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THE LATEST TREATMENTS FOR MIGRAINE

Surath Sakvithi Wickramatunga

Scientific supervisor: Ph.D., associate professor *N. N. Usova*

Educational Establishment
«Gomel State Medical University»
Gomel, Republic of Belarus

Introduction

Migraine is one of the most common neurological diseases at present. It mostly occurs in women than in men with a ratio of 3:1. The prevalence of migraine in Western countries is 13 %. Also 90 % of migraine patients have to restrict their daily activities during attacks. An attack can be present with neuro-ophthalmic features including visual auras, which is the most common type of migraine aura. Additionally symptoms involving the orbit such as red and tearing eyes, miosis and ptosis, eyelids swelling, nasal congestion or runny nostrils, redness and sweating above the eyebrow often occurs along with pain.

Goal

To provide an overview on the current treatment methods used to treat migraine globally and to provide a better understanding on the advances of new treatment methods used to treat migraine and to show how successful these treatment methods are, using clinical trials which have been carried out globally as examples.

Material and methods of the research

The search of information was conducted through the research of scientific articles and systematic literature and the results were screened for the relevance review topic and also new articles were added based on the clinical knowledge of the author on the specific area. Statistical information was also obtained from clinical trials conducted on the area of review.

Results of the research and their discussion

There are 4 phases of a migraine headache, they are prodrome, aura, headache and postdrome. In response to changes in physiological and emotional homeostasis hypothalamic neurons activate nociceptive pathways and trigeminovascular pathways through increased parasympathetic tone. Low cyclical brain stem activity causes the lowering of threshold for hypothalamic and brainstem neurons to transmit nociceptive and trigeminovascular signals. The aura is caused by cortical spreading depression slowly propagating wave of depolarization followed by hyperpolarization in cortical neurons and glia. Initiated by local elevations in extracellular potassium ions that chronically depolarizes neurons. The throbbing pain is as a result of trigeminovascular pathway activation. Nociceptive neurons are stimulated and release vasoactive neuropeptides causing vasodilation of large cerebral arteries. Alongside input from trigeminal nerve this stimulates trigeminal neurons in an axon like reflex which converges with input in adjacent skin and muscle to trigger the trigeminal cervical complex. Ascending pathways then transmit signals to

brainstem, thalamic, hypothalamic and cortical neurons leading to the phenotypic expression of migraine pain and its associated symptoms. In the trigeminal synapse calcitonin gene related peptide (CGRP) signaling occurs. This CGRP acts as the neurotransmitter in the trigeminal nerve synapses.

The first line treatment of migraine is mostly pharmacological but surgical treatment can be available as well. Because of the invasive nature of surgical treatment usually pharmacological treatment is preferred. The table 1 below shows some types of drugs with examples that can be used for oral administration against migraine.

Table 1 — Drugs used against migraine

Drug group	Examples
Beta-blockers	Propranolol,metoprolol
Anticonvulsants	Valproate, topiramate
Calcium-channel blockers	Flunarazine
Tricyclic antidepressants	Amitriptyline, nortriptyline
Serotonin antagonists	Pizotifen, methysergide
Antihypertensives	Lisinopril, candesartan
Antidepressants (serotonin norepinephrine reuptake inhibitors)	Venlafaxine
Antidepressants (selective serotonin reuptake inhibitors)	Paroxetine, fluvoxamine
Antidepressants (noradrenergic and specific serotonergic antidepressants)	Mirtazapine

OnabotulinumtoxinA (OBT-A) has shown to be effective and generally well tolerated treatment for the prevention of migraine in Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials. OBT-A when injected to the trigeminally-innervated cranio-facial-cervical region it inhibits the release of CGRP from peripheral nociceptive neurons and interferes with TRP channels thereby reducing neuronal hyperexcitability and peripheral and central sensitization.

Topiramate had reduced headache days when compared with placebo and was relatively well tolerated in patients with migraine. But in two large randomized controlled trials it was recorded that topiramate gave side effects such as paresthesia, memory, concentration disturbances, nausea and fatigue. It is said that topiramate has the ability to prevent cortical spreading depression associated with migraine by modulating ion channels.

There are several newly emerging treatments used for migraine targeting the calcitonin gene related peptide (CGRP) receptors. These molecules of CGRP receptor antagonists act by blocking the CGRP receptors in the central nervous system and peripheral tissues. This inhibits the physiological and cellular effects of CGRP. This targeting of the CGRP pathway may be effective in preventing migraine. Telcagepant is drug that has been proven in randomized controlled trials by showing a reduction in headache days versus placebo. But its clinical development was stopped due to its hepatotoxicity and also several other CGRP receptor antagonists has also been discontinued due to safety concerns. Atogepant, rimegepant and ubrogepant are three CGRP receptor antagonists that are currently in phase III development for migraine.

There is also another type of drug known as anti-CGRP/R monoclonal antibodies. These are macromolecules that bind to CGRP ligand or its receptors neutralizing the effect of excessive CGRP released in the trigeminal sensory nerve fibers during migraine attacks. Currently there are three anti-CGRP/R monoclonal antibodies that are approved in the FDA and Europe for the prophylactic treatment of migraine. They are fremanezumab and galcanezumab which target the CGRP ligand, and erenumab which targets the CGRP receptor. These three drugs are administered subcutaneously. Eptinezumab which is the fourth anti-CGRP/R antibody against the CGRP ligand is currently under review of the FDA. Eptinezumab is administered intravenously. These are highly specific for the CGRP/R targets and are not able to cross the blood brain barrier and bypass liver metabolism so central

nervous system related side effects and hepatotoxicity will not occur. The only side effects were mild to moderate injection site reactions.

Due to the vasoconstricting effect of triptans, 5-HT1B/D receptor agonists there is a risk of cardiovascular disease. Therefore 5-HT1F receptor agonists are used, which are known as ditans. Following phase-III clinical trials lasmiditan is the first ditan to be approved by the FDA. PCAP has an experimental evidence in migraine pathophysiology. Glutamate based targets have also been considered as therapeutic targets in migraine. Memantine a NMDA-R (N-methyl-D-aspartate receptor) agonist has undergone clinical trials for preventive treatment of migraine. The amylin blocking drugs may also become migraine treatments in the future.

Migraine can be caused by potassium channel opening. To check this an experiment was conducted using Maxipost, a large(big)-conductance calcium-activated potassium (BKca) channel opener to check whether it can induce migraine and cause cephalic vasodilation in individuals with migraine. This was conducted with twenty-six migraine patients without aura. They received an infusion of Maxipost or placebo on two study days separated by at least one week. The difference in incidence of migraine attacks after Maxipost was compared with placebo. Out of the twenty-two patients who completed the study twenty-one patients (95%) developed migraine attacks after Maxipost compared with none after placebo. Also a significant increase in the velocity of blood flow and diameters of the medial cerebral artery, superficial temporal artery and radial arteries were noted. So according to the above results BKca channel opening initiates migraine attacks. So BKca channel blockers could be potential candidates for a new antimigraine drug.

Conclusion

The development of CGRP receptor antagonists and anti CGRP/R monoclonal antibodies promises a better future in the treatment of migraine for patients who are not using any prophylactic treatments or are not benefiting from their current treatments. Also the introduction of ditans fills the gap created by triptans which is the vasoconstriction which makes triptans contraindicated to patients with cardiovascular disease.

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