating lack of action at the medullary thick AscLH. They decrease positive free water clearance (very dilute urine cannot be passed in the absence of ADH), but do not affect negative free water clearance (in the presence of ADH). This strengthens the view that the site of action is in between thick AscLH and late DT. These drugs gain access to their site of action *via* organic acid secretory pathway in PT and then along the tubular fluid to early DT, where they bind to specific receptors located on the luminal membrane. Like the Na^+-K^+-$2Cl^-$cotransporter, the Na^+-Cl^- symporter is a glycoprotein with 12 membrane spanning domains, but it does not bind furosemide or any other class of diuretics. It has been cloned and shown to be specifically expressed on the luminal membrane in the DT.

Some of the thiazides and related drugs have additional CAse inhibitory action in PT; intensity of this action differs among different compounds (Table 19.1) but it is generally weak and clinically insignificant. However, it may confer some proximal tubular action to the compounds.

Under their action, increased amount of Na^+ is presented to the distal nephron, more of it exchanges with K^+ → urinary K^+ excretion is increased in parallel to the natriuretic response. The maximal diuresis induced by different agents falls in a narrow range; chlorothiazide is least potent and least efficacious (has gone out of use); others have nearly the same maximal efficacy as hydrochlorothiazide, though potency (reflected in daily dose) differs markedly. Nevertheless, they are moderately efficacious diuretics because nearly 90% of the glomerular filtrate has already been reabsorbed before it reaches their site of action. They have a flat dose response curve; little additional diuresis occurs when the dose is increased beyond 100 mg of hydrochlorothiazide or equivalent. They donot cause significant alteration in acid-base balance of the body.

By their action to reduce blood volume, as also intrarenal haemodynamic changes, they tend to reduce g.f.r. This is one reason why they are not effective in patients with low g.f.r. They decrease renal Ca^{2+} excretion and increase Mg^{2+} excretion by a direct distal tubular action. They also decrease urate excretion by the same mechanism as furosemide.

The *extrarenal actions* of thiazides consist of a slowly developing fall in BP in hypertensives and elevation of blood sugar in some patients due to decreased insulin release.

Pharmacokinetics All thiazides and related drugs are well absorbed orally, they are administered only by this route. Their action starts within 1 hour, but the duration is variable (Table 19.1). The more lipid soluble agents have larger volumes of distribution (some are also tissue bound), lower rates of renal clearance and are longer acting. The protein binding is also variable. Most of the agents undergo little hepatic metabolism and are excreted as such. They are filtered at the glomerulus as well as secreted in the PT by organic anion transport. Tubular reabsorption depends on lipid solubility: the more soluble ones are highly reabsorbed—prolonging duration of action.

Chlorthalidone It is a particularly long acting agent with a t½ > 40–50 hours, used mainly as antihypertensive.

Metolazone In common with loop diuretics, it is able to evoke a clinically useful response even in severe renal failure (g.f.r. ~15

ml/min), and has additive action when combined with furosemide. An additional proximal tubular action has been demonstrated—inhibits PO_4 reabsorption. It is excreted unchanged in urine.

Table 19.1

Thiazides and related diuretics

Drug	*Trade Name (Tab. Strength) (mg)*	*Daily Dose (mg)*	*Case Inhibition*	*Duration of action (Hr)*
Chlorothiazide	—	500–2000	++	6-12
Hydrochlorothiazide	ESIDREX (50), HYDRIDE (12.5, 25)	25–100	+	8-12
Benzthiazide	FOVANE (25)	25–100	++	12-18
Hydroflumethiazide	NACLEX (25)	25–100	±	12
Chlorthalidone	HYTHALTON (100)	50–100	++	48
Metolazone	XAROXOLYN (5, 10)	5–20	+	18
Xipamide	XIPAMID (20)	20–40	+	24
Indapamide	LORVAS (2.5)	2,5–5	-	24-36
Clopamide	BRINALDIX (20)	10–60	±	12-18

Some other compounds, similar in action but are not available in India. Chlorexolone, Quinethazone, Mefruside—are nonthiazides.

Xipamide It has a pronounced diuretic action similar to low doses of furosemide. Because of longer duration of action—hypokalemia is more prominent.

Indapamide It has little diuretic action in the usual doses, probably because it is highly lipid soluble, is extensively metabolized and only small quantity of unchanged drug is present in the tubular fluid. However, it retains antihypertensive action and is used for that purpose only.

Uses

1. *Edema* Thiazides are the preferred drugs for mild to moderate cases. For mobilization of edema fluid more efficacious diuretics are employed initially, but thiazides are considered better for maintenance therapy. They act best in cardiac edema, less effective in hepatic or renal edema. They are powerless in the presence of renal failure. Cirrhotics often develop refractoriness to thiazides due to development of secondary hyperaldosteronism.

2. *Hypertension* They are one of the first line drugs (Ch. ANTIHYPERTENSIVE DRUGS).

3. *Diabetes insipidus* They reduce urine volume (*see* Ch. ANTIDIURETICS).

4.*Hypercalciuria* with recurrent calcium stones in the kidney. They act by reducing Ca^{2+} excretion.

Complications of high ceiling and thiazide type diuretic therapy

Most of the adverse effects of these drugs are related to fluid and electrolyte changes caused by them. They are remarkably safe in low doses used over short periods. Many subtle metabolic effects *have been* reported in their long term use as antihypertensives at the relatively higher doses used in the past.

1. *Hypokalemia* This is the most significant problem. It is rare at low doses, but may be of grave consequence when brisk diuresis is induced or on prolonged therapy, specially if dietary K^+ intake is low. Degree of hypokalemia appears to be related to the length of action of the diuretic. The usual manifestations are weakness, fatigue, muscle cramps; cardiac arrhythmias are serious complications. Hypokalemia is less common with standard doses of high ceiling diuretics than with thiazides, possibly because of shorter duration of action of the former which permits intermittent operation of compensatory repletion mechanisms. It can be prevented and treated by:

(a) High dietary K^+ intake or

(b) Supplements of KC1 (24–72 mEq/day) or

(c) Concurrent use of K^+ sparing diuretics. Measures (b) and (c) are not routinely indicated but only when hypokalemia has been documented or in special risk situations, e.g. cirrhotics, cardiac patients—specially post MI, those receiving digitalis or tricyclic antidepressants and elderly patients. Serum K^+ levels are only rough guide to K^+ depletion because K^+ is primarily an intracellular ion. Nevertheless, an attempt to maintain serum K^+ at or above 3.5 mEq/L should be made. Combined tablets of diuretics and KC1 are not recommended because:

(a) they generally contain insufficient quantity of K^+ (8–12 mEq only)

(b) may cause gut ulceration by releasing KC1 at one spot

(c) K^+ is retained better if given after the diuresis is over

K^+ sparing diuretics are more efficacious and more convenient in correcting hypokalemia than are K^+ supplements. Captropril given with thiazides has been found to prevent development of hypokalemia.

Alkalosis may occur with hypokalemia, because more H^+ exchanges with Na^+ in DT when less K^+ is available for exchange.

2. *Acute saline depletion* Over enthusiastic use of diuretics, particularly high ceiling ones, may cause dehydration and fall in BP (specially in erect posture). Serum Na^+ and Cl^- levels remain normal because isotonic saline is lost. It should be treated by saline infusion.

3. *Dilutional hyponatremia* Occurs in CHF patients in whom vigorous diuresis is induced with high ceiling agents, rarely with thiazides. Kidney tends to retain water though it is unable to retain salt due to the diuretic; e.c.f. gets diluted, hyponatremia occurs and edema persists despite natriuresis. Patients may feel very thirsty. Treatment of this distortion of fluidelectrolyte balance is difficult: withhold diuretics, restrict water intake and give glucocorticoids which enhance excretion of water load. If hypokalemia is present, its correction helps.

4. *GIT and CNS disturbances* Nausea, vomiting and diarrhoea may occur with any drug, but are commonest with ethacrynic acid. Headache, giddiness, weakness, paresthesias, impotence are occasional complaints with thiazides as well as loop diuretics.

5. *Hearing Loss* Occurs rarely, only with high ceiling diuretics, specially ethacrynic acid, or when these drugs are used in the presence of renal insufficiency. Increased salt content of endolymph and a direct toxic action on the hair cells in internal ear appear to be causative.

6. *Allergic manifestations* Rashes, photosensitivity occur specially in patients hypersensitive to sulfonamides. Blood dyscrasias are rare; any diuretic may be causative.

7. Thiazides have sometimes *aggravated renal insufficiency,* probably by reducing g.f.r.

8. Brisk diuresis induced in cirrhotics may precipitate *mental disturbances* and hepatic coma. It may be due to hypokalemia, alkalosis and increased blood NH_3 levels.

9. Diuretics should not be used in *toxaemia of pregnancy* in which blood volume is low despite edema. Diuretics may further reduce it and compromise placental circulation → miscarriage, foetal death. Thus, diuretics are contraindicated in pregnancy induced hypertension.

10. *Hyperuricaemia* Long term use of thiazides in hypertension has caused rise in blood urate level in upto 30% of recipients. Most of them remain asymptomatic but 2% develop clinical gout. Furosemide produces a lower incidence of hyperuricaemia. This effect can be counteracted by allopurinol. Probenecid is better avoided because it may interfere with the diuretic response, particularly of loop diuretics.

11. *Hyperglycaemia and hyperlipidemia* Have occurred in the use of diuretics as antihypertensive. These metabolic changes are minimal at low doses now recommended.

12. *Hypercalcaemia* Occurs with thiazides while *hypocalcaemia* occurs with high ceiling diuretics when these are administered chronically.

13. *Magnesium depletion* It may develop after prolonged use of thiazides as well as loop diuretics. This may increase the risk of ventricular arrhythmias, specially after MI or when patients are digitalized. K^+ sparing diuretics given concurrently minimise Mg^{2+} loss.

Interactions

1. Thiazides and high ceiling diuretics potentiate all other antihypertensives. This interaction is intentionally employed in therapeutics.

2. Hypokalemia induced by these diuretics: Enhances digitalis toxicity. Increases the incidence of polymorphic ventricular tachycardia due to quinidine and other antiarrhythmics. Potentiates competitive neuromuscular blockers and reduces sulfonylurea action.

3. High ceiling diuretics and aminoglycoside antibiotics are both ototoxic; produce additive toxicity; should not be used together.

4. High ceiling diuretics enhance nephrotoxicity of aminoglycosides, first generation cephalosporins and amphotericin B.

5. Cotrimoxazole given with diuretics has caused higher incidence of thrombocytopenia.

6. Indomethacin and most NSAIDs diminish the action of high ceiling diuretics. Inhibition of PG synthesis in the kidney, through which furosemide and related drugs induce intrarenal haemodynamic changes which secondarily affect salt output, appears to be the mechanism. Antihypertensive action of thiazides and furosemide is also diminished by NSAIDs.

7. Probenecid competitively inhibits tubular secretion of furosemide and thiazides: decreases their action by reducing the concentration in the tubular fluid through which they reach the site of action, while diuretics diminish uricosuric action of probenecid.

8. Serum lithium level rises when diuretic therapy is instituted. This is due to enhanced reabsorption of Li^+ in PT.

Resistance to high ceiling diuretics Refractoriness (progressive edema despite escalating oral/i.v. diuretic therapy) is more common with thiazides, but occurs under certain circumstances to high ceiling diuretics as well. The causes and mechanism of such resistance include:

Cause	*Mechanism*
1. Renal insufficiency (including advanced age)	Decreased access of diuretic to its site of action due to low g.f.r. and proximal tubular secretion.
2. Nephrotic syndrome	Binding of diuretic to urinary protein, other pharmacodynamic causes.
3. Cirrhosis of liver	Abnormal pharmacodynamics; hyperaldosteronism; mechanism not clear.
4. CHF	Delayed absorption due to intestinal congestion, increased salt reabsorption in PT.

Long term use of loop diuretics causes distal nephron hypertrophy → resistance. Addition of metolazone or a thiazide which act on distal tubule overcome the refractoriness in many cases. Further increase in dose and/or fractionation of daily dose may restart diuresis. Bed rest may also help.

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase (CAse) is an enzyme which catalyses the reversible reaction $H_2O + CO_2 \rightleftarrows H_2CO_3$. Carbonic acid spontaneously ionizes $H_2CO_3 \rightleftarrows H^+ + HCO_3^-$ (Fig. IX.2). It thus functions in CO_2 and HCO_3^- transport and in H^+ ion secretion. The enzyme is present in renal tubular cell (specially PT) gastric mucosa, exocrine pancreas, ciliary body of eye, brain and RBC. In these tissues a gross excess of CAse is present, more than 99% inhibition is required to produce effects.

Acetazolamide

It is a sulfonamide derivative which noncompetitively but reversibly inhibits CAse in PT cells resulting in slowing of hydration of CO_2 → decreased availability of H^+ to exchange with luminal Na^+ through the Na^+-H^+ antiporter. Inhibition of brush border CAse retards dehydration of H_2CO_3 in the tubular fluid so that less CO_2 diffuses back into the cells. The net effect is inhibition of HCO_3^- (and accompanying Na^+) reabsorption in PT → prompt but mild alkaline diuresis ensues.

Secretion of H^+ in DT and CD is also inhibited. Though H^+ is secreted at this site by a H^+-ATPase, it is generated in the cell by CAse mediated reaction. Thus, this is a subsidiary site of action of CAse inhibitors. The distal Na^+ exchange takes place only with K^+ which is

lost in excess. For the same degree of natriuresis CAse inhibitors cause the most marked kaliuresis compared to other diuretics. The urine produced under acetazolamide action is alkaline and rich in HCO_3^- which is matched by both Na^+ and K^+. Continued action of acetazolamide depletes body HCO_3^- and causes acidosis; less HCO_3^- (on which its diuretic action depends) is filtered at glornerulus → self limiting diuretic action.

The extrarenal actions of acetazolamide are:

(i) Lowering of intraocular tension due to decreased formation of aqueous humour (it is rich in HCO_3^-).

(ii) Decreased gastric HC1 and pancreatic $NaHCO_3$ secretion: This action requires very high doses—clinically not significant.

(iii) Raised level of CO_2 in brain and lowering of pH → raising of seizure threshold, sedation.

(iv) Alteration of CO_2 transport in lungs and tissues: these actions are masked by compensatory mechanisms.

Pharmacokinetics Acetazolamide is well absorbed orally and excreted unchanged in urine. Action of a single dose lasts 8-12 hours.

Uses Because of self limiting action, production of acidosis and hypokalemia, acetazolamide is no longer used as diuretic. Its current clinical uses are:

1. Glaucoma: as adjuvant to other ocular hypotensives.
2. To alkalinise urine: for urinary tract infection or to promote excretion of certain acidic drugs.
3. Epilepsy: as adjuvant in absence seizures when primary drugs are not fully effective.
4. Acute mountain sickness: symptomatic relief as well as prophylaxis.
5. Periodic paralysis.

Dose 250 mg OD-BD; DIAMOX, SYNOMAX 250 mg tab. IOPAR-SR 250 mg SR cap.

Adverse effects are frequent. Acidosis, hypokalemia, drowsiness, paresthesias, fatigue, abdominal discomfort. Hypersensitivity reactions—fever, rashes. Bone marrow depression is rare but serious. It is contraindicated in liver disease: may precipitate hepatic coma by interfering with urinary elimination of NH_3 (due to alkaline urine). Acidosis is more likely to occur in patients of COPD.

Some topical CAse inhibitors have been developed for use in glaucoma.

POTASSIUM SPARING DIURETICS

These are either aldosterone antagonist or directly inhibit Na^+ channels in DT and CD cells to indirectly conserve K^+.

Spironolactone (Aldosterone antagonist)

It is a steroid, chemically related to the mineralocorticoid aldosterone. Aldosterone acts on the late DT and CD cells by combining with an intracellular mineralocorticoid receptor → induces the formation of 'aldosterone induced proteins' (AIPs) which promote Na^+ reabsorption by a number of mechanisms and K^+ secretion. Spironolactone acts from the interstitial side of the tubular cell, combines with the mineralocorticoid receptor and inhibits the formation of AIPs in a competitive manner. It has no effect on Na^+ and K^+ transport in the absence of aldosterone, while under normal circumstances it increases Na^+ and decreases K^+ excretion.

