CURRENT THERAPIES IN EPISODIC MIGRAINE MANAGEMENT

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ABSTRACT

Migraine is a common neurological disease characterized by severe, recurrent episodes of throbbing, unilateral, headache.
Non-pharmacologic migraine treatment refers to the patient behavioral modification in order to avoid trigger.
Current therapies in migraine attack treatment are non-specific drugs (non-steroidal anti-inflammatory drugs, aspirin, antiemetics) and specific antimigraine drugs (ergot alkaloids, serotonin 5-HT1B/1D receptor agonists – triptans).
For migraine prophylaxis are recommended beta-blockers (metoprolol, propranolol), calcium channel blockers (flunarizine), antiepileptic drugs (valproic acid, topiramate), antidepressants (amitriptilyne, fluoxetine).

Keywords: migraine, ergot alkaloids, triptans, antiepileptic drugs

INTRODUCTION

Migraine is a common neurological disease characterized by severe, recurrent episodes of throbbing, unilateral, headache aggravated by movement, accompanied by nausea, vomiting and sensitivity to afferents – such as light, sound, odors – **migraine without aura.** (1)

One third of migraine sufferers experience aura – transitory visual or sensorio-motor dysfunction that precedes or accompanies the headache **(migraine with aura).** (1)

Migraine is a primary disorder of the brain, caused by dysfunction of an ion channel in the aminergic brain-stem nuclei that normally modulates sensory inputs and exerts neural influences on cranial vessels.

Migraine is a neurovascular headache – the primary neural events determine the dilatation of blood vessels, which, in turn, produce pain and further nerve activation.

Pain-producing intracranial structures (large cerebral vessels, pial vessels, large venous sinuses and dura mater) have trigeminal innervation, they are surrounded by unmyelinated fibers that arise from trigeminal ganglion (trigeminal-vascular system).

The neurons from trigeminal ganglion contain substance P and calcitonin-gene-related peptide (CGRP). Antidromic stimulation of trigeminal nerve releases substance P, CGRP that interact with vessel wall resulting in vasodilatation, plasma extravasation and neurogenic inflammation.

Migraine was previously considered a vascular disorder (Wolff), but in last years a large body of evidences (clinical, electrophysiological, and imagistical) indicates that it **is a brain disorder.**

Premonitory symptoms (fatigue, concentration impairment, mood change) and photo, phono or osmophobia associated to the migraine attacks are the clinical marks of brain involvement.

In migraineurs there is a dysfunction in neuromodulatory brainstem structures, PET studies demonstrated activation in dorsolateral pons.(2)

Current strategies in episodic migraine management reffers to non-paharmacologic and pharmacologic treatment – for acute migraine attack and for migraine prophylaxis.

The first step in migraine treatment is a correct diagnosis together with the development of a good

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doctor-patient relationship and patient education. It should be explained that is a recurrent disorder, that migraine patients have lower threshold for triggering attacks than non-migraineurs.

Non-pharmacologic migraine treatment refers to the patient behavioral modification in order to avoid triggers – such as stress management, regular physical exercise, regular eating and sleep habits, eliminating excessive caffeine intake and dietary triggers (alcohol, cheese, fasting, nitrites, monosodium glutamate, and aspartame), physiotherapy.

Individualized non-pharmacological strategies should be added to pharmacological treatment to each patient.

Comorbidity indicates an association between two disorders more than coincidedental. In migrainerus there is a high prevalence of stroke, epilepsy, mitral valve prolaps, Reynaud syndrome, psychological disorders (anxiety, depression) – that must be considered in drug selection.

Using headache diaries patient could identify his trigger factors and the physician could follow the treatment efficacy and a possible medication overuse.

Pharmacologic migraine treatment is used for acute (abortive) treatment of headache and also as preventive (prophylactic) therapy.

I. Pharmacological treatment of migraine attack consists of non-specific and specific migraine-drugs **(EFNS guidelines)** (3).

Non-specific migraine drugs used in migraine attack are simple analgesics acetaminophen (paracetamol) 1000 mg, aspirin up to 1000 mg, metamizol 1000 mg, and non-steroidal anti-anti-inflammatory drugs NSAIDs (diclofenac 50-100 mg, tolfenamic acid 200 mg, ibuprofen 200-800 mg, naproxen 500-1000 mg).

They have important gastrointestinal effects and also the risk of medication overuse headache limit their use up to 15 days per month or 10 days per month in combinations.

NSAIDs and acetylsalicylic acid are fist-line acute migraine treatment. They inhibit cyclo-oxygenase, inhibiting the conversion of arachidonic acid to prostaglandin H2, a precursor to prostanoids that acts as inflammation mediators.

