NEW MIGRAINE PREVENTIVE OPTIONS: AN UPDATE WITH PATHOPHYSIOLOGICAL CONSIDERATIONS

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BACKGROUND: The pharmacological treatment of migraine may be acute or preventive. Frequent, severe and long-lasting migraine attacks require prophylaxis. Multiple threads of research over the last 15 years have led to the concept that migraine is generated from a hyperexcitable brain. A variety of causes for hyperexcitability of the brain in migraine have been suggested. These causes include low cerebral magnesium levels, mitochondrial abnormalities, dysfunctions related to increased nitric oxide or the existence of a P/Q type calcium channelopathy. The better knowledge about migraine pathophisiology led us to discuss new treatment options.

OBJECTIVES: The aim of the present study is to present an evidence-based review of some new drugs or some agents that even though available for a long time, are not frequently used.

METHODS/RESULTS: We present a review of anticonvulsants with various mechanisms of action such as lamotrigine, gabapentin, topiramate, tiagabine, levetiracetam and zonisamide. We also review natural products, like riboflavin and magnesium, botulinum toxin A, a specific CGRP antagonist and the anti-asthma medication montelukast, with pathophysiological discussion.

CONCLUSIONS: We aimed to present an update of newer or less frequently used preventive migraine therapies, drugs that might reduce the burden and the costs of a disease that should be considered as a public health problem all around the world.

DESCRIPTORS: **Migraine. Preventive treatment. Prophylactic treatment. Update.**

INTRODUCTION

Multiple threads of research over the last 15 years have led to the concept that migraine is generated from a hyperexcitable brain[1]. In spite of the fact that we are not sure whether migraine is generated in the cortex or brainstem, one possible scenario would include a cascade of events beginning with cortical activation, followed by brainstem activation, leading to activation of ascending and descending pathways, with initiation of a perimeningeal vasodilatation and neurogenic inflammation[2-4]. A variety of causes for hyperexcitability of the brain in migraine have been suggested. These include low cerebral magnesium levels, mitochondrial abnormalities, dysfunctions related to increased nitric oxide or the existence of a P/Q type calcium channelopathy[5-8].

Effective migraine treatment begins with making an accurate diagnosis, ruling out alternate causes, and addressing the headache's impact on the patient. The treatment involves non-pharmacologic behavioral and physical measures and pharmacotherapy. The pharmacological treatment of migraine may be acute or preventive, remembering that they are not mutually exclusive. A significant number of patients will benefit from a combined approach.

The aim of the present study is to present an evidence-based review of some new drugs or some agents that even though available for a long time, are not frequently used.

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PREVENTIVE TREATMENT

Preventive medications are usually taken in a daily basis, to reduce the frequency, duration or severity of attacks. Some good reasons for migraine prevention are: 1 – Frequently recurring migraine that significantly interferes with the patient's daily routine, despite using an appropriate acute treatment; 2 – Failure, contraindication or adverse events when using acute medications; 3 – Overuse of acute medications; 4 – Patient preference.

The major medication groups for preventive migraine treatment include B-adrenergic blockers, antidepressants of all types, calcium channel antagonists, serotonin antagonists and anticonvulsivants. We will focus on new and not frequently used options.

1 – Natural Products

A – Vitamin B2 (riboflavin)

A mitochondrial dysfunction resulting in impairment of oxygen metabolism and low cellular energy levels may play a role in migraine pathogenesis[7]. Riboflavin (vitamin B2) is the precursor of flavin mononucleotide and flavin adenine dinucleotide, which are required for the activity of flavoenzymes involved in the electron transport chain in the mitochondria of the cells[9]. Given to patients with mitochondriopathies, riboflavin improved some clinical and biochemical parameters[10].

A double blind study of large doses of riboflavin (400 mg / day) compared with placebo in migraine prevention showed that riboflavin was significantly superior at reducing the attack frequency, headache intensity and other indexes after three months of therapy. The proportion of patients that improved at least 50% was 15% for placebo and 59% for riboflavin. No serious adverse events were reported[11].

B – Magnesium

As mentioned above, low levels of magnesium are probably associated with the cascade of events that might trigger migraine. It seems reasonable that this ion had been studied in the preventive and acute treatments of migraine.

Some studies have demonstrated low intracellular magnesium in the migrainous brain[12-13]. Two studies evaluated the effects of magnesium supplementation in the preventive treatment of migraine, with contradictories results. The first one enrolled 81 patients in a placebo-controlled study. The attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in placebo group. Adverse events were diarrhea and gastric irritation[14]. The other study evaluated 69 patients and was discontinued because they were not able to identify benefits in magnesium group. These patients had severe diarrhea and may not have absorbed the magnesium from the gastrointestinal tract[15].

