

## PROPHYLACTIC TREATMENT OF MIGRAINE BY VALPROATE

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**Summary.** Migraine is a common episodic headache disorder. A comprehensive headache treatment plan includes acute attack treatment to relieve pain and impairment and long-term preventive therapy to reduce attack frequency, severity and duration. Circumstances that might warrant preventive treatment include very frequent and severe migraine that interferes with the patient's daily routine, failure to acute treatment, special circumstances such as hemiplegic migraine or patient preference. The drug has to be started at a low dose and each treatment has to be given an adequate trial with avoiding interfering overused and contraindicated drugs. Co-morbidity has to be considered. Drugs that have documented high efficacy and mild to moderate adverse events include beta-blockers, amitriptyline and valproates.

Valproate has been shown to be an effective prophylactic treatment in migraine. Investigation of the mechanism of its antimigraine action is difficult due to the broad range of its biochemical effects and the complex nature of migraine pathophysiology. Valproate increases brain GABA levels and may suppress migraine related events in the cortex, perivascular parasympathetics or trigeminal nucleus caudalis. There is experimental evidence that it suppresses neurogenic inflammation and directly attenuates nociceptive neurotransmission. In addition, valproate reportedly alters levels of excitatory and inhibitory neurotransmitters and exerts direct effects on neuronal membranes in vitro. Valproate's observed effects may ultimately result from a combination of actions at different loci.

**Key words:** Migraine, prophylaxis, valproate

### Introduction

Migraine is a common, chronic, neurovascular disease characterized by repeated attacks of severe headaches, in combination with neurological, gastrointestinal and autonomous symptoms.

Yearly prevalence of migraine (patients with migraine who had at least one attack during previous year) is 10-12% for adults (18% for women and 6% for men) and 4% for children, where there is no gender difference (1).

Classification system of International Headache Society (IHS) recognizes 6 types of migraine (Table 1) with clearly defined diagnostic criteria (2).

Table 1. Migraine Classification

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1.1 Migraine without aura
1.2 Migraine with aura
1.3 Childhood periodic syndromes that are commonly precursors of migraine
1.4 Retinal migraine
1.5 Complications of migraine
1.6 Probable migraine

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Pathophysiological basis of migraine is probably a spontaneous, excessive activity and abnormal amplification of nociceptive and other sensory pathways of brainstem. The actual concept of migraine etiopathogenesis favors primary role of neuronal structures which

together with fibers for innervation of cranial arteries make *trigemonovascular* system. Relative lack of 5-hydroxytryptamine (5-HT) can be a direct etiological factor and is connected with action mechanism of most of the medicines. Current researches are mostly focused on the significance of calcium-channel abnormality, and neuropeptides (for example calcitonin gene-related peptide CGRP) in migraine etiopathogenesis and point to possible future therapeutic goals (3).

Evolution of migraine attack or migraine cascade develops in 9 stages: initiation, cortical events, vascular and autonomous events, primary activation of afferent fibers, release of vasoactive peptides, nociception transmission through trigeminal nerve, nociception integration within trigeminal nucleus rostral nociception projection and cortical pain integration.

### Treatment plan for migraine

Treatment plan for migraine includes a combination of several procedures: patient education, prevention of attack by avoidance of triggers; use of non-pharmacological therapy (relaxation methods, change of lifestyle); acute treatment of attacks with purpose of pain termination or discontinuation of its advance; long-term prevention with purpose of reduction of frequency, intensity and length of the attacks; use of alternative methods

of treatment (acupuncture...) if necessary; and of course, periodical evaluation and possible change of plan.

Pharmacological treatment of migraine can be acute (abortive) and preventive (prophylactic).

*Acute treatment* should stop the attack and impede its progress and possible appearance of neurological changes. This treatment should not be applied more than two or three times per week.

*Preventive therapy* is given continuously and in absence of headache as an attempt to reduce frequency and intensity of anticipated headache attacks. Patients with strong headaches and frequent attacks usually demand both types of treatment (4).

### Criteria for use of preventive therapy

If patient has frequent attacks (2 or more attacks per month) with functional disability which lasts 3 or more days, or has fewer attacks but functional disability is pronounced and longer than 3 days; if present therapy is contraindicated, failure or if side effects of acute treatment are distinct; if there is a tendency towards drug overuse in acute treatment; if migraine is complicated by neurological damage and the risk of it becoming permanent, these patients fall into category of those who require preventive therapy.

This group also includes patients with attacks more frequent than twice a week as well as those demonstrating progression of frequency and having a risk of appearance of rebound headache due to drug overuse, as well as patients whose individual choice is to have as least number of attacks as possible or not to have attacks at all (5).