Spironolactone is a mild saluretic because majority of Na^+ has already been reabsorbed proximal to its site of action. However, it antagonises K^+ loss induced by other diuretics and slightly adds to their natriuretic effect. The K^+ retaining action develops over 3-4 days. It increases Ca^{2+} excretion by a direct action on renal tubules.

Pharmacokinetics The oral bioavailability of Spironolactone from microfine powder tablet is 75%. It is highly bound to plasma proteins and completely metabolized in liver; converted to active metabolites, the most important of which is *Canrenone* that is responsible for ½-⅔ of its action *in vivo*. It undergoes some enterohepatic circulation.

Dose: 25-50 mg BD-QID; ALDACTONE, 25, 100 mg tabs.

ALDACTIDE: Spironolactone 25 mg + hydroflumethiazide 25 mg tab. LACILACTONE, SPIROMIDE: Spironolactone 50 mg + furosemide 20 mg tab.

Use Spironolactone is a weak diuretic in its own right and is used only in combination with other more efficacious diuretics.

1. Edema: It is more useful in cirrhotic and nephrotic edema: aldosterone levels are generally high. It breaks resistance to thiazide diuretics that develops due to secondary hyperaldosteronism and reestablishes the response. Thus, it is particularly employed in refractory edema.

2. To counteract K^+ loss due to thiazide and loop diuretics.

3. Hypertension: it has thiazide like antihypertensive action, but is indicated only at low dose in combination with a thiazide to prevent hypokalemia.

4. CHF: As additional drug to conventional therpay in moderate to severe CHF; can retard disease progression and lower mortality.

Interactions

1. Given together with K^+ supplements—dangerous hyperkalemia can occur.

2. Aspirin blocks Spironolactone action by inhibiting tubular secretion of canrenone.

3. Spironolactone blocks carbenoxolone sod. induced Na^+ and water retention: also its therapeutic effect in peptic ulcer.

4. Spironolactone increases plasma digoxin concentration.

Adverse effects Drowsiness, confusion, abdominal upset, hirsutism, gynaecomastia, impotence and menstrual irregularities. Most serious is hyperkalemia that may occur specially if renal function is inadequate. Acidosis occurs particularly in cirrhotics. Peptic ulcer may be aggravated.

Directly Acting Agents (Inhibitors of Renal Epithelial Na^+Channel)

Triamterene and Amiloride are two nonsteroidal organic bases with identical actions. Their most important effect is to decrease K^+ excretion, particularly when it is high due to large K^+ intake or use of a diuretic that enhances K^+ loss, along with a small increase in Na^+ excretion. The excess urinary Na^+ is accompanied by Cl^- and variable amounts of HCO_3^-; urine is slightly alkalinized. The effect on urinary electrolyte pattern is superficially similar to Spironolactone but their action is independent of aldosterone.

Mechanism of action: The luminal membrane of late DT and CD cells expresses a distinct 'amiloride sensitive' or 'renal epithelial' Na^+ channel through which Na^+ enters the cell down its electrochemical gradient which is generated by Na^+K^+ ATPase operating at the basolateral membrane. This Na^+ entry partially depolarizes the luminal membrane creating a -15 mV transepithelial potential difference which promotes secretion of K^+ into the lumen through K^+ channels. Though there is no direct coupling between Na^+ and K^+ channels, more the delivery of the Na^+ to the distal nephron—greater is its entry through the Na^+ channel—luminal membrane is more depolarized—driving force for K^+ secretion is augmented. As such, all diuretics acting proximally (loop diuretics, thiazides, CAse inhibitors) promote K^+ secretion. Amiloride and triamterene block the luminal Na^+ chan-

nels—indirectly inhibit K^+ excretion, while the net excess loss of Na^+ is minor (most of it has already been absorbed).

The intercalated cells in CD possess an ATP driven H^+ pump which secretes H^+ ions into the lumen. This pump is facilitated by lumen negative potential. Amiloride, by reducing the lumen negative potential, decreases H^+ ion secretion as well.

Both triamterene and amiloride are used in conjunction with thiazide type or high ceiling diuretics: prevent hypokalemia and slightly augment the natriuretic and antihypertensive response. They should not be given with K^+ supplements, dangerous hyperkalemia may develop. Hyperkalemia is also more likely in patients receiving ACE inhibitors, and those with renal impairment. Both drugs elevate plasma digoxin levels.

Triamterene It is incompletely absorbed orally, partly bound to plasma proteins, largely metabolized in liver to an active metabolite and excreted in urine. Plasma t½ is 4 hours, effect of a single dose lasts 6–8 hours.

Side effects are infrequent: consist of nausea, dizziness, muscle cramps and rise in blood urea. Impaired glucose tolerance and photosensitivity are reported, but urate level is not increased.

Dose: 50–100 mg daily; DITIDE, triamterene 50 mg + benzthiazide 25 mg tab; FRUSEMENE, triamterene 50 mg + furosemide 20 mg tab.

Amiloride It is 10 times more potent than triamterene (dose 5–10 mg OD-BD). At higher doses it also inhibits Na^+ reabsorption in PT, but this is clinically insignificant. It decreases Ca^{2+} excretion and increases urate excretion. Thus, hypercalcaemic action of thiazides is augmented but hyperuricaemic action is partly annuled.

Only ¼ of an oral dose is absorbed. It is not bound to plasma proteins and not metabolized. The t½ (10-20 hours) and duration of action are longer than triamterene.

BIDURET, KSPAR: Amiloride 5 mg + hydrochlorothiazide 50 mg tab, LASIRIDE, AMIMIDE amiloride 5 mg + furosemide 40 mg tab.

Usual side effects are nausea, diarrhoea and headache.

Amiloride blocks entry of Li^+ through Na^+ channels in the CD cells and mitigates diabetes insipidus induced by lithium.

Given as an aerosol it affords symptomatic improvement in cystic fibrosis by increasing fluidity of respiratory secretions.

OSMOTIC DIURETICS

Mannitol

Mannitol is a nonelectrolyte of low molecular weight (182) that is pharmacologically inert—can be given in large quantities sufficient to raise osmolarity of plasma and tubular fluid. It is not metabolized in the body; freely filtered at the glomerulus and undergoes limited reabsorption: therefore excellently suited to be used as osmotic diuretic. Mannitol (and other osmotic diuretics) appears to limit tubular water and electrolyte reabsorption in a variety of ways:

1. Expands extracellular fluid volume—increases g.f.r. and inhibits renin release.

2. Increases renal blood flow, specially to the medulla—medullary hypertonicity is reduced—corticomedullary osmotic gradient is dissipated—passive salt reabsorption is reduced.

3. Retains water isoosmotically in PT—dilutes luminal fluid which opposes NaCl reabsorption.

4. Inhibits transport processes in the thick AscLH by an unknown mechanism—which quantitatively appears to be the most important cause of diuresis.

Though the primary action of mannitol is to increase urinary volume, excretion of all cations and anions is also enhanced.

Administration Mannitol is not absorbed orally; has to be given i.v. as 10–20% solution. It is excreted with a t1/2 of 0.5–1.5 hour.

MANNITOL 10%, 20%, in 100, 350 and 500 ml vac.

Uses Mannitol is never used for the treatment of chronic edema or as a natriuretic. Its indications are:

1. Increased intracranial or intraocular tension (acute congestive glaucoma, head injury, stroke etc.): by osmotic action it encourages movement of water from CSF and aqueous humour; 1-1.5 g/kg may be infused over 1 hour as 20% solution to transiently raise plasma osmolarity. It is also used before and after ocular/brain surgery to prevent acute rise in intraocular/intracranial pressure.

2. To maintain g.f.r. and urine flow in impending acute renal failure, e.g. in shock, severe trauma, cardiovascular surgery, haemolytic reactions: 500–1000 ml of the solution may be infused over 24 hours. If acute renal failure has already set in, kidney is incapable of forming urine even after an osmotic load; mannitol is contraindicated: it will

then expand plasma volume → pulmonary edema and heart failure may develop.

3. Forced diuresis in hypnotic or other poisonings. Decreased water reabsorption in the tubules reduces reabsorption of the poison also. Moreover, tubules are exposed to lower concentration of the toxic substance due to dilution of urine.

4. To counteract low osmolality of plasma/e.c.f. due to rapid haemodialysis or peritoneal dialysis.

Table 19.2

Urinary electrolyte pattern and natriuretic efficacy of some diuretics

Urinary Electrolyte Excretion					*Max. % of Filtered Na^+ Excreted*	*Efficacy*
Diuretic	Na^+	K^+	*Cl^-*	*HCO_3^-*		
1. Furosemide	↑↑↑	↑	↑↑	↑	25%	High
2. Ethacrynic acid	↑↑↑	↑	↑↑↑	—	25%	High
3. Thiazide	↑↑	↑	↑	↑	8%	Intermediate
4. Acetazolamide	↑	↑↑	↓↑	↑	5%	Mild
5. Spironolactone	↑	↓	↑	—, ↑	3%	Low
6. Triamterene	↑	↓	↑	—, ↑	3%	Low
7. Mannitol	↑↑	↑	↑	↑	20%	High

Mannitol is *contraindicated* in acute tubular necrosis, anuria, pulmonary edema; acute left ventricular failure, CHF, cerebral haemorrhage. Headache due to hyponatremia is common, nausea and vomiting may occur; hypersensitivity reactions are rare.

Isosorbide and glycerol These are orally active osmotic diuretics which may be used to reduce intraocular or intracranial tension.

Dose: 1.5 g/kg as oral solution.

XANTHINES

Theophylline It is a methylxanthine; pharmacology is described in Ch. DRUGS FOR COUGH AND BRONCHIAL ASTHMA. It produces mild transient diuresis. Mechanisms are—increased renal blood flow and g.f.r., but more importantly direct inhibition of tubular reabsorption by blocking renal adenosine A_1 receptors. It is not used as a primary diuretic, but may augment response to other diuretics.

DRUGS AFFECTING COAGULATION; BLEEDING AND THROMBOSIS

Haemostasis and blood coagulation involve complex interactions between the injured vessel wall, platelets and coagulation factors. A cascading series of proteolytic reactions is started by:

(i) Contact activation of Hageman factor: *intrinsic system,* in which all factors needed for coagulation are present in plasma. This is slow and takes several minutes to activate factor X.

(ii) Tissue thromboplastin: extrinsic *system,* needs a tissue factor, but activates factor X in seconds. The subsequent events are common in the two systems and result in the formation of fibrin mesh work in which blood cells are trapped and clot is formed.

Two *in vitro* tests 'activated partial thromboplastin time' (aPTT) and 'prothrombin time' (PT) are employed for testing integrity of the intrinsic, extrinsic and common pathways of the coagulation cascade. The results are interpreted as:

	PT	αPTT
Intrinsic pathway interfered	Normal (12-14S)	Prolonged
Extrinsic pathway interfered	Prolonged	Normal (26-32S)
Common pathway interfered	Prolonged	Prolonged

Most clotting factors are proteins present in plasma in the inactive (zymogen) form: By partial proteolysis they themselves become an active protease and activate the next factor. On the other hand, factors like *antithrombin, protein C, anti-thromboplastin* and the *fibrinolysin system* tend to oppose coagulation and lyse formed clot. Thus, a check and balance system operates to maintain blood in a fluid state while in circulation and allows rapid haemostasis following injury.

COAGULANTS

These are agents which promote coagulation, and are indicated in haemorrhagic states.

Fresh whole blood or plasma provide all the factors needed for coagulation and are the best therapy for deficiency of any clotting factor; also they act immediately. Other drugs used to restore haemostasis are:

1. *Vitamin K*

K_1 (from plants, fat soluble):Phytonadione (Phylloquinone)

K_2 (produced by bacteria):Menaquinones
K_3 (synthetic)
—Fat soluble :Menadione, Acetomenaphthone
—Water soluble :Menadione sod. bisulfite Menadione sod. diphosphate
2. *Miscellaneous* :Fibrinogen (human)
:Antihaemophilic factor
:Adrenochrome monosemicarbazone
:Rutin, Ethamsylate

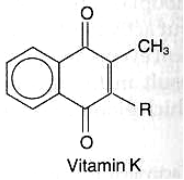
VITAMIN K

It is a fat soluble dietary principle required for the synthesis of clotting factors.

Dam (1929) produced bleeding disorder in chicken by feeding deficient diet. This was later found to be due to decreased concentration of prothrombin in blood and that it could be cured by a fat soluble fraction of hog liver. This factor was called *Koagulations vitamin* (vit K) and soon its structure was worked out. A similar vitamin was isolated in 1939 from alfalfa grass and labelled vit K_1, while that from sardine (sea fish) meal was labelled K_2. Synthetic compounds have been produced and labelled K_3.

Chemistry and Source Vit K has a basic napht-hoquinone structure, with or without a side chain (R) at position 3. The side chain in K_1 is *phytyl,* in K_2 *prenyl,* while in K_3 there is no side chain. Dietary sources are—green leafy vegetables, such as cabbage, spinach; and liver, cheese etc.

Daily requirement It is uncertain, because variable amount becomes available from colonic bacteria. Even 3–10 μg/day external source may be sufficient. However, the total requirement of an adult has been estimated to be 50–100 μg/ day.



Vitamin K

Action Vit K acts as a cofactor at a late stage in the synthesis by liver of coagulation proteins—prothrombin, factors VII, IX and X. The vit K dependent change (γ carboxylation of glutamate residues of

these zymogen proteins) confers on them the capacity to bind Ca^{2+} and to get bound to phospholipid surfaces—properties essential for participation in the coagulation cascade.

Utilization Fat soluble forms of vit K are absorbed from intestine *via* lymph and require bile salts for absorption, while water soluble forms are absorbed directly into portal blood. An active transport process in the jejunum has been demonstrated for K_1 while K_2 and K_3 are absorbed by simple diffusion. Vit K is only temporarily concentrated in liver but there are no significant stores in the body. It is metabolized in liver by side chain cleavage and glucuronide conjugation; metabolites are excreted in bile and urine.

Deficiency Deficiency of vit K occurs due to liver disease, obstructive jaundice, malabsorption, long term antimicrobial therapy which alters intestinal flora. However, deficient diet is rarely responsible. The most important manifestation is bleeding tendency due to lowering of the levels of prothrombin and other clotting factors in blood. Haematuria is usually first to occur; other common sites of bleeding are g.i.t, nose and under the skin—ecchymoses.

Preparations

Phytonadione: VITAMIN-K, KENADION 10 mg/ml for i.m. injection.

Menadione: 0.66 mg in GYNAE CVP with vit C 75 mg, ferrous gluconate 67 mg, Cal. lactate 300 mg and citras bioflavbnoid 150 mg per cap:

Acetomenaphthone: ACETOMENADIONE 5, 10 mg tab; KAPILIN 10 mg tab.

Menadione sod, bisulfite: 20 mg, in CADISPER-C with vit C 100 mg, adrenochrome monosemicarbazone, 1 mg, rutin 60 mg, methylhesperidin 40 mg, Cal. phosphate 100 mg per tab.

STYPTOCID 10 mg with adrenochrome monosemicarbazone 0.5 mg, rutin 50 mg, vit C 37.5 mg, vit D 200 i.u., Cal. phosphate 260 mg per tab.

Menadiol sod. diphosphate: SYNKAVIT 5 mg tab, 10 mg/ml inj. (i.m./i.v.).

Use The only use of vit K is in prophylaxis and treatment of bleeding due to deficiency of clotting factors in the following situations:

(i) Dietary deficiency of vit K: is very rare in adults. However, when it occurs 5–10mg/day oral or parenteral vit K rapidly corrects the defects.

(ii) Prolonged antimicrobial therapy: treat in the same way as dietary deficiency of vit K.

(iii) Obstructive jaundice or malabsorption syndromes (sprue, regional ileitis, steatorrhoea etc.): vit K 10 mg i.m./day, or orally alongwith bile salts.

(iv) Liver disease (cirrhosis, viral hepatitis): associated bleeding responds poorly to vit K. Because of hepatocellular damage, synthesis of clotting factors is inadequate despite the presence of vit K. However, vit K may be of some use if its absorption had been affected due to lack of bile salts.