The studies differed in the amount of magnesium (24 vs. 20 mmol) and in the salt (dicitrate vs. aspartate). These differences may explain at least part of the contradictory conclusions. Despite these conflicting results, many clinicians believe that magnesium can be useful in some patients. It can be tapered from 64 mg bid (Slow-Mag) to 128 mg bid, or be used in higher doses of other salts at a level of 200 mg bid or 400 mg QD.

2 – Antiepileptic Drugs

C – Gabapentin

Gabapentin is an anticonvulsant agent structurally related to the inhibitory neurotransmitter Gamma-aminobutyric acid (GABA) [16]. Although gabapentin was developed as a structural analog of GABA that would penetrate the blood-brain barrier (unlike GABA) and mimic the action of GABA at inhibitory neuronal synapses, the drug has no direct GABA-mimetic action and its precise mechanism of action has not been elucidated[17].

Gabapentin seems to be an anticonvulsant particularly effective in treating chronic pain syndromes. A recent double-blind trial that used gabapentin from 1800 mg to 2400 mg per day showed this drug to be superior to placebo in reducing frequency and intensity of pain[18]. Gabapentin was effective in 46% of patients, against 14% of placebo that had failed to other therapies. The most common adverse events of this drug are dizziness, drowsiness and weight gain.

D – Topiramate

Topiramate is a structurally unique anticonvulsant, rapidly and almost completely absorbed. It is eliminated predominantly unchanged in the urine. This drug differs structurally from other currently available anticonvulsant agents[19]. The spectrum of topiramate's anticonvulsant activity resembles that of carbamazepine and phenytoin[19], although differences in certain animal models have been observed and additive effects appear to occur when the drug is combined with these anticonvulsants[20]. It has been associated with weigh loss, not weight gain, which is a common reason to discontinue preventive medication. Almost all patients complain about slight peripheral paresthesias in the hands and feet. A rare side effect is cognitive dysfunction, fully reversed with therapy discontinuation.

One study that used topiramate in migraine and chronic daily headache reported one third of the patients with significant improvement, one third with moderate improvement and another third without improvement[21].

A second double-blind study showed that topiramate produced more than 50% decrease in pain in 46.7% of patients vs. 6.7% of placebo. A third

double blind study, using a mean topiramate dose of 125 mg (range 25 to 200 mg) also showed a significant improvement against placebo. Topiramate must be gradually increased from a 15 or 25 mg per day dose in order to avoid side effects[22].

E – Tiagabine

Although the precise mechanism of action of tiagabine is unknown, the drug enhances inhibitory neurotransmission mediated by GABA[23]. Tiagabine increases the amount of GABA available in extracellular spaces of the globus pallidus, ventral pallidum, and substantia nigra suggesting a GABA-mediated anticonvulsant mechanism of action[24].

Tiagabine is an antiepileptic drug still poorly studied as a preventive migrainous option. An open-label clinical trial with 41 patients, all previously treated with divalproex and discontinued due to lack of efficacy or adverse events, showed that 5 patients had remission and 33 had significant reduction of the frequency of attacks. The mean dose was 10 mg /day[25].

F – Levetiracetam

Levetiracetam, a pyrrolidine derivative, is an anticonvulsant agent that is structurally unrelated to other currently available anticonvulsants[26]. The mechanism of anticonvulsant action of levetiracetam is unknown and does not appear to be related to any known mechanisms involved in excitatory or inhibitory neurotransmission[27]. In animal models, levetiracetam conferred no protection against single seizures induced by electrical current or different chemoconvulsants and offered only limited protection in submaximal stimulation and threshold tests. Protection was observed against secondarily generalized activity from focal seizures induced by two chemoconvulsants known to induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam also showed inhibitory properties in the kindling model in rats, another model of human complex partial seizures[27].

Levetiracetam is not extensively metabolized in humans, with 66% of an administered dose excreted unchanged in urine. About 24% of an administered dose is metabolized to an inactive metabolite by enzymatic hydrolysis of the acetamide group, which does not depend on hepatic cytochrome P-450 (CYP) isoenzymes[27].

Using the rational that virtually all commercially available anticonvulsivants have shown efficacy in the treatment of migraine, this drug has recently been evaluated for this use. One first open study with 30 patients that had previously failed to at least two other agents has been levetiracetam added to their current preventive treatment. Fourteen (46.7%) reported more than 50% reduction in their migraine frequency and intensity with 3 months of active therapy. Dosage was adjusted from 2,000 to 4,500 mg per day in two or three doses. The authors concluded that levetiracetam could be an option in the treatment of refractory headaches[28].

A second study, with the same design, reported similar conclusions. The adverse event rates (no serious events were reported) was 16.1%[29].

