

Memantine for the Prophylaxis of Migraine: A Report of Three Cases and Discussion of Pharmacology

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Abstract

Memantine was recently approved by the Food and Drug Administration for the treatment of Alzheimers Disease. The authors propose a putative mechanism for the use of memantine in the prophylaxis of migraine, review the pharmacology, and describe three case reports.

Introduction

In July, 2004, memantine, a non-specific glutamate antagonist, received regulatory approval for marketing as treatment for Alzheimers Disease in the U.S. Antagonism of certain glutamate receptors has been proposed and studied as a mechanism for the acute treatment of migraine headache.^{1,2,3} However, the usefulness of memantine as a migraine prophylactic agent has been doubted because of the non-specific nature of its activity. Also, researchers have noted that the anti-nociceptive dose of memantine is predicted to be considerably higher than standard doses used for Alzheimer's Disease, increasing risk of nausea, sedation, and other central nervous system side-effects. We have noted favorable clinical responses in a number of patients treated with standard Alzheimer's Disease doses of memantine and propose a call for controlled studies to evaluate its effectiveness as a migraine prophylaxis drug.

Patient histories

Patient 1. – A 42-year-old female computer operator with a history of headaches since childhood presented to our clinic for evaluation and treatment. Her baseline headache frequency had previously been 4 to 5 attacks monthly for many years, but had gradually escalated to chronic daily headache over the previous four to eight months. Her headache severity had increased to the point that she required emergency facility presentations approximately once per month for acute treatment of refractory attacks. The headaches were unilateral, lasting 24 to 72 hours, and were associated with nausea, vomiting, photophobia, phonophobia, and cervical tenderness. The pain was described as sharp and throbbing, and they were frequently incapacitating requiring hibernation for as much as an entire day. The patient also had the significant past medical history of coronary artery disease, past coronary artery stent placement, hypertension, hyperlipidemia, and type 2 diabetes mellitus. Therefore, triptans and other vasoconstrictors were contraindicated. For acute headache abortive therapy, the patient used oral diclofenac sodium 50 mg and/or tramadol 50 mg on a daily or near-daily basis, sometimes 3 or 4 times per day. If these medications were not effective, she then resorted with hydrocodone/acetaminophen, requiring approximately 20 tablets per month. She

had been on a variety of prophylactic medications without success, including tizanidine, metoprolol, bupropion, and amitriptyline. At her initial visit to our clinic, the patient was on moderate doses of bupropion, but was not tolerating this medication because of sedation. Memantine 5 mg daily was started as a prophylactic medication, and then was titrated to 5 mg BID after one week, followed by 10 mg BID on the third week. She was reevaluated three weeks after achieving a stable dosing regimen. At that time the patient reported only one significant migraine since reaching the 10mg BID dose and stated that her chronic daily headaches had ceased. Three months later, review of her headache diaries revealed that she was experiencing 1 or 2 migraines per month, and was only taking 3-4 hydrocodone/acetaminophen tablets per month. She had not required any further emergency room visits since starting memantine. There were no mental status changes or neurologic side-effects. The patient was continued on memantine 10 mg BID.

Patient 2. – A 56-year-old female homemaker with a history of headaches since 1957, presented for chronic headache evaluation. She had previously functioned in a challenging career but had ceased working outside the home several years ago due to severe incapacitating headaches. At her initial visit, she reported 15 to 20 headache days per month, and this frequency had been present and unrelenting for at least 3 years. Her headache pain was described as unilateral and incapacitating, accompanied by nausea, photophobia and phonophobia. Multiple prophylactic medications had been tried and failed, including topiramate, oxcarbazepine, montelukast, valdecoxib, tizanidine, trazodone, desipramine, quetiapine, doxepin, protriptyline, donepezil, sulindac, cyproheptadine, atenolol, verapamil, phenytoin, and divalproex. The patient was taking zolmitriptan for acute therapy, and fortunately still obtained an acceptable abortive response. However, due to the cost of her abortive therapy and insurance restrictions, she could only acquire 12 tablets per month. Consequently, she had begun treating some migraine attacks with naratriptan, but with less effectiveness. Her diaries demonstrated that she took abortive medication of one kind or the other at least 15 days per month, suggesting the possibility of medication over-use headache. The patient was placed on memantine 5 mg daily for prophylaxis. At her follow up visit 2 months later, the number of headaches was significantly reduced to two per week, and she was rarely taking abortive medication. Memantine was increased to 10 mg daily and she has tolerated this well and maintained adequate migraine control. At follow-up, the patient stated that she was “more hopeful than ever” about her headaches.