(v) Newborns: All newborns have low levels of prothrombin and other clotting factors. Further decrease occurs in the next few days. The cause is both lower capacity to synthesize clotting factors as well as deficiency of vit K. The defect is exaggerated in the premature infant. Vit K 1 mg i.m. soon after birth has been recommended routinely. Some prefer administering 5–10 mg i.m. to the mother 4–12 hours before delivery. Haemorrhagic disease of the newborn can be effectively prevented / treated by such medication.

Menadione (K_3) should not be used for this purpose (see below).

(vi) To reverse the effect of overdose of oral anticoagulants: Phytonadione (K_1) is the preparation of choice, because it acts most rapidly; dose depends on the severity of hypoprothrombinemia (measured INR) and bleeding. Unnecessary high dose is to be avoided because it will render the patient unresponsive to oral anticoagulants for several days.

Severe: 10 mg i.m. followed by 5 mg 4 hourly; bleeding generally stops in 6–12 hours, but normal levels of coagulation factors are restored only after 24 hr. This dose of vit K will block anticoagulant action for 7–10 days.

Moderate: 10 mg i.m. followed by 5 mg once or twice according to response.

Mild: Just omit a few doses of the anticoagulant.

(vii) Prolonged high dose salicylate therapy causes hypoprothrombinemia; vit K should be given prophylactically. If bleeding occurs—treat as for oral anticoagulants.

Toxicity Rapid i.v. injection of emulsified vit K produces flushing, breathlessness, a sense of constriction in the chest, fall in BP; few deaths are on record. It is probably due to emulsion form of the preparation.

Menadione and its water soluble derivatives can cause haemolysis in a dose dependent manner. Patients with G-6-PD deficiency and neonates are specially susceptible. In the newborn menadione or its salts can precipitate kernicterus:

(a) by inducing haemolysis and increasing bilirubin load.

(b) by competitively inhibiting glucuronidation of bilirubin. Glucuronide conjugation is, as such, inadequate in neonates.

Fibrinogen The fibrinogen fraction of human plasma is employed to control bleeding in haemophilia, antihaemophilic globulin (AHG) deficiency and acute afibrinogenemic states; 0.5 g is infused i.v.

FIBRINAL 0.5 g/bottle for i.v. infusion.

Antihaemophilic factor It is concentrated human AHG prepared from pooled human plasma. It is indicated (along with human fibrinogen) in haemophilia and AHG deficiency. It is highly effective in controlling bleeding episodes, but action is short lasting (1 to 2 days).

Dose 5–10 U/kg by i.v. infusion, repeated 6–12 hourly.

FIBRINAL-H, ANTIHAEMOPHILIC FACTOR: 150 U or 200 U + fibrinogen 0.5 g/bottle for i.v. infusion.

Adrenochrome monosemicarbazone It is believed to reduce capillary fragility, control oozing from raw surfaces and prevent microvessel bleeding, e.g. epistaxis, haematuria, retinal haemorrhage, secondary haemorrhage from wounds etc. Its efficacy is uncertain.

Dose: 1–5 mg oral, i.m.

STYPTOCHROME 3 mg/2 ml inj., STYPTOCID: 2 mg/2 ml inj; in CADISPER-C, STYPTOCID 1 mg, 0.5 mg tab, with other ingredients.

Rutin It is a plant glycoside claimed to reduce capillary bleeding. It has been used in a dose of 60 mg oral BD-TDS alongwith vit C which is believed to facilitate its action. Its efficacy is uncertain.

In CADISPER-C 60 mg tab, in KERUTIN-C 100 mg tab in STYPTOBION 100 mg tab, 200 mg/2 ml inj.

Ethamsylate It reduces capillary bleeding when platelets are adequate; probably exerts antihyaluronidase action—improves capillary wall stability. It is also claimed to inhibit PGI_2 production and correct abnormal platelet function, but does not stabilize fibrin (not an antifibrinolytic). It has been used in the prevention and treatment of capillary bleeding in menor-rhagia, after abortion, PPH, epistaxis, malena, hematuria, after tooth extraction. Side effects are nausea, rash, headache, and fall in BP (only after i.v. injection).

Dose: 250–500 mg TDS oral/i.v.; ETHAMSYL, DICYNENE, HEMSYL, K. STAT 250, 500 mg tabs; 250 mg/2 ml inj.

LOCAL HAEMOSTATICS (STYPTICS)

These are substances used to stop bleeding from a local approachable site. They are particularly effective on oozing surface, e.g. tooth socket, open wounds etc. They should never be injected.

1. Thrombin Obtained from bovine plasma, it is applied as dry powder or freshly prepared solution on the bleeding surface. It has been used in haemophilia, neurosurgery, skin grafting etc.

2. Fibrin It is prepared from human plasma and is dried. It is used as sheets or foam for covering or packing bleeding surfaces. It is left *in situ*—gets absorbed in the body.

3. Gelatin foam It is spongy gelatin available in various shapes. It is moistened with saline or thrombin solution and used for packing wounds. It gets absorbed in 1–2 months if left inside; use is similar to fibrin foam.

4. Russels viper venom Applied locally, it acts as a thromboplastin. It has been used to stop external bleeding in haemophilias.

5. Vasoconstrictors Like 1% solution of Adr may be soaked in sterile cotton guaze and packed to stop epistaxis or other similar bleeding.

6. Astringent Like tannic acid (20% in glycerine) is used for bleeding gums, bleeding piles etc.

SCLEROSING AGENTS

These are irritants, cause inflammation, coagulation and ultimately fibrosis, when injected into haemorrhoids (piles) or varicose vein mass. They are used only for local injection.

1. Phenol (5%) in almond oil or peanut oil: 2–5 ml.
2. Ethanolamine oleate (5% in 25% glycerine and 2% benzyl alcohol): 1–5 ml inj.
3. Sod. tetradecyl sulfate (3% with benzyl alcohol 2%): 3–6 ml. SETROL inj.
4. Polidocanol (3% inj): 2 ml; ASKLEROL inj.

ANTICOAGULANTS

These are drugs used to reduce the coagulability of blood. They may be classified into:

I. *Used in vitro*

A. Heparin: 150 U to prevent clotting of 100 ml blood.

B. Calcium complexing agents:

Sodium citrate: 1.65 g for 350 ml of blood; used to keep blood in the fluid state for transfusion; ANTICOAGULANT ACID CITRATE DEXTROSE SOLUTION 2.2 g/100 ml (75 ml is used for 1 unit of blood).

Sodium oxalate: 10 mg for 1 ml blood
Sodium edetate: 2 mg for 1 ml blood
} used in blood taken for investigations

II. Used in vivo

A. Heparin, Low molecular weight heparin. Heparinoids—Heparan sulfate, Danaparoid, Lepirudin, Ancrod.

B. *Oral anticoagulants*

(i) *Coumarin derivatives:* Bishydroxycoumarin (dicumarol), Warfarin sod, Acenocouma-rol (Nicoumalone), Ethylbiscoumacetate

(ii) *Indandione derivative:* Phenindione.

HEPARIN

McLean, a medical student, discovered in 1916 that liver contains a powerful anticoagulant. Howell and Holt (1918) named it 'heparin' because it was obtained from liver. However, it could be used clinically only in 1937 when sufficient degree of purification was achieved.

Chemistry and occurrence Heparin is a non-uniform mixture of straight chain mucopoly-saccharides with MW 10,000 to 20,000. It contains polymers of two sulfated disaccharide units:

D-elucosamine-L-iduronic acid
D-glucosamine-D-glucuronic acid
} chain length and proportion of the two disaccharide units varies. Some glucosamine residues are N-acetylated.

It carries strong electronegative charges and is the strongest organic acid present in the body. It occurs in mast cells as a much bigger molecule (MW ~75,000) loosely bound to the granular protein. Thus, heparin is present in all tissues containing mast cells; richest sources are lung, liver and intestinal mucosa. It is commercially produced from ox lung and pig intestinal mucosa.

ACTIONS

1. Anticoagulant Heparin is a powerful and instantaneously acting anticoagulant, effective both *in vivo* and *in vitro.* However, it acts indirectly by activating plasma antithrombin III (AT III, a serine proteinase inhibitor) and may be other similar cofactors. The heparin-AT

III complex then binds to clotting factors of the intrinsic and common pathways (Xa, IIa, IXa, XIa, XIIa and XIIIa) and inactivates them but not factor VIIa operative in the extrinsic pathway. At low concentrations of heparin, factor Xa mediated conversion of prothrombin to thrombin is selectively affected. The anticoagulant action is exerted mainly by inhibition of factor Xa as well as thrombin (IIa) mediated conversion of fibrinogen to fibrin.

Low concentrations of heparin prolong aPTT without significantly prolonging PT. High concentrations prolong both. Thus, low concentrations interfere selectively with the intrinsic pathway, while high concentrations affect the common pathway as well.

Antithrombin III is itself a substrate for the protease clotting factors; binds with the protease to form a stable complex (suicide inhibitor). However, in the absence of heparin, the two interact very slowly. Heparin enhances the action of AT III in two ways:

(a) Long heparin molecule provides a scaffolding for the clotting factors (mainly Xa and IIa) as well as AT III to get bound and interact with each other.

(b) Heparin induces conformational change in AT III to expose its interactive sites.

Inhibition of IIa requires both the mechanisms, but Xa inhibition can occur by mechanism 'b' alone. This probably explains why low molecular weight heparin, which is insufficient to provide a long scaffolding, selectively inhibits factor Xa.

Higher doses of heparin given for some time cause reduction in AT-III levels, probably a compensatory phenomenon. Sudden stoppage of conventional therapy may result in rebound increase in coagulability for few days.

2. Antiplatelet Heparin in higher doses inhibits platelet aggregation and prolongs bleeding time.

3. Lipemia clearing Injection of heparin clears turbid postprandial lipemic plasma. However, *in vitro* addition of heparin to turbid plasma has no such effect. Heparin releases a lipoprotein lipase from the vessel wall and tissues, which hydrolyses triglycerides of chylornicra and very low density lipoproteins to free fatty acids; these then pass into tissues and the plasma looks clear. This action requires lower concentration of heparin than that needed for anticoagulation.

Facilitation of fatty acid transport may be the physiological function of heparin; but since, it is not found in circulating blood and its storage form in tissues is much less active, this seems only conjectural.

PHARMACOKINETICS

Heparin is a large, highly ionized molecule; therefore not absorbed orally. Injected i.v. it acts instantaneously, but after s.c. injection anticoagulant effect develops after ~60 min. Bioavailability of s.c. heparin is inconsistent. Heparin does not cross blood-brain barrier or placenta (it is the anticoagulant of choice during pregnancy). It is metabolized in liver by heparinase and fragments are excreted in urine.

Heparin released from mast cells is degraded by tissue macrophages—it is not a physiologically circulating anticoagulant.

After i.v. injection of doses < 100 U/kg, the t½ averages 1 hr. Beyond this, dose dependent inactivation is seen and t½ is prolonged to as much as 5 hrs. The t½i is longer in cirrhotics and kidney failure patients, and shorter in patients with pulmonary embolism.

Unitage and administration Because of variable molecular size, heparin is standardized only by bioassay: 1 U is the amount of heparin that will prevent 1 ml of citrated sheep plasma from clotting for 1 hour after the addition of 0.2 ml of 1% $CaCl_2$ solution. Heparin sod.\mg has 120–140 U of activity.

HEPARIN SOD., BEPARINE, NUPARIN 1000 and 5000 U/ml in 5 ml vials for injection.

Heparin should not be mixed with penicillin, tetracyclines, hydrocortisone or NA in the same syringe or infusion bottle. Heparinized blood is not suitable for blood counts (alters the shape of RBCs and WBCs), fragility testing and complement fixation tests.

Dosage Heparin is conventionally given i.v. in bolus doses of 5,000–10,000 U (children 50–100 U/kg) every 4–6 hours, or the initial bolus dose is followed by continuous infusion of 750–1000 U/hr which may reduce the total dose needed and the incidence of bleeding. The dose and frequency is controlled by aPTT measurement which is kept at 50–80 sec. or 1.5–2.5 times the patient's pretreatment value. If this test is not available, whole blood clotting time should be measured and kept at ~2 times the normal value.

Deep s.c. injection of 10,000–20,000 U every 8–12 hrs can be given if repeated i.v. injection or infusion is not possible. Needle used

should be fine and trauma should be minimum to avoid haematoma formation. Haematomas are more common with i.m. injection—this route should not be used.

Low dose (s.c.) regimen 5000 U is injected s.c. every 8–12 hours, started before surgery and continued for 7–10 days or till the patient starts moving about. This regimen has been found to prevent post operative deep vein thrombosis without increasing surgical bleeding. It also does not prolong aPTT or clotting time. However, it should not be used in case of neurosurgery or when spinal anaesthesia is to be given. The patients should not be receiving aspirin or oral anticoagulants. It is ineffective in high risk situations, e.g. hip joint or pelvic surgery.

ADVERSE EFFECTS

1. Bleeding due to overdose is the most serious complication of heparin therapy. Haematuria is generally the first sign. With proper monitoring, serious bleeding is reported in 1–3% patients.

2. Thrombocytopenia is another common problem. Generally it is mild and transient; occurs due to aggregation of platelets. Occasionally, antibodies are formed to the heparin-platelet complex and marked depletion of platelets occurs—heparin should be discontinued. Even LMW heparins are not safe in such patients.

3. Transient and reversible alopecia is infrequent. Serum transaminase levels may rise.

4. Osteoporosis may develop on long term use of relatively high doses.

5. Hypersensitivity reactions: are rare—urticaria, rigor, fever and anaphylaxis. Patients with allergic diathesis are more liable.

Contraindications

1. Bleeding disorders, thrombocytopenia.

2. Severe hypertension, (risk of cerebral haemorrhage), threatened abortion, piles, g.i. ulcers (aggravated bleeding).

3. Subacute bacterial endocarditis (embolism), large malignancies (bleeding in the central necrosed area of the tumour), tuberculosis (hemoptysis).

4. Ocular and neurosurgery, lumbar puncture.

5. Chronic alcoholics, cirrhosis, renal failure.

6. Aspirin and other antiplatelet drugs should be used very cautiously during heparin therapy.

Low molecular weight (LMW) heparins

Heparin has been fractionated into LMW forms (MW 3000–7000) by different techniques. LMW heparins have a different anticoagulant profile; selectively inhibit factor Xa with little effect on IIa. They act only by inducing conformational change in AT III and not by bringing together AT III and thrombin. As a result LMW heparins have smaller effect on aPTT and whole blood clotting time than unfractionated heparin (UFH) relative to antifactor Xa activity. Also they appear to have lesser antiplatelet action—less interference with haemostasis. Thrombocytopenia is less frequent. A lower incidence of haemorrhagic complications compared to UFH has been reported in some studies, but not in others. However, major bleeding may be less. The more important advantages of LMW heparins are pharmacokinetic:

- Better subcutaneous bioavailability (70–90%) compared to UFH (20–30%): Variability in response is minimized.
- Longer and more consistent monoexponential t½: once daily s.c. administration.
- Since aPTT/clotting times are not prolonged, laboratory monitoring is not needed; dose is calculated on body weight basis.

Most studies have found LMW heparins to be equally efficacious to UFH. Indications of LMW heparins are:

1. Prophylaxis of deep vein thrombosis and pulmonary embolism in high risk patients undergoing surgery, stroke or other immobilized patients.
2. Treatment of established deep vein thrombosis.
3. Unstable angina.
4. To maintain patency of cannulae and shunts in dialysis patients, and in extracorporeal circulation.

A number of LMW heparins have been marketed. They differ in composition, pharmacokinetics and dosage

Enoxaparin: CLEXANE 20 mg (0.2 ml) and 40 mg (0.4 ml) prefilled syringes; 20–40 mg OD, s.c. (start 2 hour before surgery).

Reviparin: CLIVARINE 13.8 mg (eq. to 1432 ami Xa IU) in 0.25 ml prefilled syringe; 0.25 ml s.c. once daily for 5–10 days.

Nadroparin: FRAXIPARINE 3075 IU (0.3 ml) and 4100 IU (0.4 ml) inj., CARDIOPARIN 4000 anti Xa IU/0.4 ml, 6000 anti Xa IU/0.6 ml, 100, 000 ami Xa IU/10 ml inj.