During pregnancy, criteria for introduction of prophylactic therapy are somewhat stricter, but if a pregnant woman has severe and incapacitating attacks accompanied by nausea, vomiting and possible dehydration, than she is in a group of patients where prophylactic therapy is needed (6).

There are several groups of medicines for prophylactic therapy at our disposal (Table 2).

Table 2. Medicines in migraine prevention

<b>Anticonvulsants</b>
valproate, gabapentin, topiramate*
<b>Antidepressants</b>
TCA, SSRI, MAOI
<b><math>\beta</math>-adrenergic blockers</b>
propranolol, nadolol, metoprolol, atenolol, timolol
<b>Calcium-channel antagonists</b>
verapamil, flunarizine
<b>Serotonergic antagonists</b>
metizergid, metergin
<b>Others</b>
NSAIDs, riboflavin, magnesium, Botulinum toxin

\* positive results but demand further clinical confirmation  
TCA-tricyclic antidepressive;  
SSRI-selective serotonin reception inhibitors;  
MAOI- Monamine oxidase inhibitors;  
NSAIDs-non-steroid anti-inflammatory drugs

### Principles of preventive therapy

When using preventive therapy, certain principles should be obeyed:

1. Therapy should be started with a small dose and gradually increased until therapeutic effect appears or until a dose with intolerable side effects is reached.
2. Every drug should be given in an adequately long period ranging from 2 to 6 months, since therapeutic efficiency is expected after 4 weeks and is progressively increased in the following three months.
3. It is important to avoid drug interaction, drug overuse as well as contraindicated drugs. Special care is warranted in use of possible overuse of analgesics, opioids or ergot derivatives
4. When headaches become well controlled, the dose should be reduced or if possible, treatment should be discontinued - principle of reevaluation of therapy.
5. Women in reproductive period should be acquainted with the fact that there are potential risk factors during pregnancy, which affect the choice of drug having the least side effects for fetus. When using valproate, women should be given folic acid.
6. It is important to strive towards maximal compliance
7. Before choice of medicine, co-morbidity should be taken into consideration, above all cerebrovascular insult, epilepsy, mitral valve prolapse, Reynaud's syndrome, psychological disturbances such as anxiousness, depression, manic states, panic state.

### Pathophysiological effects of valproate

It is experimentally proven that during a migraine attack there is a disturbance of GABA metabolism, as well as a disturbance of balance of concentration of inhibitory (GABA) and excitatory neurotransmitters (glutamate and aspartate) in plasma.

Valproate increases GABA level in brain synapses by stimulating enzyme synthesis (glutamate decarboxylase) and inhibition of degrading enzymes (GABA-transaminase and succinyl-semialdehyde dehydrogenase) involved in GABA metabolism. Valproate also increase conductivity of  $Ca^{2+}$  with effect of neuron hyperpolarization, reduce aspartate level in brain by inhibition of its release, inhibit NMDA related transitory polarization in pyramidal cells and reduce NMDA or quisqualate receptors stimulated influx of  $Ca^{2+}$  into hippocampus cells.

Valproate effect is seen in the increase of the amount of homovanillic acid, enkephalin in striatum, brainstem, hypothalamus and cortex. A significant effect of valproate is the reduction of plasmatic extravasation. In Moskowitz model of neurogenic inflammation by interaction with  $GABA_A$  receptors. Valproate interact with central 5-HT system thereby reducing the effect of "inflammation" of serotonergic neurons of brainstem.

## Valproate in migraine cascade

Migraine cascade is a result of interaction of internal and external factors with nervous system vulnerable and sensitized by other factors. There are at least 9 stages in pathophysiology of evolution of migraine attack which appear successively or simultaneously (7).

### 1. Initiation

The exact localization and nature of neurochemical migraine event is still not completely known, although prodroma in form of affective and vegetative symptoms point to subcortical localization or to limbic system as a place of migraine origin. It is not known by means of what mechanism valproate achieves initiation suppression.

### 2. Cortical events

Aura as a distinct neurological symptom is associated with cerebral cortex. It is caused by a slowly expanding depression that is by a wave of cortex depolarization expanding by rate of 2-6 mm per minute, during which time neurons do not show spontaneous or evoked activity. It is caused by the action of excitatory amino acids,  $H^+$  and  $K^+$  ions as well as by arachidonic acid metabolites which activate nociception fibers (8,9). Slowly expanding depression is followed by slowly expanding oligemia. Valproate mediates increase of GABA-ergic neurotransmission as well as reduction of the level of excitatory amino acids and suppression of NMDA mediated transitory depolarization and calcium influx can lead to a discontinuation of initiated slowly expanding depression or to a stopping of its facilitation (10,11).