G – Zonisamide

Zonisamide, an anticonvulsivant recently introduced in the US, has a unique combination of pharmacologic actions: it inhibits voltage-gated Na^+ channels and also blocks T—type calcium channels[30]. Both of these mechanisms may play a role in headache and pain modulation, possibly via neuronal stabilization. An open study was performed on 27 patients, all with refractory headaches, that received zonisamide in addition to the preventive treatment. One hundred mg was given in the evening every third day and then increased every 2 weeks until a maximum dose of 600 mg a day in 4 or 5 doses. Six (22.2%) patients reported a 65% or better decrease in frequency of migraines; 8 (29.6%) had from 25% to 50% . Four (14.8%) patients stopped due to side-effects[30] . A second study used from 10 mg to 400 mg, reported similar efficacy profiles. Paresthesias, fatigue, anxiety and weight loss were the most frequent adverse events reported[31].

3 - Miscellaneous

H – Montelukast sodium

Leukotrienes and other inflammatory mediators have been implicated in the inflammatory cascade believed to be associated with the pathophysiology of migraine[32]. The name "leukotriene" is derived both from the parent molecule, which was originally isolated from leukocytes, and from its three double-bond carbon backbone or triene structure. Both prostaglandins and leukotrienes are derived from the metabolism of arachidonic acid, with prostaglandins coming off the cyclooxygenase pathway and leukotrienes derived via the enzyme 5-lipoxygenase. Both prostaglandins and leukotrienes mediate inflammatory responses[33].

Nonsteroidal anti-inflammatory agents have been used widely in the treatment of migraine. It is reasonable to think that medications that could antagonize leukotriene functions could be effective in migraine prevention. The clinical observation of a decrease in migraine frequency in patients with comorbid asthma taking montelukast, a specific D4 leukotriene receptor antagonist, lead to the first open study, by Sheftell et al.[34], using montelukast sodium, 10 or 20 mg, in the prevention of migraine. In this study montelukast was extremely well tolerated, and no adverse events were reported by any of

the patients. Fifty-three percent showed a reduction greater than 50% (P<.025) in the frequency of severe attacks, with 41% showing a reduction greater than 60%. Responders, including modest responders, rated the drug as excellent. The authors concluded that montelukast shows potential as an effective, well-tolerated prophylactic agent in migraine, double-blinded, placebo-controlled studies being necessary. Recently, a poster was presented at the 2001 International Headache Congress showing the efficacy and safety of this drug in children and adolescents[35].

I – Lisinopril

Lisinopril (LSN) is a dicarboxyl-containing angiotensin converting enzyme (ACE) inhibitor proven efficient to treat hypertension and heart failure. It is structurally related to enalapril and it was the third ACE inhibitor approved for use in the United States. *In vitro*, LSN is slightly more potent than enalaprilat, an injectable ACE inhibitor, even though it is its lysine analog. After oral administration LSN is slowly, variably and incompletely (30%) absorbed; peak plasma concentrations are achieved in about 7 hours. It is cleared as the intact compound by the kidney, and its half-life in plasma is about 12 hours. LSN does not accumulate in tissues. The suggested oral doses for hypertension ranges from 5 to 40 mg daily (in single or divided doses), with 10 mg daily being appropriate for the initiation of therapy[36,37].

LSN was studied in a randomized, placebo-controlled, crossover trial[38] for the prophylactic treatment of migraine. The study involved sixty patients, aged 19-59 years, that presented two to six migraine attacks in a 4-week run-in phase. In the 47 participants who completed the study, hours with headache, days with headache, days with migraine, and headache severity index were significantly reduced by 20%, 17%, 21%, and 20% respectively, with LSN compared with placebo. Days with migraine were fewer by at least 50% in 14 patients for active treatment versus PCB. LSN was well tolerated and side effects observed were those know to be associated with ACE inhibitors. Eight patients reported coughing (vs. 3 in placebo group, 3 patients of LSN group withdrew due to coughing), 3 reported fatigue (vs. 3 in placebo group), 7 presented dizziness (vs. 4 in PCB) and 3 reported tendency to faint (vs. 0 in PCB) (total side effects 24 LSN patients vs. 13 PCB patients, p=0.07).

LSN has various pharmacological effects that may be relevant in migraine. In addition to blocking the conversion of angiotensin I to angiotensin II, it also alters the sympathetic activity, inhibits free radical activity, increases prostacyclin synthesis, and blocks the degradation of bradykinin, encephalin, and substance P[39]. Of particular relevance to LSN efficacy in migraine prevention, may be the recent finding that migraine without aura seems to be more common in people with the angiotensin converting enzyme DD gene, and the fact that migraineurs with this gene also have higher angiotensin converting enzyme activity and a higher frequency of attacks than other migraine sufferers[39].