Dalteparin: 2500 IU OD for prophylaxis; 100 U/Kg 12 hourly or 200 U/Kg 24 hourly for treatment of deep vein thrombosis. FRAGMIN 2500, 5000 IU prefilled syringes.

Pamparin: 0.6 ml s.c. OD for unstable angina and prophylaxis of DVT; FLUXUM 3200 IU (0.3 ml), 6400 IU (0.6 ml) inj.

Ardeparin: 2500-5000 IU OD; INDEPARIN 2500 IU, 5000 IU prefilled syringes.

HEPARINOIDS

Heparan sulfate It is a heparin like natural substance found on cell surface and intercellular matrix in many tissues. It is a less potent anticoagulant than heparin, but may have a more favourable profile of action. It is believed to be a physiological antithrombotic at the surface of vascular endothelium.

Danaparoid is a preparation containing mainly heparan sulfate, obtained from pig gut mucosa, which is used in cases with heparin induced thrombocytopenia.

Lepirudin This recombinant preparation of hirudin (a polypeptide anticoagulant secreted by salivary glands of leech) acts by inhibiting thrombin directly. It is indicated in patients with heparin induced thrombocytopenia.

Ancrod It is an enzyme obtained from Malayan pit viper venom. It degrades fibrinogen into an unstable form of fibrin which is taken up by RE cells. Thus, fibrinogen gets depleted and an apparent heparin like effect results. It is given only by slow infusion: 2 U/kg over 6 hours for deep vein thrombosis in patients who develop thrombocytopenia or hypersensitivity reactions to heparin.

HEPARIN ANTAGONIST

Protamine sulfate It is a strongly basic, low molecular weight protein obtained from the sperm of certain fish. Given i.v. it neutralises heparin weight for weight, i.e. 1 mg is needed for every 100 U of heparin. Due consideration must be given to the amount of heparin that may have been degraded by the patient's body in the mean time. However, it is needed infrequently because the action of heparin disappears by itself in a few hours, and whole blood transfusion is indicated to replenish the loss when bleeding occurs. It is more commonly used when heparin action needs to be terminated rapidly, e.g. after cardiac or vascular surgery.

In the absence of heparin, it itself acts as a weak anticoagulant by interacting with platelets and fibrinogen. Being basic in nature it can release histamine in the body. Hypersensitivity reactions have occurred. Rapid i.v. injection causes flushing and breathing difficulty.

PROTA, PROTAMINE SULFATE 50 mg in 5 ml inj.

ORAL ANTICOAGULANTS

A haemorrhagic disease was described in cattle in 1924 which was due to feeding them on spoiled sweet clover hay. The disorder was found to be due to prothrombin deficiency and the toxic principle was identified as bishydroxycoumarin in 1939. It was cured by feeding alfalfa grass. First clinical use of bishydroxycoumarin was made in 1941 and many congeners were added later. Warfarin was initially used as rat poison; demonstration of its safety led to clinical trial; it *is* now a commonly employed oral anticoagulant.

Action and Mechanism

Warfarin and its congeners act as anticoagulants only *in vivo* not *in vitro.* This is so because they act indirectly by interfering with the synthesis of vit K dependent clotting factors in liver. They apparently behave as competitive antagonists of vit K and reduce the plasma levels of functional clotting factors in a dose dependent manner. In fact, they interfere with regeneration of the active hydroquinone form of vit K (Fig. 42.2) which carries out the final step of γ carboxylating glutamate residues of prothrombin and factors VII, IX and X. This carboxylation is essential for the ability of the clotting factors to bind Ca^{2+} and to get bound to phospholipid surfaces, necessary for coagulation sequence to proceed.

Factor VII has the shortest plasma to (6hr), its level falls first when warfarin is given, followed by factor IX (to 24 hr), factor X (to 40 hr) and prothrombin (to 60 hr). Though the synthesis of clotting factors diminishes within 2–4 hours of warfarin administration, anticoagulant effect develops gradually over the next 1–3 days as the levels of the clotting factors already in plasma decline progressively. Thus, there is always a delay between administration of the drug and the anticoagulant effect. Larger initial doses hasten the effect only slightly.

Therapeutic effect occurs when synthesis of clotting factors is reduced by 40–50%. The differences between different oral anticoagulants are primarily pharmacokinetic and in the adverse side effects produced by them. These are summarized in Table 20.1.

Protein C, protein *S,* osteocalcin and some other proteins contain glutamate residues that require vit. K dependent γ carboxylation. These are also inhibited by oral anticoagulants, but density of adult bone is not affected, though new bone formation may be depressed.

Recemic Warfarin sod It is the most popular oral anticoagulant. The commercial preparation of warfarin is a mixture of R (dextrorotatory) and S (levorotatory) enantiomers. The S form is more potent and is metabolized relatively faster by ring oxidation, while R form is less potent and degraded by side chain reduction. Both are partially conjugated with glucuronic acid and undergo some enterohepatic circulation; finally excreted in urine.

Warfarin is rapidly and completely absorbed from intestines and is 99% plasma protein bound. It crosses placenta and is secreted in milk; however, quantity of active form is generally insufficient to affect the suckling infant.

UNIWARFIN, 1,2,5 mg tabs; WARF-5: 5 mg tab

Table 20.1

Pharmacokinetic and adverse effect profile of oral anticoagulants

Drug	t½	*Duration of Action*	*Dose <mg)*		*Adverse Side Effects (nonhaemorrhagic)*
			Loading	*Maintenance**	
1. Bishydroxycoumarin	25–100 hr (dose dependent)	4–7 days	200 for 2 days	50–100	Frequent g.i.t. disturbances
2. Warfarin sod.	36–48 hr	3–6 days	10–15	2–10[£]	Alopecia, dermatitis, diarrhoea
3. Acenocoumarol (Nicoumalone)	18–24 hr	2–3 days	8–12	2–8	Oral ulceration, g.i.t. disturbances, dermatitis, urticaria, alopecia
4. Ethylbiscoumacetate	2 hr	1–3 days	900	300–600	Alopecia, bad taste
5. Phenindione	5 hr	1–3 days	200	50–100	Orange urine, rashes, fever, leukopenia, hepatitis, nephropathy, agranulocytosis

* Daily maintenance dose: to be adjusted by measurement of prothrombin time.

[£] To be taken in a single dose at the same hour (usually bed time) each day.

Bishydroxycoumarin (Dicumarol) It is slowly and unpredictably absorbed orally. Its metabolism is dose dependent—t½ is prolonged at higher doses. Has poor g.i. tolerance.

DICOUMAROL 50 mg tab

Acenocoumarol (Nicoumalone) It has a t½ of 8 hours but produces an active metabolite, so that overall t½ is about 24 hours. Acts more rapidly.

ACITROM, 1, 2, 4 mg tabs.

Ethyl biscoumacetate It has a rapid and brief action; occasionally used to initiate therapy, but difficult to maintain.

Phenindione It produces more serious nonhaemorrhagic toxic effects: should not be used.

DINDEVAN 50 mg tab.

Adverse effects Bleeding as a result of extension of the desired pharmacological action is the most important problem: ecchymosis, epistaxis, hematuria, bleeding in the g.i.t., intracranial or other internal haemorrhages may be fatal. This is more likely if therapy is not properly monitored or interacting drugs / contraindications are present.

Treatment: of bleeding due to oral anticoagulants consists of:

- Withhold the anticoagulant.
- Give fresh blood transfusion: supplies cloning factors and replenishes lost blood. Alternatively fresh frozen plasma may be used as a source of clotting factors.
- Give vit K_1—specific antidote but it takes 6–24 hours for the clotting factors to be resynthesized and released in blood after vit K administration.

Adverse effects unrelated to anticoagulation are given in Table 20.1. Cutaneous necrosis is a rare complication that can occur with any oral anticoagulant.

Phenindione produces serious toxicity; should not be used (though still available).

Warfarin and acenocoumarol are considered to be the most suitable and better tolerated drugs.

Dose regulation The dose of oral anticoagulant must be individualised by repeated measurement of *prothrombin time;* the aim is to achieve a therapeutic effect without unduely increasing the chances of bleeding.

The optimum ratio of PT during treatment to the normal value (of the testing laboratory) has been defined for various indications. But

this value differs depending on whether rabbit brain or human brain thromboplastin (Tp) has been used for the test. A standardized system called International Normalized Ratio (INR) based on the use of human brain Tp has been developed by WHO and adopted in all countries.

	PT Ratio	
	Rabbit Tp	*INR (Human Tp)*
1. Prophylaxis of deep vein thrombosis and similar indications	1.2–1.5	2–2.5
2. Treatment of deep vein thrombosis, pulmonary embolism, TIAs, hip surgery	1.3–1.7	2–3
3. Recurrent thromboembolism, arterial disease (MI), prosthetic heart valves	1.5–2.0	3–4.5

Factors enhancing effect of oral anticoagulants are:

- Debility, malnutrition, malabsorption and prolonged antibiotic therapy: the supply of vit K to liver is reduced in these conditions.
- Liver disease, chronic alcoholism: synthesis of clotting factors may be deficient.
- Hyperthyroidism: the clotting factors are degraded faster.
- Newborns: have low levels of vit K and clotting factors (there should be no need of these drugs in neonates anyway).

Factors decreasing effect of oral anticoagulants are:

- Pregnancy: plasma level of clotting factors is higher.
- Nephrotic syndrome: drug bound to plasma protein is lost in urine.
- Genetic warfarin resistance: the affinity of warfarin (as well as of vit K epoxide) to bind to the reductase enzyme, which generates the active vit K hydroquinone, is low. Dose of oral anticoagulant is 4–5 times higher.

Contraindications All contraindications to heparin apply to these drugs as well. Factors which enhance the effect of oral anticoagulants (*see* above) should also be taken into consideration.

Oral anticoagulants should not be used during pregnancy. Warfarin given in early pregnancy increases birth defects, specially skeletal abnormalities: foetal warfarin syndrome—hypoplasia of nose, eye socket, hand bones, and growth retardation. Given later in pregnancy, it can cause CNS defects, foetal haemorrhage, foetal death and accentuates neonatal hypoprothrom-binemia.

Drug interactions A large number of drugs interact with oral anticoagulants at pharmacokinetic or pharmacodynamic level, and either enhance or depress their effect. These interactions are clinically important (may be fatal if bleeding occurs) and may involve more than one mechanism; the exact mechanism of an interaction is not always definable.

Enhanced anticoagulant action

1. Broad spectrum antibiotics, inhibit gut flora and reduce vit K production.

2. Newer cephalosporins (cefamandole, moxa-lactam, cefoperazone) cause hypoprothrombinemia by the same mechanism as warfarin—additive action.

3. Aspirin: inhibits platelet aggregation and causes g.i. bleeding—this may be hazardous in anticoagulated patients. High doses of salicylates have synergistic hypoprothrom-binemic action and also displace warfarin from protein binding site.

4. Phenylbutazone: decreases protein binding of warfarin and inhibits the metabolism of the more active S enantiomer while inducing that of R enantiomer—action is increased without a change in blood level or t½. It also inhibits platelet function.

5. Long acting sulfonamides, indomethacin, phenytoin and probenecid: displace warfarin from plasma protein binding.

6. Chloramphenicol, erythromycin, celecoxib, cimetidine, allopurinol, amiodarone and metronidazole: inhibit warfarin metabolism.

7. Tolbutamide and phenytoin: inhibit warfarin metabolism and *vice versa.*

8. Liquid paraffin (habitual use): reduces vit K absorption.

Reduced anticoagulant action

1. Barbiturates and other hypnotics (but not benzodiazepines), rifampin and griseofulvin induce the metabolism of oral anticoagulants. The dose of anticoagulant determined during therapy with these drugs would be higher: if the same is continued after withdrawing the inducer—marked hypoprothrombinemia can occur—fatal bleeding is on record.

2. Oral contraceptives: increase blood levels of clotting factors.

USES OF ANTICOAGULANTS

The aim of using anticoagulants is to prevent thrombus extension and embolic complications by reducing the rate of fibrin formation.

They do not dissolve already formed clot, but prevent recurrences. Heparin is utilized for rapid and short lived action, while oral anticoagulants are suitable for maintenance therapy. Generally, the two are started together; heparin is discontinued after 4–7 days when warfarin has taken effect.

1. Deep vein thrombosis and pulmonary embolism Because venous thrombi are mainly fibrin thrombi, anticoagulants are expected to be highly effective. The best evidence of efficacy of anticoagulants comes from treatment and prevention of venous thrombosis and pulmonary embolism. Prophylaxis is needed by bedridden, old, postoperative, postpartum, poststroke and leg fracture patients. When deep vein thrombosis/ pulmonary embolism has occurred, 3 months anticoagulant therapy (continued further if risk factor persists) has been recommended by American College of Chest Physicians (concensus conference 1998).

Introduction of low dose heparin prophylaxis for patients undergoing elective surgery has considerably reduced the incidence of leg vein thrombosis and pulmonary embolism in the postoperative period. It has been extended to other situations needing prolonged immobilization. It is based on the premise that inhibition of small amount of activated factor X prevents further amplification of active products—particularly thrombin. This is the regimen of choice: does not need laboratory monitoring; spontaneous bleeding does not occur. LMW heparin is being preferred for this purpose.

Anticoagulants are of little value in chronic peripheral vascular diseases.

2. Myocardial infarction (Ml) Arterial thrombi are mainly platelet thrombi; anticoagulants are of questionable value. Their use in acute MI has declined. They do not alter immediate mortality of MI. It was hoped that anticoagulants will prevent extension of the thrombus and ward off a recurrent attack. This has not been supported by the collected statistics. They may benefit by preventing mural thrombi at the site of infarction and venous thrombi in leg veins. Thus, anticoagulants may be given for a short period till patient becomes ambulatory. For secondary prophylaxis against a subsequent attack—anticoagulants are inferior to antiplatelet drugs.

Heparin (i.v.) for 2–8 days followed by oral anticoagulants for 3 months or low dose s.c. heparin are generally given after recanalization of

coronary artery by fibrinolytic therapy. Heparin is also used during coronary angioplasty and stent placement.

3. Unstable angina Short term use of heparin has reduced the occurrence of MI in unstable angina patients; aspirin is equally effective. Current recommendation is to use aspirin + heparin followed by warfarin.

4. Rheumatic heart disease, Atrial fibrillation (AF) Warfarin/low dose heparin/low dose aspirin are effective in preventing stroke (due to embolism from fibrillating atria). The 'stroke prevention in Atrial Fibrillation' trial and a metaanalysis have shown warfarin to be more effective than aspirin. Current guideline is to give warfarin to a target INR of 2–3 in AF patients with high risk for stroke (elderly, heart failure etc.), and to reserve aspirin for low risk patients or for those unable to take warfarin. Anticoagulants are given for 3–4 weeks before and after attempting conversion of AF to sinus rhythm.

Table 20.2

Some comparative aspects of heparin and oral anticoagulants

	Heparin	*Warfarin*
1. Chemistry	Mucopolysaccharide	Coumarin derivative
2. Source	Hog lung, pig intestine	Synthetic
3. Route of admin.	Parenteral (i.v., s.c.)	Oral
4. Onset of action	Immediate	Delayed (1–3 days)
5. Duration of action	4–6 hrs	3–6 days
6. Activity	*In vitro* and *in vivo*	*In vivo* only
7. Mechanism	Blocks action of factor X and thrombin	Inhibits synthesis ofclotting factors
8. Antagonist	Protamine sulphate	Vit K
9. Variability in response	Little	Marked
10. Lab. control	a PTT/clotting time (desirable)	Prothrombin time/INR (essential)
11. Drug interactions	Few and not significant	Many and significant
12. Use	To initiate therapy	For maintenance

5. Cerebrovascular disease Anticoagulants are of little value in cerebral thrombosis. Neurological sequelae are similar whether they are used or not. Moreover, in the initial stages it is difficult to rule out cerebral haemorrhage (unless CAT scan is done) in which they can be

devastating. They may be used in cerebral embolism, because showers of emboli are often recurrent and can be prevented by anticoagulants. A late start (one week) anticoagulant therapy is advocated by many in case of large embolic stroke. Oral anticoagulants may be beneficial in transient ischaemic attacks (TIAs), but antiplatelet drugs are simpler to use and probably better.