### 3. Vascular and autonomous events

Meningeal and meningeal blood vessels are the most important pain-producing structures of the head (12). Blood vessels are densely innervated by nociceptive, sympathetic and parasympathetic fibers. There are experimental proofs confirming that valproate modifies meningeal neurogenic inflammation.

### 4. Activation of primary afferent fibers

Regardless of initial trigger, in order for headache to appear, activation of primary afferent fibers is needed. Nociceptive fibers which innervate meningeal blood vessels originate from the cells of trigeminal ganglion and transfer impulses through trigeminal nerve (13). It still hasn't been proven that valproate produces direct modulation of the threshold of meningeal afferent activation.

Activation of trigeminal afferent neurons results in the following two stages of migraine cascade.

### 5. Release of vasoactive neuropeptides from activated sensory nerve ends

In animal models, levels of substance P, neurokinin A, and calcitonin gene-related peptide (CGRP) in sagittal sinus are increased after stimulation of trigeminal

system (14). In humans, during migraine attack, increased value of CGRP have been registered in v. jugularis interna (15).

These vasoactive neuropeptides lead to processes known as *neurogenic inflammation* (NI) which in normal circumstances has a protective role in prevention of tissue damage. Components of this response are a) release of plasma and plasmatic proteins from small blood vessels into surrounding tissue b) vasodilatation c) mastocyte activation as a part of local cellular immune defense system (16,17). Neurogenic inflammatory response can be biologically useful, promoting toxin dilution or bacteria elimination. If neurogenic inflammatory response is not initiated by a pathological process, the phenomenon becomes maladaptive and can be associated with processes such as asthma (18), arthritis (19), or headaches. When it appears in meningeal (or in other tissues), neurogenic inflammatory response can increase sensitivity of perivascular fibers, causing normally negligible stimuli to become extremely painful (20). Neurogenic inflammation can also be a mechanism by means of which migraine pain is amplified and lengthened after initial migraine event.

Valproate in clinically relevant dose (3 mg/kg) reduces plasmatic extravasation in model of meningeal neurogenic inflammation. In an animal model valproic acid attenuates substance P induced plasmatic extravasation (21).

### 6. Transmission through n.V.

Activated meningeal afferent fibers conduct nociceptive information through trigeminal ganglion and then to medullar trigeminal nuclear complex, especially to its caudal subnucleus. Although valproate in large doses can affect transfer of action potential, there are no clear proofs that they block impulse transmission through trigeminal afferent fibers.

### 7. Integration in caudal nucleus n.V.

Within caudal trigeminal nucleus, synapses of primary afferent fibers and nociceptive signals are modulated by interneurons and descending inhibitory systems. After activation, secondary neurons within caudal nucleus n.V. show momentary gene c-fos reaction, measured by immunohistochemical techniques. Expression of c-fos is a well defined marker of functional condition of neuron activity and has been seen in lamina I and II of spinal cord and in caudal nucleus after meningeal nociceptive stimulation (22-24).

Valproate in doses of 10mg/kg reduce the number of activated cells by 52%, selectively in laminae I and II (25). Other potential mechanism of action is serotonin modulation in caudal nucleus n.V. Substantia gelatinosa of spinal cord (area analogous to superficial laminae of caudal medullar nucleus n.V.) receives downward serotonergic fibers from rostroventral medulla. These fibers make direct contact with upward nociceptive neurons of spinothalamic system (26). If valproate increase serotonergic activity within caudal nucleus, as they do

in other regions of brain, its inhibitory effect on expression of c-fos can partly be consequence of serotonergic modulation (27).

#### 8. Rostral projection of caudal part of the nucleus n.V.

From caudal trigeminal nucleus, rostral projections go to more rostral parts of trigeminal complex, in pontine parabrachial nucleuses and cerebellum as well as in ventrobasal, lateral and medial thalamus. From rostral part of brainstem nociceptive information go to other parts of the brain (for example limbic system) which are thought to be involved in emotional and vegetative pain responses. Our knowledge of valproate effects on nociception in thalamus and other subcortical structures is still not sufficient.

#### 9. Reception of pain information to somatosensory part of frontal cortex

Projections from ventrobasal thalamus go to somatosensory cortex which discriminates and localizes the pain. Medial thalamus is projected in frontal cortex which gives affective and motivational aspect of the pain (28). Valproate effect concerning discriminative and motivational aspect of the pain in cerebral cortex is not known.