Coxibs are not recommended for acute migraine treatment, due to undetermined cerebrovascular adverse events.

Opioids should be used in selective patients, due to addiction risk.

Antiemetics treat vegetative symptoms and improve resorbtion of analgesics It is recommended metoclopramid 20 mg in adults and domperidone 10 mg in children (3).

Specific antimigraine drugs are **ergot alkaloids** (ergotamine tartate ET/dihidroergotamine – DHE) and **triptans** (serotonin 5-HT1B/1D agonists).

Ergot alkaloids were the first antimigraine specific drugs. Experimentally, DHE blocks neurovascular inflammation in the trigeminal nerve terminals.

Ergot alkaloids are poor tolerated due to side effects – nausea, vomiting, paresthesia, ergotism – and they cause vasoconstriction (coronary, cerebral, peripheral). Ergot alkaloids are contraindicated cardiovascular and cerebrovascular disease, Reynaud's syndrome, in pregnancy, uncontrolled arterial hypertension, renal and liver failure.

Because of their long half-time and low headache recurrence rate, ergots are used in patients with very long duration of headache attacks or with high risk of recurrence of headache.

Ergot alkaloids have a poor oral bioavailability and modest improvement with intranasal forms (40%), partly due to oropharyngeal deposits. Intravenous DHE is safe and effective in intractable headache (4).

A new oral inhaled DHE is under study. The new device distributes the drug over a wider pulmonary surface area, improving pulmonary systemic absorption (5).

Triptans (serotonin 5-HT1B/1D agonists) were developed as migraine specific drugs, marketed in 1990's.

Migraine patients have low interictal plasma levels of serotonin (5-HT) and increased release of a major 5-HT metabolite – hydroxyindole acetic acid (5H1AA) during acute attacks. Based on this findings serotonin 5-HT1B/1D agonists were elaborated (6).

Triptans (serotonin 5-HT1B/1D agonists) determine presynaptic inhibition of the peripheral trigeminovascular neurons and also acts centrally along trigeminonociceptive pathways.

Sumatriptan was the first triptan available, followed by: rizatriptan, eletriptan, almotriptan, zolmitriptan, naratriptan and frovatriptan.

Earlier triptans are taken the better is their efficacy (Burstein at al. 2004; Dowson et al. 2004). The best time of application is at very onset of headache. Due to safety reasons, triptans should not be taken during aura.

Triptans should not be used in patients with ischemic heart disease, Prinzmetal's angina, vertebro-basilar migraine. They cause non-cardiac chest pressure in 4% patients, electrocardiogram should be made at patients over 40 year old before triptan use.

Common side effects are the local injection side effects (sumatriptan), dizziness, neck pain, dysphonia, recurrence headache.

A „triptan" can be efficacious if one or more were not. Triptans appear to offer differing treatment effects.

In a first meta-analysis of 53 clinical trials with triptans, involving 24089 patients, mean results for 100 mg sumatriptan were compared with other the other triptans (9).

The results for 100 mg sumatriptan were:

- 59% for 2 h headache response (improvement from moderate or severe to mild or no pain);
- 29% for 2 h pain free (improvement to no pain);
- 20% for sustained pain free (pain free by 2 h and no headache recurrence or use of rescue medication 2-24 h post dose);
- and 67% (63-70) for consistency (response in at least two of three treated attacks);
- placebo-subtracted proportions for patients with at least one adverse event (AE) were 13%, for at least one central nervous system AE 6%, and for at least one chest AE 1.9%.

Rizatriptan 10 mg is a little more effective than sumatriptan 100 mg, showed better efficacy and consistency, and similar tolerability.

Eletriptan 80 mg eletriptan showed better efficacy, similar consistency, but lower tolerability.

Almotriptan 12.5 mg showed similar efficacy at 2 h but better other results.

Naratriptan 2.5 mg and 20 mg eletriptan showed lower efficacy and better tolerability.

Zomitriptan 2.5 mg and 5 mg, eletriptan 40 mg and rizatriptan 5 mg rizatriptan showed similar results to 100 mg sumatriptan (9).

A recent (2013) meta-analysis of 74 double-blind randomized trials clinical trials comparing triptans to either placebo or another triptan had as primary outcomes pain-free response at two hours and 24-hour sustained pain-free response and as secondary outcomes were headache response at two hours and 24-hour sustained headache response.

All triptans were significantly superior to placebo for all outcomes, with the exception of naratriptan for 24-hour sustained pain-free response.

Eletriptan consistently yielded the highest treatment effect estimates. Rizatriptan yielded the second highest treatment effects followed by zolmitriptan (10).