6. Vascular surgery, prosthetic heart valves, retinal vessel thrombosis, extracorporeal circulation, haemodialysis Anticoagulants are indicated along with antiplatelet drugs for prevention of thromboembolism.

Heparin flushes (200 U in 2 ml) every 4–8 hr are used to keep patent long term intravascular cannulae/catheters.

7. Defibrination syndrome or'disseminated intravascular coagulation' occurs in abruptio placentae and other obstetric conditions, certain malignancies and infections. The coagulation factors get consumed for the formation of intravascular microclots and blood is incoagulable. Heparin paradoxically checks bleeding in such patients by preserving the clotting factors. However, in some cases heparin may aggravate bleeding.

FIBRINOLYTICS (Thrombolytics)

These are drugs used to lyse thrombi/clot to recanalyse occluded blood vessels (mainly coronary artery). They are curative rather than prophylactic; work by activating the natural fibrinolytic system.

Haemostatic plug of platelets formed at the site of injury to blood vessels is reinforced by fibrin deposition to form a thrombus. Once repair is over the fibrinolytic system is activated to remove fibrin. The enzyme responsible for digesting fibrin is a serine protease *Plastnin* generated from *plasminogen* by tissue plasminogen activator (t-PA), which is produced primarily by vascular endothelium. Plasminogen circulates in plasma as well as remains bound to fibrin. The t-PA selectively activates fibrin bound plasminogen within the thrombus, and any plasmin that leaks is inactivated by circulating antiplasmins. Fibrin bound plasmin is not inactivated by antiplasmins because of common binding site for both fibrin and antiplasmin.

When excessive amounts of plasminogen are activated (by administered fibrinolytics), the α_2 antiplasmin is exhausted and active plasmin persists in plasma. Plasmin is a rather nonspecific protease: de-

grades coagulation factors (including fibrinogen) and some other plasma proteins as well. Thus, activation of circulating plasminogen induces a lytic state whose major complication is haemorrhage. Even selective activation of thrombus bound plasmin can cause bleeding by dissolving physiological thrombi.

In general venous thrombi are lysed more easily than arterial, and recent thrombi respond better: little effect on thrombi > 3 days old. Three fibrinolytics *Streptokinase, Urokinase and Alteplase* (rt-PA) are available in India for clinical use.

Streptokinase It is obtained from β haemolytic *Streptococci* group C. It is inactive as such: combines with circulating plasminogen to form an activator complex which then causes limited proteolysis of other plasminogen molecules to plasmin. Antistreptococcal antibodies present due to past infections inactivate considerable fraction of the initial dose of Streptokinase: a loading dose is necessary in the beginning. Its t½ is estimated to be 30–80 min.

Streptokinase is antigenic; can cause hyper-sensitivity reactions and anaphylaxis, specially when used second time in a patient; also less effective due to neutralization by antibodies. Fever is common, hypotension and arrhythmias are reported. However, it is the least expensive of the 3 fibrinolytics.

STREPTASE, (freeze dried powder in vials) 2.5 lac, 7.5 lac and 15 lac lU / vial, ESKINASE, CARDIOSTREP 7.5 lac, 15 lac lU/vial.

For MI: 7.5–15 lac IU infused i.v. over 1 hr.

For deep vein thrombosis and pulmonary embolism: 2.5 lac IU loading dose over ½-1 hr, followed by 1 lac lU/hr for 24 hr.

Urokinase It is an enzyme isolated from human urine; now prepared from cultured human kidney cells. It activates plasminogen directly and has a plasma ½ of 10–15 min. It is nonantigenic. Fever occurs during treatment, but hypotension and allergic phenomena are rare. Indicated in patients in whom streptokinase has been used for an earlier episode.

UROKINASE, KD-UNASE, 2.5 lac, 5 lac, 10 lac IU per vial inj.

For Ml: 2.5 lac IU i.v. over 10 min followed by 5 lac IU over next 60 min (stop in between if full recanalization occurs) or 6000 IU/min for upto 2 hr.

For venous thrombosis and pulmonary embolism: 4400 IU/kg over 10 min i.v. followed by 4400 IU/kg/hr for 12 hr.

Alteplase *(recombinant tissue Plasminogen Activator (r t-PA)* Produced by recombinant DNA technology from human tissue culture, it specifically activates gel phase plasminogen already bound to fibrin, and has little action on circulating plasminogen. It is rapidly cleared by liver and has a plasma t½ of 4–8 min. It is nonantigenic, but nausea, mild hypotension and fever may occur. It is expensive.

ACTILYSE 50 mg vial with 50 ml solvent water. *For MI:* 15 mg i.v. bolus injection followed by 50 mg over 30 min, then 35 mg over the next 1 hr. *For pulmonary embolism:* 100 mg i.v. infused over 2 hr.

Uses of Fibrinolytics

1. *Acute myocardial infarction* is the chief indication; now considered a first line approach if fibrinolytic therapy can be instituted within 12 hr of symptom onset. Recanalization of thrombosed coronary artery has been achieved in 50–90% cases. Time lag in starting infusion is critical for reducing area of necrosis, preserving ventricular function and reducing mortality. The need for early reperfusion (preferably within 3–6 hr) while MI is still evolving and other considerations have made i.v. route preferable over intracoronary. The benefits of i.v. thrombolytic therapy have been established by large multicentric studies. Heparin with or without aspirin is generally started concurrently or soon after thrombolysis to prevent reocclusion.

Alteplase may have advantages over streptokinase, including higher thrombolytic efficacy. However, incidence of haemorrhage is not lower; may even be higher. Its stronger lytic effect on physiological haemostatic plugs may compensate for the lesser systemic fibrinolytic state.

Fibrinolytic therapy has also been used in unstable angina, because many such patients have coronary thrombi.

2. *Deep vein thrombosis* in leg, pelvis, shoulder etc.; upto 60% patients can be successfully treated. The main advantage is preservation of venous valves and may be a reduced risk of pulmonary embolism, but clearcut evidence for this is lacking.

3. *Pulmonary embolism* Fibrinolytic therapy is indicated in large, life threatening pulmonary embolism. The lung function may be better preserved, but reduction in mortality is not established.

4. *Peripheral arterial occlusion* Fibrinolytics recanalise ~40% limb artery occlusions, specially those treated within 72 hr. However,

it is indicated only when surgical thrombectomy is not possible. Regional intraarterial fibrinolytics have been used for limb arteries with greater success. Peripheral arterial thrombolysis is followed by short-term heparin and long-term aspirin therapy.

Fibrinolytics have no role in chronic peripheral vascular diseases.

Evaluation Thrombolytic therapy is expensive, complex, requires skill, experience and other intensive care facilities. Haemorrhage is the main complication; its incidence is related to duration of drug infusion. Shorter course protocols are now being used in MI and are associated with less bleeding episodes. However, longer courses are needed for deep vein thrombosis and pulmonary embolism; incidence of bleeding is higher. With concurrent use of heparin, major bleeding (including cerebral haemorrhage) occurs in 2–4% patients. The incidence of bleeding is similar with streptokinase, urokinase and alteplase. Some recent trials have shown that exclusion of heparin reduces bleeding and that it affords no extra benefit over fibrinolytic + aspirin. The Global Utilization of Streptokinase and t-PA for Occluded coronary arteries (GUSTO) megatrial has shown that alteplase with heparin affords better survival benefit than streptokinase + heparin, but most prefer streptokinase due to lower cost and less major bleeding.

Thrombolytic therapy is contraindicated in all situations where the risk of bleeding is increased, such as—recent trauma, surgery, biopsies, stroke or peptic ulcer, severe hypertension, aneurysms, bleeding disorders, diabetes, acute pancreatitis etc. It is not recommended for stroke, and its use in retinal vessel occlusion has been abandoned.

ANTIFIBRINOLYTICS

These are drugs which inhibit plasminogen activation and dissolution of clot.

Epsilon amino-caproic acid (EACA) It is an analogue of the amino acid lysine: combines with the lysine binding sites of plasminogen and plasmin so that the latter is not able to bind to fibrin and lyse it. It is a specific antidote for fibrinolytic agents and has been used in many hyperplasminemic states associated with excessive intravascular fibrinolysis resulting in bleeding, e.g.:

- Overdose of streptokinase/urokinase/alteplase.
- To prevent recurrence of subarachnoid and g.i. haemorrhage.

- Certain traumatic and surgical bleedings (prostatectomy, tooth extraction in haemophiliacs).
- Abruptio placentae, PPH and certain cases of menorrhagia.

However, the usefulness of EACA in most of the above conditions is equivocal, except in overdose of fibrinolytics. In haematuria it can cause ureteric obstruction by the unlysed clots. Therefore, fibrinolysis must be established firmly before using it. It can cause intravascular thrombosis. Rapid i.v. injection results in hypotension, bradycardia and may be arrhythmias. It should be used cautiously when renal function is impaired. Myopathy occurs rarely.

Initial priming dose is 5 g oral/i.v., followed by 1 g hourly till bleeding stops (max. 30 g in 24 hrs).

AMICAR, HEMOCID, HAMOSTAT 0.5 g tab., 1.25 g/5 ml syr., 5 g/20 ml inj.

Tranexaemic acid Like EACA it binds to the lysine binding site on plasminogen and prevents its combination with fibrin and is 7 times more potent. It has been used for prevention of excessive bleeding in:

- Overdose of fibrinolytics
- After cardio-pulmonary bypass surgery.
- After tonsillectomy, prostatic surgery, tooth extraction in haemophiliacs.
- Menorrhagia, specially due to IUCD.
- Recurrent epistaxis, ocular trauma, bleeding peptic ulcer.

Main side effects are nausea and diarrhoea. Headache, giddiness and thromboflebitis of injected vein are other adverse effects.

Dose: 10–15 mg/kg 2-3 times a day or 1–1.5 g TDS oral, 0.5–1 g TDS by slow i.v. infusion. CYCLOKAPRON 500 mg tab, 100 mg/ml inj.

Aprotinin It is a polypeptide isolated from bovine tissues with polyvalent protease inhibitory activity: trypsin, chymotrypsin, kallikrein and plasmin are inhibited. It can be administered only i.v. and has a t½ of 2 hr. It has been employed in selected situations:

Administered at the beginning of cardiopulmonary bypass surgery—it reduces blood loss.

Traumatic, haemorrhagic and endotoxic shock—has adjuvant value.

Acute pancreatitis (trypsin may be released in circulation which may be fatal).

Fibrinolytic states, prostatic surgery, carcinoid: may afford symptomatic relief.

Dose: 5 lac KIU (Kallikrein inactivator unit) initially, followed by 2 lac KIU every 4 hr, all as slow iv. infusion; TRASYLOL INF 5 lac KIU in 50 ml inj; APROGEN 1 lac KIU (10 ml) and 5 lac KIU (50 ml) inj.

ANTIPLATELET DRUGS (Antithrombotic Drugs)

These are drugs which interfere with platelet function and may be useful in the prophylaxis of thromboembolic disorders.

Platelets stick to the damaged vessel wall, then they stick to each other (aggregate) and release ADP, thromboxane A_2 (TXA_2) which promote further aggregation. Thus, a 'platelet plug' is formed. In veins, due to sluggish blood flow, a fibrinous tail is formed which traps RBCs 'the red tail'. In arteries, platelet mass is the main constituent of the thrombus. Antiplatelet drugs are, therefore, more useful in arterial thrombosis, while anticoagulants are more effective in venous thrombosis.

Prostacyclin (PGI_2), synthesized in the intima of blood vessels, is a strong inhibitor of platelet aggregation. A balance between TXA_2 released from platelets and PGI_2 released from vessel wall appears to control intravascular thrombus formation. Platelets also play a role in atherogenesis. Drugs interfering with platelet function are:

Aspirin	Clopidogrel
(other NSAIDs)	Abciximab
Dipyridamole	(GP IIb/IIIa antagonist)
Ticlopidine	

Aspirin It acetylates and inhibits the enzyme cyclooxygenase and TX-synthetase—inactivating them irreversibly. Because platelets are exposed to aspirin in the portal circulation before it is deacetylated during first pass in liver and because platelets cannot synthesize fresh enzyme (have no nuclei) TXA_2 formation is suppressed at very low doses and till fresh platelets are formed. Thus, aspirin induced prolongation of bleeding time lasts 5–7 days. Effect of daily doses cumulates and it has now been shown that doses as low as 40 mg/day are effective and maximal inhibition of platelet function occurs at ~160 mg aspirin per day.

Aspirin also inhibits PGI_2 synthesis in vessel wall. However, since intimal cells can synthesize fresh enzyme, activity returns rapidly. It is possible that at low doses (75–150 mg/day or 300 mg twice weekly)

TXA_2 formation by platelets is selectively suppressed, whereas higher doses (> 900 mg/day) may decrease both TXA_2 and PGI_2 production.

Aspirin inhibits the release of ADP from platelets and their sticking to each other. However, it has no effect on platelet survival time and their adhesion to damaged vessel wall.

ASA 50 mg tab., COLSPRIN, DISPRIN CV-100: aspirin 100 mg soluble tab, LOPRIN 75 mg tab, ASPICOT 80 mg tab, ECOSPRIN 75, 150 mg tab.

Other NSAIDs are reversible inhibitors of COX, produce short lasting inhibition of platelet function—are not clinically useful.

Dipyridamole It is a vasodilator which was introduced for angina pectoris. It inhibits phosphodiesterase and blocks uptake of adenosine to increase platelet cAMP which potentiates PGI_2 and interferes with aggregation. Levels of TXA_2 or PGI_2 are not altered but platelet survival time reduced by disease is normalized.

Dipyridamole alone has little clinically significant effect, but improves the response to warfarin, along with which it is used to decrease the incidence of thromboembolism in patients with prosthetic heart valves.

Dipyridamole has also been used to enhance the antiplatelet action of aspirin, but trials have failed to demonstrate additional benefit in prophylaxis of MI. Risk of stroke in patients with transient ischaemic attacks (TIAs) may be additively reduced.

Dose: 150–300 mg/day. PERSANTIN, 25, 100 mg tabs, THROMBONIL 75, 100 mg tabs, DYNASPRIN: dipyridamole 75 mg + aspirin 60 mg e.c. tab.; THROMBOSPRIN: dipyridamole 75 mg + aspirin 100 mg tab.

Ticlopidine It is the first thienopyridine which alters surface receptors on platelets and inhibits ADP as well as fibrinogen induced platelet aggregation. The Gi coupled $P2Y_{AC}$ type of purinergic receptors which mediate adenylyl cyclase inhibition by ADP are blocked by ticlopidine. As a result, activation of platelets is interfered. It prevents fibrinogen binding to platelets without modifying GPIIb/IIIa receptor. There is no effect on platelet TXA_2, but bleeding time is prolonged and platelet survival in extra-corporeal circulation is increased. Because of different mechanism of action, it has synergistic effect on platelets with aspirin: combination is a potent platelet inhibitor.

Ticlopidine is well absorbed orally, is converted in liver to an active metabolite, cumulates in the body—peak antiplatelet effect is produced after 8–10 days therapy. The plasma t½ after single dose is 8 hr, but after multiple doses it is 8 days.

Ticlopidine has produced beneficial effects in stroke prevention, TIAs, intermittent claudication, unstable angina, coronary artery bypass grafts and secondary prophylaxis of MI. Combined with aspirin it has markedly lowered incidence of restenosis after percutaneous transluminal coronary angioplasty (PTCA) and stent thrombosis.

Side effects: Diarrhoea, vomiting, abdominal pain, headache, tinnitus, skin rash, bleeding, rarely neutropenia, thrombocytopenia and jaundice.

Dose: 250 mg BD with meals; effect persists several days after discontinuation; TYKLID, TICLOVAS, TICLOP, 250 mg tab; ASTIC ticlopidine 250 mg + aspirin 100 mg tab.

