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Review Article

RECENT ADVANCES IN MIGRAINE PROPHYLAXIS

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ABSTRACT
Migraine is a chronic neurological disorder with heterogeneous characteristics resulting in a range of symptom profiles, burden, and disability. Migraine affects nearly 12% of the adult population in occidental countries, imposing considerable economic and social losses. The pharmacologic treatment of migraine includes preventive and acute strategies. A better understanding of the migraine pathophysiology along with the discovery of novel molecular targets has lead to a growing number of upcoming therapeutic proposals. This review focuses on new and emerging agents for the treatment of migraine.
KEY WORDS: Pain, migraine, non steroidal anti-inflammatory drugs, levetiracetam, tiagabine, zonisamide, petasites, carvedilol, tizanidine, quetiapine, botulinum toxin, topiramate

INTRODUCTION

Migraine is a chronic neurovascular disorder characterized by moderate to severe headaches, and nausea. It is about three times more common in women than in men[1].

The phenomenon is a primary neurological disorder with a clear genetic basis[2]. The most common mutation affects a gene on chromosome 19 that encodes for a neuronal calcium channel[3]. During the migraine attack, neural events result in the dilatation of meningeal blood vessels that, in turn, causes pain, further nerve activation, and inflammation[4]. Because neural events are linked to vascular events, migraine is considered a neurovascular headache disorder.

Migraine probably results from dysfunction of brainstem areas involved in the modulation of craniovascular afferent fibers. Brainstem activation may also lead to activation of ascending and descending pathways, with initiation of a perimeningeal vasodilatation and neurogenic inflammation[4].The past 15 years has witnessed the development of an arsenal of drugs that act on excitatory glutamate-mediated activity or inhibitory gamma-amino butyric acid (GABA)-mediated activity, actions that theoretically provide cortical stabilization, therefore counteracting the imbalance supposedly existent in the migraineur's brain[4]. In addition, the progressive knowledge about the sequence of phenomena occurring during a migraine attack has stimulated interest in agents that may block the cortical spreading depression, a presumed substrate of migraine. Other targets include the blockage of pro inflammatory substances released at the level of the trigeminal end, including neuropeptides involved in initiating the pain of migraine, and substances that may block the sensitization of peripheral and central trigeminal nociceptive pathways[5,6].

Brief review of existing treatments

Pharmacologic treatment of migraine is divided into acute and prophylactic modalities. Acute treatment can be subdivided into nonspecific agents (such as aspirin, acetaminophen, non steroidal anti-inflammatory drugs, opiates, and combination analgesics) and migraine-specific treatments (ergotamine, dihydroergotamine, and the triptans). The US Headache Consortium Guidelines recommend stratified care that is based on the level of disability to help physicians target patients who require careful assessment and treatment[7].

Recent advances in migraine prophylaxis

In this section we highlight drugs that recently received approval for migraine treatment (TPM) or are available and sometimes used off-label. All drugs discussed in this section are for the preventive treatment of migraine.

1) TPM (Topiramate)

TPM was recently approved by the US Food and Drug Administration (FDA) for migraine prophylaxis. It is a neuromodulator with a structurally unique formula that provides multiple mechanisms of action and can influence the activity of some types of voltage-activated Na+ and Ca++ channels, the GABAA receptor, and the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate subtype of glutamate receptors. TPM also has inhibition properties on specific carbonic anhydrase (CA) II and CA IV isozymes of CA[8,9]. TPM exerts its effects on voltage-activated Na+ and Ca++ channels, GABAA receptors, and AMPA/kainate receptors through protein phosphorylation. Because some of its effects are influenced by the phosphorylation state of these receptors, it has been postulated that TPM may bind to the membrane channel complexes and modulate the ionic conductance through the channels[8].

From open-label studies[10] and multicenter, randomized, double-blind, placebo-controlled trials in migraine prevention confirmed the usefulness of this drug. [11, 12].In both trials, participants were given varying doses of TPM or placebo. The best results were achieved at a dose of 100 mg or 200 mg, with no difference in efficacy observed between the 2 doses.

TPM may be useful for pediatric migraineurs as well. Campistol and colleagues[13] evaluated 24 patients aged 6-14 years in a 4-month trial.

2) Tiagabine

Tiagabine (TGB) is an effective add-on therapy for partial seizures. TGB inhibits the neuronal and glial reuptake of GABA and therefore enhances GABA-mediated inhibition. TGB does not induce or inhibit the function of hepatic enzymes and does not displace tightly protein-bound drugs, such as carbamazepine, theophylline, warfarin, and digoxin. Total and unbound TGB concentrations are increased in

patients with hepatic dysfunction but are unaffected in patients with renal failure[14].