Sumatriptan subcutaneous has the fastest onset of efficacy of about 10 minutes. New drug delivery systems for acute migraine treatment are in development, in order to reach peak plasma concentration with maximal efficiency and fewer vasoconstrictor side effects.

A new needle-free subcutaneous delivery system for sumatriptan is developed (11).

A transdermal formulation of sumatriptan reported significant improvement over placebo (12).

Sumatriptan nasal spray was tested with positive result in adolescents of 12-17 years, 20 mg sumatriptan being efficient with good tolerability (13).

Combination of sumatriptan 85 mg and naproxen sodium 500 mg is on the market and combination of triptans with caffeine or acetaminophen are being tested (14).

II. Pharmacological treatment in migraine prophylaxis (EFNS guidelines) (3)

Migraine is a recurrent, disabling neurological disease. Prophylactic treatment should be considered when:

- there is important impairment of quality of life, impairment of business duties accomplishment and school attendance
- fight frequency of migraine attacks
- unresponsiveness of attacks to acute drug treatment
- frequent, long uncomfortable auras.

A migraine preventive drug is considered successful if the frequency of migraine attacks per month is decreased by al least 50% within 3 months. (3)

Recommended substances for migraine prophylaxis are:

a) **beta-blockers** – metoprolol 50-200 mg, propranolol 40-240 mg.

Bisoprolol, timolol and atenolol might be effective.Beta-blockers are especially useful inpatients with comorbid angina or hypertension.

Beta-blocker are contraindicated in patients with congestive heart failure, Raynaud's disease, insulin-dependent diabetes.

b) **calcium channel blockers** – flunarizine (5-10 mg)

Flunarizine is useful in familial hemiplegic migraine, but with antidopaminergic activity – the symptoms of parkinsonism limits its use.

Familial hemiplegic migraine is now recognised to be due to several gene mutations: CACNA1A (19p13 – encoding α_1 subunit of the voltage-gated

P/Q-type calcium channel) (15), ATP1A2 (1q23 – encoding the α_2 subunit of the Na^+/K^+ pump) (16) and SCN1A (2q24 – leading to dysfunction of neuronal sodium voltage-gated channel) (17).

c) **antiepileptic drugs** – valproic acid 600-1800 mg and topiramate 25-100 mg.

Sodium valproate (VPA) facilitates the effects of the inhibitory neutotransmitter gamma-aminobutyric acid (GABA).

It is very useful when migraine is comorbid with epilepsy, anxiety disorders or manic-depressive illness. It can be administrated in patients who have contraindications to beta-blockers (depression, Raynaud's disease, asthma. diabetes).

Hepatotoxicity is the most serious side effectsof sodium valproate. Other side effects includes sedation, hair loss, tremor and changes in cognitive performances (18,19).

Topiramate (TPM) has unique mecanism of action – blockade of Na^+ channels and AMPA glutamate receptors, agonists activity at $GABA_A$ receptors and weak carbonic anhydrase activity.

Topiramate most common side effects are anorexia and weight loss, therefore TPM is useful in migraine prophylaxis in obese patients.

Topiramate side effects also include ataxia, poor concentration, confusion, dysphasia, dizziness, fatigue, paresthesia, somnolence, word-finding difficulties and cognitive slowing. It increase the risk of nephrolithiasis and should be avoided in patients with history of kidney stones.

Topiramate therapy was well-tolerated and effective in reducing the frequency and severity of migraine in migraine patients (20-22).

Other new antiepileptic drug – zonisamide – who acts as another type of carbonic anhydrase inhibitor – could be effective for migraine prophylaxis refractory to topiramate, or intolerable patients due to topiramate-induced paresthesia (23).

Other antiepileptic drug used in migraine are lamotrigine – effective in reducing the frequency of migraine auras (24).

d) **antidepressants** – amitriptilyne 10-150 mg, fluoxetine 10-40 mg.

Antidepressants are especially useful in patients with comorbid depression and anxiety disorders.

Tricyclic antidepressants are often use for patients with a sleep disturbance. Their side effects are of muscarinic type (dry mouth, sedation), increase of apetite with weight gain, cardiac toxicity, ortostatic hypotension.

Selective serotonin reuptake inhibitors (SSRI) have favourable side-effect profile, fluoxetine is valuable in chronic daily headache.

CONCLUSION

Triptans increase quality of life of many migraine patients, but only one third of patients are pain-free after 2 hours, so novel treatment options are needed (25).

The drugs used in epilepsy were a good opportunity for migraine preventive treatment (26). Valproate sodium an topiramate are officialy approved for the prophylactic treatment of migraine headaches.

Migraine is a genetic disease, the use of genome-wide studies and pharmacogenetics will alllow in future to tailor the treatment in an individual patient.

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