J – Botulinum toxin

Botulinum toxin type A injections often reduce the pain associated with conditions such as cervical dystonia, achalasia, rectal fissures, and myofascial pain syndrome[40]. Some open-label, noncontrolled studies of botulinum toxin type A suggested benefits for patients with migraine. A recent double-blind study[40], evaluating 25-U and 75-U doses showed that, compared with vehicle treatment, subjects in the 25-U botulinum toxin type A treatment group showed significantly fewer migraine attacks per month, a reduced maximum severity of migraines, a reduced number of days using acute migraine medications, and reduced incidence of migraine-associated vomiting. Both the 25-U and 75-U botulinum toxin type A groups were significantly better than the vehicle group on subject global assessment. Botulinum toxin A treatment was well tolerated, with only the 75-U treatment group exhibiting a significantly higher rate of treatment-related adverse events than vehicle. They concluded that pericranial injection of botulinum toxin type A, 25 U, was found to be a safe treatment that significantly reduced migraine frequency, migraine severity, acute medication usage, and associated vomiting. It is symmetrically injected into glabellar, frontalis and temporalis muscles and eventually in other pericranial regions. The major side effect is mild ptosis that usually stays less than one week. Injections should be repeated every 3 months[40]. Clinical impression shows that some patients have a great response with this treatment, while other patients show practically absence or results.

4 – Future Possibilities

K – Calcitonin gene-related peptide antagonism.

This kind of potentially promising migraine treatment is undergoing preclinical research. Calcitonin gene-related peptide (CGRP) is one of the most potent endogenous vasodilators known. This peptide is increased during migraine attacks and has been implicated in the pathogenesis of migraine headache. Its first small molecule selective CGRP antagonist has been synthesized: BIBN4096BS. In vitro, this compound is extremely potent at primate CGRP receptors exhibiting an affinity (Ki) for human CGRP receptors. In an in vivo model, BIBN4096BS in doses between 1 and 30 micrograms kg-1 (i.v.) inhibited the

effects of CGRP, released by stimulation of the trigeminal ganglion, on facial blood flow in marmoset monkeys[41].

CONCLUSIONS

Analysis of preventive migraine therapies pose methodological issues[42]. Many early studies done prior to the International Headache Society Classification[43] used loose criteria to define migraine. Many preventives studies were poorly performed, did not provide adequate details of statistical methods or were reported only as abstracts, making proper analysis of the evidence difficult. Despite some of these drawbacks persisting until nowadays, we aimed to present an update of newer or less frequently used preventive migraine therapies, drugs that might reduce the burden and the costs of a disease that should be considered as a public health problem all around the world.

RESUMO

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BIGAL ME e col. - Novas opções para o tratamento preventivo da migrânea: revisão com considerações fisiopatológicas. **Rev. Hosp. Clín. Fac. Med. S. Paulo 57**(6): 293-298 2002.

INTRODUÇÃO: O tratamento farmacológico da migrânea pode ser dividido em agudo e preventivo. Crises de migrânea severas, de longa duração e incapacitante requerem profilaxia. Múltiplas linhas de pesquisa ao longo dos últimos 15 anos sedimentaram o conceito de que a migrânea é gerada a partir de um cérebro hiperexcitável. Variadas causas para essa hiperexcitabilidade têm sido sugeridas e incluem baixo nível de magnésio cerebral, anormalidades mitocondriais, disfunções relacionadas ao óxido nítrico e a existência de distúrbios nos canais de cálcio do tipo P/Q. O melhor conhecimento sobre a fisiopatologia da migrânea nos permite discutir novas opções terapêuticas.

OBJETIVOS: O objetivo do presente estudo é apresentar revisão baseada em evidências de novos agentes e outros que, embora disponíveis há mais tempo, não são freqüentemente utilizados, com considerações fisiopatológicas.

MÉTODOS/RESULTADOS: Serão revistos anticonvulsivantes com vários mecanismos de ação, como gabapentina, lamotrigina, topiramato, tiagabina, levetiracetam e zonisamida. Serão revistos também produtos naturais, como riboflavina e magnésio, toxina botulínica do tipo A, um antagonista CGRP específico e uma nova opção para o tratamento da asma, o montelukast.

CONCLUSÕES: Objetivamos apresentar artigo de atualização em opções novas ou não freqüentemente utilizadas no tratamento preventivo da migrânea, drogas que podem reduzir o fardo e os custos de uma doença que deve ser considerada um problema de saúde pública em todo o mundo.

DESCRITORES: **Migrânea. Tratamento preventivo. Tratamento profilático. Atualização.**

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