Clopidogrel This newer congener of ticlopidine has similar mechanism of action, ability to inhibit platelet function and therapeutic efficacy, but appears to be better tolerated (CLASSICS study). The clopidogrel *vs* aspirin in patients at risk of ischaemic events (CAPRIE) trial has found clopidogrel recipients to have a slightly lower annual risk of primary ischaemic events than aspirin recipients. A lower frequency of neutropenia and thrombocytopenia compared to ticlopidine has been recorded till date. Side effects are diarrhoea, epigastric pain and rashes.

Clopidogrel + aspirin is as effective in stented patients as ticlopidine + aspirin. Clopidogrel is 50% absorbed orally and like ticlopidine, it is a prodrug.

Dose: 75 mg OD; CLODREL, CLOPILET, DEPLATT 75 mg tab.

Glycoprotein (GP) llb/llla receptor antagonists GP IIb/IIIa antagonists are a new class of potent platelet aggregation inhibitors which act by blocking the key receptor involved in platelet aggregation. The GP IIb/IIIa is an adhesive receptor (integrin) for fibrinogen and von Willebrand factor through which agonists like collagen, thrombin, TXA_2, ADP, etc. induce platelet aggregation. Agonist action induces binding of fibrinogen and von Willebrand factor to platelet surface which anchor them to each other and to damaged surfaces. Thus GP IIb/IIIa antagonists block aggregation induced by all platelet agonists.

Abciximab It is the Fab fragment of a chimeric monoclonal antibody against GP IIb/IIIa. Given along with aspirin + heparin during

PTCA it has markedly reduced the incidence of restenosis, subsequent MI and death. After a bolus dose platelet aggregation remains inhibited for 12–24 hr, while the remaining antibody is cleared from blood with a t½ of 10–30 min.

Dose: 0.25 mg/kg i.v. 10–60 min before PTCA, followed by 10 μg/min for 12 hr. REOPRO 2 mg/ml inj.

Abciximab is nonantigenic. The main risk is haemorrhage, incidence of which can be reduced by carefully managing the concomitant heparin therapy. Thrombocytopenia is another complication. Constipation, ileus and arrhythmias can occur. It is very expensive, but is being tried in unstable angina and as adjuvant to coronary thrombolysis.

Eptifibatide and Tirofiban are peptide GP IIb/IIIa receptor antagonists, developed as alternatives to abciximab.

Uses of antiplatelet drugs

1. ***Coronary artery disease MI:*** Low dose aspirin started immediately after MI has been found to reduce mortality and prevent reinfarction. It also improves survival when used along with thrombolytic therapy, with or without heparin. Ticlopidine and clopidogrel are alternatives.

Aspirin is now routinely used to prevent reocclusion after thrombolytic therapy. It is also given along with heparin to cover PTCA, and then continued indefinitely. Ticlopidine, clopidogrel or abciximab used along with aspirin have markedly improved the outcome of PTCA and stent procedures.

Unstable angina Aspirin reduces the risk of MI and sudden death in patients with unstable angina. For maximum benefit aspirin (100–150 mg / day) is given along with heparin—followed by warfarin. Ticlopidine or clopidogrel can be used as alternatives or adjuvant to aspirin.

Primary and secondary prevention of MI On the basis of trials in post-MI as well as in those with no such history, it has been recommended that aspirin 75–150 mg/day be given to all individuals with evidence of coronary artery disease and in those with risk factors for the same, but routine use in the whole population is not warranted. Aspirin reduces the incidence of fatal as well as nonfatal MI, but increases the risk of cerebral haemorrhage; overall mortality is marginally reduced.

2. ***Cerebrovascular disease*** Antiplatelet drugs do not alter the course of stroke due to cerebral thrombosis. However, aspirin has reduced the incidence of TIAs, of stroke in patients with TIAs or persis-

tent atrial fibrillation and in those with history of stroke in the past. It is recommended in all such individuals. Ticlopidine and clopidogrel also reduce TIAs and stroke.

3. ***Coronary bypass implants*** The patency of implanted bypass vessel is improved and incidence of reocclusion is reduced by aspirin and/or ticlopidine/clopidogrel.

4. ***Prosthetic heart valves and arteriovenous shunts*** Antiplatelet drugs, used with warfarin reduce formation of microthrombi on artificial heart valves and the incidence of embolism. Aspirin is clearly effective but increases risk of bleeding due to warfarin. Dipyridamole does not increase bleeding risk, but used alone its efficacy has been doubted. Incidence of thromboembolism is reduced when dipyridamole is combined with an oral anticoagulant. Antiplatelet drugs also prolong the patency of chronic arteriovenous shunts implanted for haemodialysis and of vascular grafts.

5. ***Venous thromboembolism*** Anticoagulants are routinely used. Trials have shown antiplatelet drugs also to have a prophylactic effect, but their relative value in comparison to or in addition to anticoagulants is not known.

6. ***Peripheral vascular disease*** Aspirin/'ticlopidine/clopidogrel may produce some improvement in intermittent claudication and reduce the incidence of thromboembolism.

DRUGS FOR PEPTIC ULCER

Peptic ulcer occurs in that part of the gastrointestinal tract (g.i.t.) which is exposed to gastric acid and pepsin, i.e., the stomach and duodenum. The etiology of peptic ulcer is not clearly known. It results probably due to an imbalance between the *aggressive* (acid, pepsin and H. *pylori)* and the *defensive* (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, innate resistance of the mucosal cells) factors. A variety of psychosomatic, humoral and vascular derangements have been implicated and the importance of *Helico-bacter pylori* infection as a contributor to ulcer formation and recurrence has been recognized.

In *gastric ulcer,* generally acid secretion is normal or low. In *duodenal ulcer,* acid secretion is high in half of the patients but normal in the rest. Notwithstanding whether production of acid is normal or high, it does contribute to ulceration as an aggressive factor, reduction of which is the main approach to ulcer treatment. An understanding of the mechanism and control of gastric acid secretion will elucidate the targets of antisecretory drug action.

Regulation of Gastric Acid Secretion

The terminal enzyme H^+K^+ATPase (proton pump) which secretes H^+ ions in the apical canaliculi of parietal cells can be activated by histamine, ACh and gastrin acting *via* their own receptors located on the basolateral membrane of these cells. Out of the three physiological secretagogues, histamine, acting through H_2 receptors, plays the dominant role, because the other two, gastrin and ACh act partly directly and partly indirectly by releasing histamine from paracrine enterochromaffin like cells called "histaminocytes" located in the oxyntic glands. While H_2 receptors activate H^+K^+ATPase by generating cAMP, muscarinic and gastrin /cholecystokinin (CCK_2) receptors appear to function through the phospholipase C → IP_3-DAG pathway that mobilizes intracellular Ca^{2+}. The cAMP mediated proton pump activation also involves Ca^{2+}. The secretomotor response to gastrin and cholinergic agonists is expressed fully only in the presence of cAMP generated by H_2 activation. As such, histamine participates in the acid response to gastrin and ACh at more than one levels, and H_2 antagonists suppress not only histamine but also ACh, pentagastrin and in fact any gastric acid secretory stimulus.

Gastrin is secreted from the antrum in response to rise in antral pH, food constituents and vagally mediated reflexes. The dominant muscarinic receptor mediating vagal responses is of the M_1 subtype. Its location on the ganglion cells of the intramural plexuses has been confirmed. The parietal cell muscarinic receptor is of the M_3 subtype but the subtype of muscarinic receptor on histaminocytes has not been defined. Vagus releases ACh in close proximity to histaminocytes and gastrin secreting cells, but apparently at a distance from the parietal cells. As such, vagal effects are exerted largely indirectly through histamine and gastrin.

Prostaglandins have been ascribed a "cytoprotective" role in the gastric mucosa by augmenting mucus and bicarbonate secretion, as well as other actions. PGE_2, produced by gastric mucosa, inhibits acid secretion by opposing cAMP generation (in parietal cells) and gastrin release (from antral cells).

Approaches for the treatment of peptic ulcer are:

1.*Reduction of gastric acid secretion*

(a) *H_2 antihistamines:* Cimetidine, Ranitidine, Famotidine, Roxatidine, Loxatidine

(b) *Proton pump inhibitors:* Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole

(c) *Anticholinergics:* Pirenzepine, Propanthe-line, Oxyphenonium

(d) *Prostaglandin analogues:* Misoprostol, Enprostil, Rioprostil

2. *Neutralization of gastric acid (Antacids)*

(a) *Systemic:* Sodium bicarbonate, Sod. citrate

(b) *Nonsystemic:* Magnesium hydroxide, Mag. trisilicate, Aluminium hydroxidegel, Magaldrate, Calcium carbonate

3. *Ulcer protectives:* Sucralfate, Colloidal bismuth subcitrate (CBS)

4. *Ulcer healing drugs:* Carbenoxolone sodium

5. *Anti-H. pylori drugs:* Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline

H_2 ANTAGONISTS

These are the first class of highly effective drugs for acid-peptic disease. Four H_2 antagonists cimetidine, ranitidine, famotidine and roxatidine are available in India; many others are marketed elsewhere. Their interaction with H_2 receptors has been found to be competitive

in case of cimetidine, ranitidine and roxatidine; competitive-noncompetitive in case of famotidine and noncompetitive with loxatidine. Cimetidine was the first H_2 blocker to be introduced clinically and is described as the prototype.

PHARMACOLOGICAL ACTIONS

1. **H_2 blockade** Cimetidine and all other H_2 antagonists block histamine induced gastric secretion, cardiac stimulation (prominent in isolated preparations, specially in guineapig), uterine relaxation (in rat) and bronchial relaxation (H_2 blockers potentiate histamine induced bronchospasm). They attenuate fall in BP due to histamine, specially the late phase response seen with high doses. They are highly selective: have no effect on H_1 mediated responses or on action of other transmitters/autacoids.

2. **Gastric secretion** The only significant *in vivo* action of H_2 blockers is marked inhibition of gastric secretion. All phases (basal, psychic, neurogenic, gastric) of secretion are suppressed dose dependently. Secretory responses to not only histamine but all other stimuli (ACh, gastrin, insulin, alcohol, food) are attenuated. This reflects the permissive role of histamine in amplifying responses to other secretagogues. The most prominent action is on basal acid output, but volume, pepsin content and intrinsic factor secretion are also reduced. However, normal vit B_{12} absorption is not interfered: no vit B_{12} deficiency occurs even after prolonged use.

The usual ulcer healing doses produce 60–70% inhibition of 24hr acid output. The H_2 blockers have antiulcerogenic effect. Gastric ulceration due to stress and drugs (NSAIDs, cholinergic, histaminergic) is prevented. They do not have any direct effect on gastric or esophageal motility or on lower esophageal sphincter (LES) tone.

PHARMACOKINETICS

Cimetidine is adequately absorbed orally, though bioavailability is 60-80% due to first pass hepatic metabolism. Its absorption is not interfered by presence of food in stomach. It crosses placenta and reaches milk, but penetration in brain is poor because of its hydrophilic nature. About ⅔ of a dose is excreted unchanged in urine and bile, the rest as oxidized metabolites. The elimination t½ is 2-3 hr. Dose reduction is needed in renal failure.

ADVERSE EFFECTS

Cimetidine is well tolerated by most patients: adverse effects occur in ~5%. These are generally mild.

- Headache, dizziness, bowel upset, dry mouth, rashes.
- CNS effects like confusional state, restlessness, hallucinations, delirium, convulsions and coma have occurred in elderly patients, in those with renal impairment, specially with large doses infused i.v.
- Bolus i.v. injection can release histamine—has caused bradycardia, arrhythmias and cardiac arrest: it should always be given by slow infusion.
- Cimetidine (but not other H_2 blockers) has antiandrogenic action (displaces dihydrotestosterone from its cytoplasmic receptor), increases plasma prolactin and inhibits degradation of estradiol by liver. High doses given for long periods have produced gynaecomas-tia, loss of libido, impotence and temporary decrease in sperm count.
- Fever and transient neutropenia occur rarely (not reported with other H_2 blockers).
- Transient elevation of plasma aminotransferases; but hepatotoxicity is rare.

INTERACTIONS

Cimetidine inhibits cytochrome P-450 and reduces hepatic blood flow. It inhibits the metabolism of many drugs so that they can accumulate to toxic levels, e.g. theophylline, phenytoin, phenobarbitone, sulfonylureas, metronidazole, warfarin, imipramine, lignocaine, nifedipine, quinidine, mexiletine. Metabolism of propranolol and diazepam is also retarded, but this may not be clinically significant.

Antacids reduce absorption of all H_2 blockers. When used concurrently a gap of 2hr should be allowed.

Ketoconazole absorption is decreased by cimetidine (probably by other H_2 blockers also).

USES

The H_2 blockers are widely used in conditions in which it is profitable to suppress gastric acid secretion. Used in appropriate doses, all available agents have similar efficacy. Though other forms of therapy are sometimes equally effective, the H_2 blockers are preferred because of convenience and good patient acceptability.

1. *Duodenal ulcer* Cimetidine 400 mg BD or 800 mg at bed time produces rapid and marked pain relief (within 2–3 days). It heals 60–85% ulcers at 4 weeks and 70–95% ulcers at 8 weeks.

Suppression of nocturnal secretion by single high bed time dose is equally efficacious and physiologically more sound (continuous achlor-hydria is considered undesirable—may promote microbial colonization of stomach; overgrowth of nitrosobacteria may predispose to gastric carcinoma). About ½ of the patients relapse within 1 year of healing with H_2 blockers. Maintenance therapy with 400 mg at bed time reduces the relapse rate to 15–20% per year. However, when such treatment is withdrawn relapses occur with the same frequency.

2. *Gastric ulcer* Healing rates obtained in gastric ulcer are somewhat lower (50–75% at 8 weeks); more patients require full 8 weeks therapy. However, doses remain the same.

Maintenance therapy reduces recurrences as long as continued. H_2 blockers can heal NSAID associated ulcers, but are less effective than proton pump inhibitors or misoprostol. H_2 blockers (i.v. or oral) are commonly administered in bleeding peptic ulcer, but benefits are uncertain.

3. *Stress ulcers and gastritis* Acutely stressful situations like hepatic coma, severe burns and trauma, prolonged surgery, renal failure, asphyxia neonatorum etc. are associated with gastric erosions and bleeding. Intravenous infusion of cimetidine (50 mg/hr) or equivalent H_2 blockade successfully prevents the gastric lesions and haemorrhage.

4. *Zollinger-Ellison syndrome* It is a gastric hypersecretory state due to a rare tumour secreting gastrin. Cimetidine in high doses controls hyperacidity and symptoms in many patients, but relief is often incomplete and side effects frequent. Proton pump inhibitors (PPIs) are the drugs of choice. Definitive treatment is surgical.

5. *Gastroesophageal reflux disease (GERD)* H_2 blockers afford symptomatic relief and facilitate healing of esophageal erosions by reducing acidity of gastric contents that are refluxed; long term treatment preferably with 2–3 divided daily doses is needed. However, they are less effective in this condition than PPIs; are indicated only in mild or stage-1 cases of GERD.

6. *Prophylaxis of aspiration pneumonia* H_2 blockers given preoperatively (preferably evening before also) reduce the risk of aspiration of acidic gastric contents during anaesthesia and surgery.

7. *Other uses* H_2 blockers have adjuvant beneficial action in certain cases of urticaria who do not adequately respond to an H_1 antagonist alone.

CIMETIDINE, 200 mg, 400 mg, 800 mg tabs, 200 mg/2 ml inj., LOCK-2 200 mg tab.

Ranitidine Introduced subsequent to cimetidine as a nonimidazole (has a furan ring) H_2 blocker, it has several desirable features compared to cimetidine:

- About 5 times more potent than cimetidine. Though its pharmacokinetic profile and t½ of 2–3 hr is similar to cimetidine, a longer duration of action with greater 24 hr acid suppression is obtained clinically because of higher potency. Some patients not improving with the usual doses of cimetidine have responded to ranitidine.
- No antiandrogenic action, does not increase prolactin secretion or spare estradiol from hepatic metabolism—no effect on male sexual function or gynaecomastia.
- Lesser permeability into the brain: lower propensity to cause CNS effects. Infact little effect outside g.i.t. has been observed.
- Does not significantly inhibit hepatic metabolism of other drugs; drug interactions have been reported, but mostly have no clinical relevance.
- Overall incidence of side effects is lower: headache, diarrhoea/constipation, dizziness have an incidence similar to placebo. Rashes are infrequent. Hepatic injury, CNS effects and haematological changes are rare: mostly seen in the elderly and seriously ill patients.