TGB was initially studied in patients with refractory migraine[15]. In an open-label study of 41 migraine patients with dose 4 mg, 4 times daily, who had been previously treated with divalproex and discontinued therapy because of adverse events or relative lack of efficacy, Freitag and colleagues [16.] used a mean dose of 10 mg/day. In this study, 5 patients experienced a remission of their migraine attacks, and 33 of the 41 studied had at least a 50% reduction in their attacks. The drug does not carry an FDA indication for migraine.

3) Levetiracetam

Levetiracetam (LCT) is a new AED of unknown mechanism of action, although it has proved to be a broad-spectrum anticonvulsant in animal models[17]. It is rapidly and nearly completely absorbed after oral administration; peak serum concentrations are achieved within 2 hours, and daily doses are linearly related with plasma concentrations. LCT is metabolized primarily by hydrolysis of the acetamide group to the inactive carboxylic derivative and it is poorly protein-bound (< 10%)[18]. The metabolic degradation of LCT is independent of the hepatic system of cytochrome P450, and therefore is not affected by the concomitant use of other AEDs. In children as well as in adults, steady state is achieved after 2 days of twice-daily dosing.

Anecdotal evidence suggests the usefulness of LCT in the prevention of migraine[19, 20].

Recently, in a 10-week, open-label study the efficacy and safety of LCT for pediatric migraine was evaluated in a population of 30 children or adolescents aged 6 to 19 years[21].

4) Zonisamide

Zonisamide (ZNS) is a sulfonamide derivative that is structurally and chemically unrelated to other AEDs. It has been used for adjunctive therapy of partial seizures, and it is rapidly and nearly completely absorbed after oral administration with negligible first-pass metabolism [22]. ZNS presents a unique combination of pharmacologic actions: It blocks voltage-dependent sodium and T-type (but not L-type) calcium channels; reduces glutamate-mediated excitatory neurotransmission; inhibits excessive nitric oxide (NO) production, scavenging hydroxyl and NO radicals; and inhibits carbonic anhydrase. All of these mechanisms may play a role in headache and pain modulation, possibly via neuronal stabilization[22-25.]

ZNS was studied for migraine prevention in 2 open-label trials presented. In first study ZNS was evaluated 33 patients with mixed headache disorders and refractory migraines[26].

ZNS was started at a dosage of 100 mg at bedtime every third day for 4-5 doses. The dosage frequency was then increased to every other day for another 4-5 doses, followed by the same dosage on a daily regimen. Dosage was adjusted upward every 2-3 weeks and in some cases reached as high as 600 mg/day. A total of 18% of the participants reported a 65% or better reduction in the frequency of migraine attacks and other headaches; 24.2% reported a 25% to 50% decrease in the same parameter; and 27% did not respond or were noncompliant with the protocol.

In the second study, 34 patients with migraine who were refractory to other preventive therapies received an initial dosage of 100 mg of ZNS daily, which was titrated as tolerated to 400 mg daily. Headache severity was significantly reduced as well as the other headache measures[27].

5) Petasites

Petasites is an extract from the plant Petasites hypridus (butterbur), which is a perennial shrub found throughout Europe and parts of Asia and North America. It has been used medicinally for centuries and during the middle Ages was used to treat plague and fever. In the 17th century, butterbur was used frequently in treating cough, asthma, and skin wounds. In addition, petasites has been reported to inhibit peptide-leukotriene biosynthesis, possibly through calcium channel regulation[28, 29].

The efficacy of petasites in migraine prevention was studied in 2 trials. In a small randomized, double-blind, placebo-controlled trial reported that a low dose of petasites, 50 mg twice daily, significantly reduced the number of migraine attacks per month and the number of migraine days per month[30.] In a larger double-blind, 5-month trial, Lipton and colleagues[31] randomized patients to receive either petasites 50 mg or 75 mg twice daily, or placebo. Compared with placebo-treated patients, 75 mg twice daily may be an effective alternative preventive treatment for migraine and the 4-month mean attack count was reduced by 48%[31].

6) Carvedilol

The use of beta blockers for migraine prevention is not new. The evidence for the use of this pharmacologic class was well established with propranolol, timolol, atenolol, and nadolol. The use of novel beta blockers, such as carvedilol, for the prophylactic treatment of migraine is a new concept because it offers additional alpha-1 blocking and antioxidant properties. This nonselective alpha-1 and beta-1 antagonist reduces blood pressure by reducing peripheral vascular resistance with no alteration of heart frequency or cardiac debit. The results are a very favorable adverse event profile, which may represent an appeal in migraine prevention because traditional beta blockers have limiting side effects[32].