To summarize, all our understanding of valproate mechanism in migraine is made difficult by broad range of biochemical effects and complex nature of migraine pathophysiology. Valproate increase GABA brain levels and can inhibit migraine caused changes in cortex, perivascular parasympathic network, or in caudal nucleus n.V. Valproate reduces aspartate level and activity of NMDA receptors which can stop cortical processes associated with aura or modulate nociceptive transmission within caudal nucleus n.V. There are also experimental proofs that they inhibit neurogenic inflammation and thereby directly attenuate nociceptive neurotransmission.

### Clinical experiences with valproate in migraine prevention

In controlled researches of valproate prophylactic effect in migraine, their efficiency has been proven for a dose of 800 mg (29), as well as for a dose of 1200 mg (30), in respect of reduction of frequency and intensity of migraine attacks.

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In a multi-centered, double blind, placebo controlled and dosage controlled study (31), 176 patients older than 16 years were researched, with migraine with or without aura, with at least two attacks per month during the last 3 months, untreated or unsuccessfully treated in two attempts the most. The dose was titrated for 4 weeks starting with 250 mg per day with an increase in every 4 days by 250 mg divided in two daily doses. Efficiency variables were followed: frequency, intensity and duration. The results of the study revealed that the frequency of attacks was reduced by 50% at dose of 1000 mg/day while patient receiving 1500 mg/day did not demonstrate significantly higher reduction of frequency compared to the first group but they revealed a greater number of side effects (drowsiness, gastrointestinal disturbances).

The results of this research caused official registration of valproate, by USA FDA, for preventive treatment of migraine. After this study, the ruling principle of the treatment still remained: "start low, advance slow".

Later on, American Academy of Neurology in the evidence based guidelines, classified valproate into the group 1 (medications with proven high efficacy and mild to moderate adverse events) of drugs for migraine preventive therapy (32). Consequently, the American Academy of Family Physician and the American College of Physician recommend the valproate as the first-line agent for the prevention of migraine headache (33).

### Conclusion

Present studies have proven efficiency of valproate in prophylactic therapy of patients with migraine by means of which significant reduction of frequency and intensity of attacks has been achieved. Recommended daily dose of divalproex sodium is from 500 mg to 1500 mg/d, and sodium valproate from 800 to 1500 mg/d.

Gradual titration of the drug is the best way for avoiding side effects. A recent trial of the extended-release formulation of divalproate demonstrate similar efficacy to the short-acting drug, with seemingly improved tolerability (34). It therefore seems advisable to utilize the extended-release formulation, both to improve tolerability and encourage adherence to therapy (35).

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## PROFILAKTIČKI TRETMAN MIGRENE VALPROATIMA

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*Kratak sadržaj: Migrena je epizodična glavobolja. Plan lečenja glavobolje uključuje akutni tretman sa ciljem prekidanja bola i neurološke oštete i dugotrajni preventivni tretman sa ciljem smanjivanja učestalosti, jačine i trajanja bola. Okolnosti koje zahtevaju preventivnu terapiju uključuju vrlo česte i snažne migrene koje remete pacijentove svakodnevne aktivnosti, neuspešnost akutnog tretmana, specijalne okolnosti kao što je hemiplegična migrena ili je to želja pacijenta. Lečenje treba započeti malom dozom, a svako lečenje treba da traje adekvatno dugo uz izbegavanje interakcija, predoziranja i kontraindikovanih lekova. Treba razmotiti i komorbiditet. Među lekovima koji imaju dokazanu visoku efikasnost a blage ili umerene sporedne efekte spadaju beta blokatori, amitriptilin i valproati.*

*Valproati su se pokazali kao efikasan lek u profilaktičnom tretmanu migrene. Istraživanje mehanizma njihovog antimigrenskog dejstva je teško zbog širokog spektra njihove biohemijske aktivnosti i komplikovane patofiziologije migrene. Valproati povećavaju nivo GABA i mogu suprimirati migrenske događaje u korteksu, perivaskularnoj parasimpatičkoj mreži ili u kaudalnom jedru trigeminusa. Postoji eksperimentalni dokaz da suprimiraju neurogenu inflamaciju i direktno slabe nociceptivnu neurotransmisiju. Takođe, valproati menjaju nivoe ekscitatornih i inhibitornih neurotransmitera i pokazuju direktne efekte na membranu neurona in vitro. Efekti valproata rezultiraju iz kombinacije aktivnosti na različitim mestima.*

*Ključne reči: Migrena, profilaktički tretman, valproati*