Dose: for ulcer healing 300 mg at bed time or 150 mg BD; for maintenance 150 mg at bed time. Parenteral dose—50 mg i.m. or slow i.v. inj. every 6–8 hr (rapid i.v. injection can cause hypotension), 0.1–0.25 mg/kg/hr by i.v. infusion has been used for prophylaxis of stress ulcers. For gastrinoma 300 mg 3–4 times a day.

ULTAC, ZINETAC 150 mg, 300 mg tabs; HISTAC, RANITIN, ACILOC, RANTAC 150 mg, 300 mg tabs, 50mg/2 ml inj.

Famotidine A thiazole ring containing H_2 blocker which binds tightly to H_2 receptors and exhibits longer duration of action despite an elimination t½ of 2.5–3.5 hr. It is 5–8 times more potent than ranitidine. It has no antiandrogenic action. Because of low-affinity for cytochrome P450 and the low dose, drug metabolism rnodifying propensity is minimal. Duodenal ulcer healing rates with famotidine are similar to or better than cimetidine.

The oral bioavailability of famotidine is 40–50% and it is excreted by the kidney, 70% in the unchanged form. Incidence of adverse effects is low: only headache, dizziness, bowel upset, rarely disorientation and rash have been reported. Because of the higher potency and longer duration, it has been considered more suitable for ZE syndrome and for prevention of aspiration pneumonia.

Dose: 40 mg at bed time or 20 mg BD (for healing); 20 mg at bed time for maintenance; upto 480 mg/day in ZE syndrome; parenteral dose 20 mg i.v. 12 hourly.

FAMTAC, FAMONITE, TOPCID 20 mg, 40 mg tabs; FAMOCID, FACID 20, 40 mg tabs, 20 mg/2 ml inj..

Roxatidine The pharmacodynamic, pharmacokinetic and side effect profile of roxatidine is similar to that of ranitidine, but it is twice as potent and longer acting. It has no anti-androgenic or cytochrome P450 inhibitory action.

Dose: 150 mg at bed time or 75 mg BD; maintenance 75 mg at bed time.

ROTANE, ZORPEX 75 mg, 150 mg SR tabs.

Loxatidine A recently developed powerful noncom-petitive H_2 antagonist which can produce almost complete inhibition of gastric secretion. Its position in comparison to other H_2 blockers is not established.

PROTON PUMP INHIBITORS (PPIs)

Omeprazole It is the prototype member of substituted benzimidazoles which inhibit the final common step in gastric acid secretion and have overtaken H_2 blockers for acid-peptic disorders. The only significant pharmacological action of omeprazole is dose dependent suppression of gastric acid secretion; without anticholinergic or H_2 blocking action. It is a powerful inhibitor of gastric acid: can totally abolish HC1 secretion, both resting as well as that stimulated by any of the secretagogues, without much effect on pepsin, intrinsic factor, juice volume and gastric motility.

Omeprazole is inactive at neutral pH, but at pH < 5 rearranges to two charged cationic forms (a sulphenic acid and a sulphenamide configurations) that react covalently with SH groups of the H^+K^+ATPase enzyme and inactivate it irreversibly, specially when two molecules of omeprazole react with one molecule of the enzyme. After diffusing into the parietal cell from blood it gets concentrated in the acidic pH

of the canaliculi because the charged forms generated there at the acidic pH are unable to diffuse back. Moreover it gets tightly bound to the enzyme. These features and the specific localization of H^+K^+ATPase to apical membrane of the parietal cells confer high degree of selectivity of action to omeprazole. Acid secretion resumes only when new H^+K^+ATPase molecules are synthesized. It also inhibits gastric mucosal carbonic anhydrase.

The oral absorption of omeprazole is ~50%, because of instability at acidic pH. As the gastric pH rises a higher fraction (upto ¾) may be absorbed. It is highly plasma protein bound, rapidly metabolised in liver by CYP2C19 and CYP3A4 (plasma t½ ~1 hr) and metabolites excreted in urine. No dose modification is required in elderly or in renal/hepatic impairment. Because of tight binding to its target enzyme—it can be detected in the gastric mucosa long after its disappearance from plasma. As such, inhibition of HC1 secretion occurs within 1 hr, reaches maximum at 2 hr, is still half maximal at 24 hr and lasts 3 days. With daily administration antisecretory effect increases till 4th day after which it plateus. Secretion resumes gradually over 3–5 days of stopping the drug.

Because of marked and long lasting acid suppression, compensatory hypergastrinemia has been observed. This has been found to induce proliferation of parietal cells and gastric carcinoid tumours in rats, but not in human beings. Though patients have been treated continuously for > 11 years without any problem, it may appear prudent to be apprehensive of prolonged hypergastrinemia and if possible avoid long term use of proton pump inhibitors.

Uses

1. *Peptic ulcer* Omeprazole 20 mg OD is equally or more effective than H_2 blockers. Relief of pain is rapid and excellent. Faster healing has been demonstrated with 40 mg/day: some duodenal ulcers heal even at 2 weeks and the remaining at 4 weeks. Gastric ulcer generally requires 4–8 weeks. It has caused healing of ulcers in patients not responding to H_2 blockers. Continued treatment (20 mg daily or thrice weekly) can prevent relapse. PPIs are an integral component of anti-H. *pylori* therapy. PPI_S are the drugs of choice for NSAID induced gastric/duodenal ulcers.

There is some evidence that PPIs may help control bleeding from peptic ulcer. They are probably more effective than H_2 blockers in this

setting; i.v. pantoprazole is preferred. Intravenous pantoprazole is as effective prophylactic (if not more) for stress ulcers as i.v. H_2 blockers.

2. *Gastroesophageal reflux disease (GERD)* It produces rapid symptom relief and is more effective than H_2 blockers in promoting healing of esophageal lesions. PPIs are the drugs of choice for patients with frequent or chronic symptoms and/or esophagitis/erosions; ie. stage-2 or stage-3 GERD. Dose: 20–60 mg OD. Many patients require continued therapy since cause is not corrected.

3. *Zollinger-EHison syndrome* Omeprazole is more effective than H_2 blockers in controlling hyperacidity in Z-E syndrome. However, 60–120 mg/day or more (in 2 divided doses) is often required for healing of ulcers. Inoperable cases have been treated for >6 years with sustained benefit and no adverse effects. Other gastric hypersecretory states like systemic mastocytosis, endocrine adenomas etc. also respond well. OMIZAC, NILSEC 20 mg cap. OMEZ, OCID, OMEZOL, 10, 20 mg caps, PROTOLOC 20, 40 mg caps containing enteric coated granules. Capsules must not be opened or chewed; to be taken in the morning before meals.

Adverse effects These are minimal: nausea, loose stools, headache, abdominal pain, muscle and joint pain, dizziness are complained by 3–5%. Rashes (1.5% incidence), leucopenia and hepatic dysfunction are infrequent. On pro-longed treatment atrophic gastritis has been reported occasionally.

Interactions Omeprazole inhibits oxidation of certain drugs: diazepam, phenytoin and warfarin levels may be increased.

Lansoprazole Somewhat more potent than omeprazole but similar in properties. Inhibition of H^+ K^+ ATPase by lansoprazole is partly reversible. It has been shown to have greater inhibitory effect on *H. pylori* than omeprazole. It has higher oral bioavailability, faster onset of action and slightly longer t½ than omeprazole. Dose should be reduced in liver disease. Side effects are similar, but drug interactions appear to be less significant; diazepam and phenytoin metabolism may be reduced. Ulcer healing dose: 15–30 mg OD; LANZOL, LANZAP, LEVANT, LANPRO 15, 30 mg caps.

Pantoprazole It is a newer H^+ K^+ ATPase inhibitor, similar in potency and clinical efficacy to omeprazole, but is more acid stable and less active at higher pH. It is the only PPI available for i.v. administra-

tion; particularly employed in bleeding peptic ulcer and for prophylaxis of acute stress ulcers. It has lower affinity for cytochrome P450 than omeprazole or lansoprazole: risk of drug interactions is minimal. Dose: 40 mg OD; PANTOCID, PANTODAC 40 mg enteric coated tab; PANTIUM 40 mg tab, 40 mg inj for i.v. use.

Rabeprazole This newer PPI is claimed to cause fastest acid suppression and to aid gastric mucin synthesis. However, potency and efficacy are similar to omeprazole.

Dose: 20 mg OD; ZE syndrome—60 mg/day.

RABLET, RAZO 10, 20 mg tab.

Esomeprazole It is the S-enantiomer of omeprazole; claimed to produce better control of intragastric pH than omeprazole in GERD patients. Higher healing rates of erosive esophagitis and better GERD symptom relief nave been reported in comparative trials with omeprazole. It is as effective as omeprazole in healing gastric/duodenal ulcers and in inhibi-ting *H.pylori.* Side effect and drug interaction profile is also similar to the parent drug.

Dose: 20–40 mg OD; NEXPRO, IZRA 20, 40 mg tabs.

Antichounergics

Atropinic drugs reduce the volume of gastric juice without raising its pH unless there is food in stomach to dilute the secreted acid. Stimulated gastric secretion is less completely inhibited. They also delay gastric emptying. However, effective doses of nonselective antimuscarinics (atropine, propantheline, oxyphenonium) invariably produce intolerable side effects. They have been used in the past, but the introduction of H_2 blockers has sent them into oblivion.

Plrenzepine It is a selective M_1 anticholinergic that has been used in Europe for peptic ulcer. Gastric secretion is reduced without producing intolerable side effects. Usual doses inhibit acid secretion only by 40–50% (less than H_2 blockers) and its therapeutic dose range is narrow—side effects occur with slight excess. It has not been used in India and USA.

PROSTAGLANDIN ANALOGUES

PGE_2 and PGI_2 are produced in the gastric mucosa and appear to serve a protective role by inhibiting acid secretion and promoting mucus + HCO^-_3 secretion (*see* Ch. PROSTAGLANDINS, LEUKOTIENES AND PLATELET ACTIVATING FACTOR). In addition, PGs

inhibit gastrin production, increase mucosal blood flow and probably have an ill-defined "cytoprotective" action. However, the most important appears to be their ability to reinforce the mucus layer covering gastric and duodenal mucosa which is buffered by HCO^-_3 secreted into this layer by the underlying epithelial cells.

Natural PGs have very short t½. A number of stable PG analogues which exert action for hours rather than minutes have been developed for use in peptic ulcer and *misoprostol* (methyl-PGE_1 ester) has been released in India. It inhibits acid output dose dependently; 200 μg reducing basal secretion by ~90% and stimulated secretion by ~ 80%. Reduction in 24 hrs acid production is less than H_2 blockers because of shorter duration of action (~3 hr.) Ulcer healing rates comparable to cimetidine have been obtained in 4–8 weeks, but misoprostol is poorer in relieving ulcer pain. Some patients may even complain of increased pain during the first week of therapy, though pain relief at 4 weeks is similar to cimetidine. Maintenance therapy with misoprostol is less effective in preventing relapses.

Dose: 200 μg QID; CYTOLOG 200 μg tab; MISOPROST 100 μg, 200 μg tabs.

Major problems in the use of PG analogues are—diarrhoea, abdominal cramps, uterine bleeding, abortion, and need for multiple daily doses. Patient acceptability is poor.

The primary use of PG analogues is in the prevention and treatment of NSAID associated gastrointestinal injury and blood loss. Misoprostol heals ulcers in arthritis patients who have to continue using NSAIDs and who are not responding to H_2 blockers. It is an alternative to PPIs in such patients, and may also be useful in ulcer patients who continue to smoke.

Enprostil and *Rioprostil* have been used in some countries.

ANTACIDS

These are basic substances which neutralize gastric acid and raise pH of gastric contents. Peptic activity is indirectly reduced if the pH rises above 4, because pepsin is secreted as a complex with an inhibitory terminal moiety that dissociates below pH 5: optimum peptic activity is exerted between pH 2 to 4.

Antacids do not decrease acid production; rather, agents that raise the antral pH to > 4 evoke reflex gastrin release → more acid is se-

creted, specially in patients with hyperacidity and duodenal ulcer; "acid rebound" occurs and gastric motility is increased.

The potency of an antacid is generally expressed in terms of its *acid neutralizing capacity* (ANC), which is defined as number of mEq of 1N HCl that are brought to pH 3.5 in 15 min (or 60 min in some tests) by a unit dose of the antacid preparation. This takes into consideration the equivalent weight of the compound as well as the rate at which it dissolves and reacts with HC1. This is important because a single dose of any antacid taken in empty stomach acts for 30-60 min only, since in this time any gastric content is passed into duodenum. Taken with meals antacids may act for at the most 2-3 hr, but presence of food in the stomach also decreases the rate at which an antacid will neutralize HC1.

SYSTEMIC ANTACIDS

Sodium bicarbonate It is water soluble, acts instan-taneously, but the duration of action is short. It is a potent neutralizer (1 g → 12 mEq HC1), pH may rise above 7. However, it has several demerits:

(a) Absorbed systemically: large doses will induce alkalosis. This is compensated by secreting alkaline urine; in renal insufficiency blood pH will be dangerously raised.

(b) Produces CO_2 in stomach → distention, discornfort, belching, risk of ulcer perforation.

(c) Acid rebound occurs, but is usually short lasting.

(d) Increases Na^+ load: may worsen edema and CHF; contraindicated in cardiac disease, hypertension. Use of sod. bicarbonate is restricted to casual treatment of heart burn: provides quick symptomatic relief. Other uses are to alkalinize urine and to treat acidosis.

Sodium citrate Properties similar to sod. bicarbonate; 1 g neutralizes 10 mEq HC1; CO_2 is not evolved.

NONSYSTEMIC ANTACIDS

These are insoluble and poorly absorbed basic compounds; react in stomach to form the corresponding chloride salt. The chloride salt again reacts with the intestinal bicarbonate so that HCO^-_3 is not spared for absorption—no acid-base disturbance occurs. However, small amounts that are absorbed have the same alkalinizing effect as $NaHCO_3$.

Mag. hydroxide has low water solubility: its aqueous suspension (milk of magnesia) has low concentration of OH~ ions and thus low alkalinity. However, it reacts with HC1 promptly and is an efficacious antacid (1 g → 30 mEq HC1). Rebound acidity is mild and brief.

MILK OF MAGNESIA 0.4 g/5 ml suspension: 5 ml neutralizes 12 mEq acid.

Magnesium trisilicate has low solubility and reactivity; 1 g can react with 10 mEq acid, but in clinical use only about 1 mEq is neutralized before it is passed into duodenum; pH seldom rises above 3. Silica produced by reaction with HC1 is gelatinous: it is claimed to adsorb and inactivate pepsin and to protect the ulcer base. However, contribution of these actions to clinical benefit is minor. About 5% of administered Mg is absorbed systemically—may cause problem if renal function is inadequate. All Mg salts have a laxative action—by generating osmotically active $MgCl_2$ in the stomach and through Mg^{2+} ion induced cholecystokinin release. Soluble Mg salts are used as osmotic purgatives.

Aluminium hydroxide gel It is a bland, weak and slowly reacting antacid. On keeping it slowly polymerizes to variable extents into still less reactive forms. Thus, the ANC of a preparation gradually declines on storage. Also, the product from different manufacturers may have differing ANCs; usually it varies from 1–2.5 mEq/g. Thus, 5 ml of its suspension may neutralize just 1 mEq HC1. Its neutralizing action is markedly slowed by food in stomach. As such, little worthwhile acid neutralization is obtained at conventional doses. Acid rebound is minimal.

The $A1^{3+}$ ions relax smooth muscle. Thus, it delays gastric emptying while other antacids tend to hasten it. Alum, hydrox. frequently, causes constipation due to its smooth muscle relaxant and mucosal astringent action.

Alum, hydrox. adsorbs pepsin at pH > 3, but releases it at lower pH; thus it is capable of inactivating pepsin, though concurrent use of another more potent antacid may be needed for expression of this property. It is also a demulcent: has been claimed to coat and protect the ulcer crater. But, this has not been confirmed endoscopically. It binds phosphate in the intestine and prevents its absorption—hypophosphatemia occurs on regular use. This may:

(a) cause osteomalacia

(b) be used therapeutically in hyperphosphatemia and phosphate stones.