Carvedilol was initially studied in open-label trial involving 76 patients. The dosages were from 3.125 mg/day to 6.25 mg twice daily over 2 weeks. After 6 weeks all the patients were asked to adjust the stable dose as per their need. Of the 68 patients who completed the study, 40 (59%) experienced a 50% reduction in monthly migraine attack frequency at the third month of treatment. 10 (15%) didn't present any significant response, and 18 (26%) withdrew because of lack of efficacy, or as a result of adverse events[33].

7) Tizanidine

Tizanidine hydrochloride is an alpha2-adrenergic presynaptic agonist that inhibits the release of norepinephrine in the brainstem and spinal cord. The antinociceptive effect does not involve the opioid system but is expressed on the alpha-adrenergic system at the alpha receptors located at the substantia nigra pars compacta[34]. Tizanidine is not an antihypertensive medication but contains several pharmacologic similarities to clonidine, another alpha2-adrenergic presynaptic agonist that has been advocated for migraine prophylaxis. Studies with cats demonstrated an inhibitory effect on vasoconstrictor and vasodilator responses to noradrenaline, adrenaline, isoprenaline, and angiotensin[35].

The efficacy of tizanidine in headache was shown in a controlled study involving the treatment of chronic daily headache, especially in chronic migraineurs[34]. In addition, an

open study of 220 patients demonstrated efficacy in both migraine and chronic tension-type headache[36]. which makes this drug attractive as a possible prophylactic treatment of episodic migraine and tension-type headache.

8) Quetiapine

Quetiapine (QTP) is a dibenzothiazepine derivative classified as an atypical antipsychotic drug with a low affinity for dopaminergic D1 and D2 receptors but high affinity for D4 receptors. QTP has an interesting characteristic of presenting antagonistic properties at many neurotransmitter receptors. In addition, it has interesting, more pronounced effects on mesolimbic than on nigrostriatal dopaminergic pathways, which results in better tolerability with regard to extra pyramidal symptoms[37]. QTP represents a new hope for migraineurs because it also possesses high affinity for 5-HT2 receptors, partial agonistic activity at 5-HT1A receptors, and a blocking activity at alpha1-adrenergic receptors with a consequent potential for migraine prevention[37, 38]. The role of QTP in migraine was studied in 24 migraineurs who had a history of not responding at least to 2 agents. QTP was initiated as an add-on therapy at a dose of 25 mg daily with a progressive titration to a maximum of 150 mg daily. At an average dose of 75 mg daily, 21 of the 24 patients showed significant improvement in either frequency or severity, or both, of migraine. One patient discontinued the drug because of sedation[39]. The clinical impression is that QTP may represent a very important resource for patients with refractory migraine or patients with psychological disturbances[38, 39].

9) Botulinum Toxin

Botulinum toxin (BTX) is a bacterial neurotoxin approved for the treatment of strabismus, blepharospasm, and hemifacial spasm; BTX also has been safely used for spasticity, tremor, dystonia, and other neuromuscular disorders of inappropriate muscular contraction. BTX has also been used to reduce wrinkles and hyper functional lines of the face. BTX causes long-term cholinergic blockade at the neuromuscular junction, which is thought to be responsible for its chemo enervating action and the therapeutic effect causing muscle paresis or paralysis. In addition, it has anti nociceptive properties, an effect unrelated to its inhibition of the muscle contraction[40]. BTX may work in migraine through the suggested inhibition of substance P, calcitonin gene-related peptide (CGRP), and glutamate[40, 41].

BTX has been evaluated in open-label trials and large multicenter studies[42, 43]. Silberstein and associates[43] examined the safety and efficacy of BTX in migraine prevention with a double-blind, vehicle-controlled design. A total of 123 patients from 12 headache centers were recruited in this double-blind, randomized, placebo-controlled (vehicle-controlled), parallel-group prospective study. Patients were randomized to 1 of 3 groups: BTX 25 U or 75 U, or vehicle. The sites of the injections were symmetric into the glabellar, frontalis, and temporalis muscles. The group of patients that received 25 U of BTX received a significantly better performance than the vehicle in all endpoints. The 75-U BTX treatment group was significantly more improved than the vehicle group on patient global assessment for days 31-60 but not other parameters.

CONCLUSION

The possibility of better modulating the imbalance between central neurotransmitters that occurs with migraine has created an exciting search for new pharmacologic agent. Drugs acting on the early stages of migraine and non vasoactive therapies are in the late stages of development. Neuromodulators for the prevention of multiple mechanisms related to migraine are already available. Obtaining synergies by combining agents with different sites of action is a valuable approach. The better use of available drugs, beyond conservative monotherapy, may represent an important strategy for helping migraine patients until better drugs are developed.

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