Small amount of Al^{3+} that is absorbed is excreted by kidney which is not possible in renal failure—aluminium toxicity (encephalopathy, osteoporosis) can occur.

ALUDROX 0.84 g tab, 0,6 g/10 ml susp.

Magaldrate It is a hydrated complex of hydroxymagnesium aluminate that initially reacts rapidly with acid and releases alum. hydrox. which then reacts more slowly. The freshly released alum, hydrox. is in the unpolymerized more reactive form. Thus, magaldrate cannot be equated to a physical mixture of mag. and alum. hydroxides. It is a good antacid with prompt and sustained neutralizing action. Its ANC is estimated to be 28 mEq HCl/g.

STACID 400 mg tab, 400 mg/5 ml susp.; ULGEL 400 mg with 20 mg simethicone per tab or 5 ml susp.

Calcium carbonate It is a potent and rapidly acting acid neutralizer (1 g → 20 mEq HC1), but ANC of commercial preparations is less and variable due to differing particle size and crystal structure. Though it liberates CO_2 in the stomach at a slower rate than $NaHCO_3$, it can cause distention and discomfort. The Ca^{2+} ions are partly absorbed: hypercalcaemia, hypercalciuria, alkalosis and formation of calcium stones in the kidney can occur on long term use.

The greatest drawback of $CaCO_3$ as an antacid is that Ca^{2+} ions diffuse into the gastric mucosa—increase HCl production directly by parietal cells as well as by releasing gastrin. Acid rebound is marked; total antacid requirement and gastric motiliry are increased. Cal. carbonate is constipating in most individuals, but in some it causes loose motions. The absorbed calcium can be dangerous in renal insufficiency.

Milk Alkali Syndrome In the past, large quantity of milk was prescribed with $CaCO_3$ (or $NaHCO_3$) for peptic ulcer.

Such regimen often produced a syndrome characterized by headache, anorexia, weakness, abdominal discomfort, abnormal Ca deposits and renal stones due to concurrent hypercalcaemia and alkalosis. It is rare now.

Antacid combinations A combination of two or more antacids is frequently used. These may be superior to any single agent on the following accounts:

(a) Fast (Mag. hydrox.) and slow (Alum, hydrox.) acting components yield prompt as well as sustained effect.

(b) Mag. salts are laxative while Alum, salts are constipating: combination may annul each other's action and bowel movement may be least affected.

(c) Gastric emptying is least affected; while Alum, salts tend to delay it, Mag./Cal. salts tend to hasten it.

(d) Dose of individual components is reduced; systemic toxicity (dependent on fractional absorption) is minimized.

Some available antacid combinations are:

ACIDIN: Mag. carb. 165 mg, dried alum, hydrox. gel 232 mg, cal. carb. 165 mg, sod. bicarb. 82 mg, with kaolin 105 mg and belladonna herb 30 μg per tab.

ALMACARB: Dried alum, hydrox. gel 325 mg, mag. carb. 50 mg, methyl polysilox. 40 mg, deglycyrrhizinated liquorice 380 mg per tab.

ALLUJEL-DF; Dried alum, hydrox. gel 400 mg, mag. hydrox. 400 ing, methyl polysilox. 30 mg per 10 ml susp.

DIGENE: Dried alum, hydrox. gel 300 mg, mag. alum, silicate 50 mg, mag. hydrox. 25 mg, methylpolysilox. 10 mg per tab.

DIGENE GEL: Mag, hydrox. 185 mg, alum, hydrox. gel 830 mg, sod. carboxymethyl cellulose 100 mg, methylpolysilox, 25 mg per 10 ml susp.

GELUSIL: Dried alum, hydrox. gel 250 mg, mag. trisilicate 500 mg per tab.

GELUSIL LIQUID: Mag, trisilicate 625 mg, alum, hydrox. gel 312 mg per 5 ml susp.

MUCAENE: Alum, hydrox. 290 mg, mag. hydrox. 98 mg, oxethazaine 10 mg per 5 rnl susp.

TRICAINE-MPS: Alum, hydrox. gel 300 mg, mag hydrox. 150 mg, oxethazaine 10 mg, simethicone 10 mg per 5 ml gel.

MAYLOX: Dried alum, hydrox. gel 225 mg, mag. hydrox. 200 mg, dimethicone 50 mg per tab and 5 ml susp.

POLYCROL FORTE GEL: Mag. hydrox. 100 mg, dried alum, hydrox. gel 425 mg, methylpolysilox. 125 mg per 5 ml susp.

Drug interactions By raising gastric pH and by forming complexes the non-absorbable antacids decrease the absorption of many drugs, specially tetracyclines, iron salts, fluoroquinolones, ketoconazole, H_2 blockers, diazepam, phe-nothiazines, indomethacin, phenytoin, isoniazid, ethambutol and nitrofurantoin. Stagger their administration by 2 hours. The efficacy of nitrofurantoin is also reduced by alkalinization of urine.

Uses

Antacids are no longer used for healing peptic ulcer because they are needed in large and frequent doses, are inconvenient, can cause acid rebound and bowel upset, afford little nocturnal protection and have poor patient acceptability. In view of the convenient and well tolerated single small dose of an H_2 blocker/PPI, antacids are now employed only for intercurrent pain relief and acidity, mostly self prescribed by the patients as over the counter preparations. They continue to be used for nonulcer dyspepsia and minor episodes of heartburn.

Liquid formulations of antacids are preferred over tablets. When used, tablets must be chewed and washed down with water. Methylpolysilo-xane is included in many antacid preparations. It is a surface active agent, collapses froth and is claimed to improve dispersion of the antacid and to reduce gastroesophageal reflux.

Gastroesophageal reflux In view of availability of more effective and convenient treatments, antacids are now used only off and on for prompt relief of acid eructation and heartburn. Raising the pH of gastric content reflexly improves lower esophageal sphincter (LES) tone.

ULCER PROTECTIVES

Sucralfate It is a basic aluminium salt of sulfated sucrose; a drug of its own kind. Sucralfate polymerizes at pH < 4 by cross linking of molecules, assuming a sticky gel like consistency. It preferentially and strongly adheres to ulcer base, specially duodenal ulcer; has been seen endoscopically to remain there for ~ 6 hours. It precipitates surface proteins at ulcer base and acts as a physical barrier preventing acid, pepsin and bile from coming in contact with the ulcer base. Dietary proteins get deposited on this coat, forming another layer.

Interaction of sucralfate polyanions with surface proteins of eroded mucosa interferes with binding of pepsin to digest them. It has no acid neutralizing action, but has been found to delay gastric emptying—its own stay in stomach is prolonged. Augmented gastric mucosal PG synthesis may supplement physical protective action of sucralfate.

Sucralfate is minimally absorbed after oral administration. It promotes healing of both duodenal and gastric ulcers, specially the former: efficacy has been found to be similar to cimetidine at 4 weeks. It is considered to be superior in patients who continue to smoke. Prevention of ulcer recurrence has also been demonstrated. However, su-

cralfate is infrequently used now because of need for 4 large well timed daily doses and the availability of simpler H_2 blockers/PPIs.

Dose The ulcer healing dose of sucralfate is 1 g taken 1 hour before the 3 major meals and at bed time for 4–8 weeks. To prevent recurrence, continue 1 g BD for 6 months or more. Antacids should not be taken with sucralfate because its polymerization is dependent on acid pH. ULCERFATE, SUCRACE, RECULFATE 1 g tab.

Side effects are few; constipation is reported by 2% patients. It has potential for inducing hypophosphatemia by binding phosphate ions in the intestine. Dry mouth and nausea are infrequent.

Other uses Bile reflux, gastritis, phosphate stones in the kidney are other uses.

As a suspension in glycerol, it has been tried in stomatitis. A topical formulation of sucralfate PEPSIGARD LIGHT GEL is available for application on burns, bedsores, diabetic/radiation ulcers, excoriated skin etc. as a protective.

Interactions Sucralfate adsorbs many drugs and has been shown to interfere with the absorption of tetracyclines, fluoroquinolones, cimetidine, phenytoin and digoxin. Antacids given concurrently reduce the efficacy of sucralfate.

Colloidal Bismuth Subcitrate (CBS; Tripotassium Dicitratobismuthate)

It is a colloidal bismuth compound; water soluble but precipitates at pH < 5. It is not an antacid but heals 60% ulcers at 4 weeks and 80–90% at 8 weeks. Many duodenal ulcers resistant to cimetidine heal by subsequent 4 weeks CBS treatment. The mechanism of action of CBS is not clear; probabilities are:

(i) Increased secretion of mucus and bicarbonate through stimulation of mucosal PGE_2 production.

(ii) CBS and mucus form a glycoprotein-Bi complex which coats the ulcer and acts as a diffusion barrier to HC1.

(iii) Detaches *H. pylori* from the surface of mucosa and directly kills this organism involved in causation of ulcers and relapses.

Gastritis and nonulcer dyspepsia associated with H. *pylori* are also improved by CBS. Recommended regimen for CBS is 120 mg (as Bi_2O_3) taken ½ hr before 3 major meals and at bed time for 4–8 weeks. Milk and antacids should not be taken concomitantly. TRYMO, DENOL 120 mg tab.

Most of the ingested CBS passes in the faeces. Small amounts absorbed are excreted in urine. Side effects reported are diarrhoea, headache and dizziness. Prolonged use has the potential to cause osteodystrophy and encephalopathy due to bismuth toxicity. Patient acceptance of CBS is compromised by blackening of tongue, dentures and stools; by variable and delayed symptom control and inconvenience of dosing schedule. Presently it is used occasionally as a component of triple drug anti-*H.pylori* regimen, but not by itself to heal peptic ulcer.

ULCER HEALING DRUGS

Carbenoxolone sodium It is a steroid like triterpenoid derivative of *glycyrrhetinic acid* (found in liquorice root), which was found to promote healing of gastric ulcer without altering the volume or acidity of gastric juice. Its most important action is augmentation of mucus production, specially the viscid mucus that remains adherent to the gastric mucosa. Other actions are—prolongation of lifespan of gastric epithelial cells, prevention of bile reflux and slowing of PG degradation in gastric mucosa.

The major problem with carbenoxolone is its mineralocorticoid action which results in Na^+ and water retention and K^+ loss.

The mineralocorticoid action can be counteracted by spironolactone, but strangely the therapeutic effect is also lost.

Though carbenoxolone promotes healing of gastric ulcer in ambulatory patients and achieves the same healing rates as bedrest or cimetidine, it has gone into disuse because of the adverse effects and availability of better drugs.

ANTI-HEUCOBACTER PYLORI DRUGS

H.pylori is a gram negative bacillus uniquely adapted to survival in the hostile environment of stomach. It attaches to the surface epithelium beneth the mucus, has high urease activity—produces ammonia which maintains a neutral microenvironment around the bacteria, and promotes back diffusion of H^+ ions. It has been found as a commensal in 20–70% normal individuals, and is now accepted as an important contributor to the causation of chronic gastritis, dyspepsia, peptic ulcer, gastric lymphoma and gastric carcinoma. *H.pylori* infection starts with a neutrophilic gastritis lasting 7–10 days which is usually asymptomatic. Once established, *H.pylori* generally persists for the life of the host. Upto 90% patients of duodenal and gastric ulcer have tested positive for *H.pylori.*

Eradication of *H.pylori* concurrently with H_2 blocker/PPI therapy of peptic ulcer has been associated with faster ulcer healing and lower relapse rate. Anti-*H.pylori* therapy is therefore now recommended in all ulcer patients who test positive for *H pylori.* In the absence of such testing, all cases with failed conventional ulcer therapy and relapse cases may be given the benefit of *H.pylori* eradication.

Antimicrobials that have been found clinically effective against *H.pylori* are: amoxicillin, clarithromycin, tetracycline and metronidazole/ tinidazole. However, any single drug is relatively ineffective. Resistance develops rapidly, specially to metronidazole/tinidazole. Since bismuth (CBS) is active against *H.pylori* and resistance does not develop to it, early combination regimens included bismuth, but had poor patients acceptability; are infrequently used now. In the mean time it was observed that omeprazole monotherapy reduces population of *H.pylori* in the gastric antrum, probably by altering the acid environment as well as direct inhibitory effect. A number of 2 drug and 3 drug regimens of 1 or 2 weeks duration have been tested reporting 60-96% eradication rates, but the optimum regimen is difficult to proclaim. Some of the regimens are:

Two Week Regimens (mg)

1. Clarithromycin 500 TDS/Amoxicillin 750 BD + Omeprazole 40 OD
2. Amoxicillin 500 TDS/Tetracycline 500 QID + Metronidazole 400 QID/Tinidazole 500 BD + Bismuth 120 QID
3. Amoxicillin 750 TDS + Metronidazole 500 TDS + Ranitidine 300 OD
4. Amoxicillin 1000 BD + Clarithromycin 500 BD + Lansoprazole 30 BD

One Week Regimens (mg)

1. Amoxicillin 500 TDS/Clarithromycin 250 BD + Metronidazole 400 TDS/Tinidazole 500 BD + Omeprazole 20 BD
2. Amoxicillin 500 TDS + Clarithromycin 250 TDS + Omeprazole 20 BD
3. Clarithromycin 250/500 BD + Metronidazole 400/Tinidazole 500 BD + Lansoprazole 30 BD
4. Amoxicillin 1000 BD + Clarithromycin 500 BD + Omeprazole 20 BD.

The US-FDA approved regimen is: lansoprazole 30 mg + amoxicillin 1000 mg + clarithromycin 500 mg all given twice daily for 2 weeks. It has achieved 86–92% eradication rate. High prevalence of *in vitro* nitroimidazole resistance among *H.pylori* now being detected, specially in tropical regions and better tolerability of regjmens which exclude the nitroimidazole favour the triple drug regimen of a PPI + amoxicillin +

clarithromycin. The 2 week treatment is considered more appropriate because higher relapse rate in the first year after one week regimen indicates incomplete eradication leading to recrudescence. A 4 drug regimen (PPI + tetracycline + CBS + metronidazole) has also been advocated.

All regimens are complex and expensive, side effects are frequent and compliance is poor. Longterm benefits of anti- *H.pylori* therapy include lowering of ulcer disease prevalence and prevention of gastric carcinoma/lymphoma; but benefits in nonulcer dyspepsia are equivocal.

H.pylori vaccines are under development.

Some available anti-*H.pylori* kits (one kit to be taken daily in 2 doses) HP-KIT, HELIBACT, OMXIHN: Omeprazole 20 mg 2 cap + Amoxicillin 750 mg 2 tab + Tinidazole 500 mg 2tab.

PYLOMOX: Lansoprazole 15 mg 2 cap + Amoxicillin 750 mg 2 tab + Tinidazole 500 mg 2 tab.

LAMSI KIT: Lansoprazoie 30 mg 1 cap + Amoxicillin 750 mg 1 tab + Tinidazole 500 mg 1 tab (one kit twice a day)

PYLOKIT, HELIGO: Lansoprazole 30 mg 2 cap + Clarithromycin 250 mg 2 cap + Tinidazole 500 mg 2 tab.

LANPRO AC: Lansoprazole 30 mg 2 cap + Clarithromycin 250 mg 2 tab + Amoxicillin 750 mg 2 tab.

Rote of drugs in peptic ulcer disease

Duodenal ulcer is a chronic remitting and relapsing disease lasting several years. Goals of antiulcer therapy are:

(i) Relief of pain

(ii) Ulcer healing

(iii) Prevention of complications

(iv) Prevention of relapse

The currently available drugs have adequately achieved the first two goals, partially the third, but there has been little success on the fourth performance criterion. Various strategies to maintain the disease in remission are—continuous or on demand intermittent H_2 blocker/PPI, maintenance sucralfate or antacid treatment. Out of these continuous maintenance H_2 blocker/PPI therapy is regarded the most effective and convenient. Duration of such therapy is uncertain, but should not be less than a few years.

The better approach, however, is to identify and treat *H.pylori* positive cases. Long term acid suppressive therapy would then be needed only in *H.pylori* negative cases, or those in whome this organism cannot be eradicated.

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(на английском языке)

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