Patient 3. This 52 year-old female presented for evaluation of chronic daily headache. She began experiencing migraine at the age of 14. The attacks were initially intermittent and consistent with migraine without aura. Her attacks gradually transformed into chronic migraine five years ago and had been occurring on a daily or near-daily basis for approximately four years at the time of presentation. She described daily, dull, holocephalic, pressure punctuated by twice weekly attacks of severe unilateral throbbing periorbital episodes of head pain which were accompanied by nausea, vomiting, photophobia, phonophobia, dizziness, and aggravation by routine physical activities. She had the comorbid illnesses of asthma, irritable bowel syndrome, gastroesophageal reflux disease, allergic rhinitis, and chronic cervical dystonia. Her daily medications at the time of presentation included: venlafaxine, desipramine, clonazepam, montelukast, tegaserod,

loratadine, and lansoprazole. She was receiving botulinum neurotoxin A every three months for her painful cervical dystonia. She was using sumatriptan, ibuprofen, and oxycodone/acetaminophen on a daily or near-daily basis. At her initial visit, the patient was placed on a detoxification regimen for medication overuse headache and was treated with valdecoxib and tizanidine, with doses of dihydroergotamine-45 (DHE) to be used intermittently as abortive therapy. Her usual abortive medications were discontinued. After a three-month detoxification program, the patient continued to have daily or near-daily head pain, requiring frequent doses of DHE and occasional doses of quetiapine for rescue and sedation. Five months after her initial visit, still having chronic daily headache, the patient was started on memantine 5mg nightly and titrated over one month up to 10mg twice daily. Two months later, her follow-up assessment revealed that she was still experiencing dull non-descript head pain almost daily, but had only one day of severe migraine since starting memantine. Her abortive therapy (DHE) was completely effective with one dose. She had experienced no days of incapacitation or headache related disability. The only side effect was slight constipation which did not require treatment.

Glutamate and migraine pathophysiology

Glutamate is the most common excitatory neurotransmitter in the central nervous system. Glutamate acts on N-methyl D-aspartate (NMDA) and non-NMDA receptors in post-synaptic neuronal plasma membranes to mediate fast excitatory synaptic transmission in the CNS. These NMDA receptors are voltage- and ligand-gated channels that, upon activation, allow divalent (Ca^{++}) and monovalent (Na^+) ions to enter the neuron as K^+ exits. Under normal resting conditions, Mg^{++} blocks the ion channel preventing cation flux. Simultaneous presentation of glutamate and glycine in the synaptic cleft causes the neuron to depolarize, releasing bound Mg^{++} and allowing influx of Ca^{++} through the ion channel. Calcium entry is involved in normal signaling pathways and has been shown to be critical to learning, memory, and cognition. However, excessive glutamatergic signaling may be toxic to nerve cells by altering calcium homeostasis, eventually resulting in cell death.⁴ This neuronal over-excitation has been referred to as excitotoxicity. This mechanism is felt to be partially responsible for the cognitive decline seen in Alzheimer's Dementia.^{4,5} Recently, scientists have shown that antagonism of these glutamate receptors may be helpful in treating the symptoms associated with Alzheimer's Disease.⁴ Furthermore, clinical trials have led to the approval of the NMDA antagonist, memantine, in 2004 for the treatment of AD. Interestingly, there are clinical and pre-clinical data to support a role for glutamate in the pathophysiology of migraine.⁵

As further evidence of a role in migraine pathophysiology, glutamate has been demonstrated to be the primary neurotransmitter for nociceptive c-fibers in the trigeminocervical complex.⁶ In animal models, glutamate has been shown to initiate and support cortical spreading depression. In migraineurs, glutamate has been shown to trigger migraine attacks. Increased plasma and CSF glutamate levels have been demonstrated during and immediately following migraine attacks. Glutamate also causes the release of other neuropeptides from pre-synaptic neurons resulting in vasodilation, hyperalgesia, and central sensitization.⁷ If cell death were to occur in the descending

pain inhibition pathways of the brainstem (eg, the periaqueductal gray matter) in a manner similar to the excitotoxicity phenomenon of Alzheimer's disease, those pathways might become irreparable dysfunctional, a state which has been suggested to be causally related to chronic daily headache.⁸ One could theorize that as this process develops and proceeds over time unchecked, that the entity of chronic daily headache emerges and if allowed to progress may become irreversible.

For these reasons, antagonizing the effects of glutamate at the NMDA receptor has become a target for anti-migraine therapy. The protein c-fos has been established as a marker of activity of second order nociceptive fibers in the trigeminal nucleus caudalis and is actively expressed during migraine.⁹ In animal models, the NMDA antagonist MK-801 has been shown to reduce reduce c-fos expression in these second order nociceptive fibers in the TGC complex following superior sagittal sinus stimulation in cats and capsaicin stimulation in rats.^{10,11} Other animal models have demonstrated the effectiveness of NMDA antagonists to inhibit nociception in the spinothalamic tract of neuropathic monkeys, in rat spinal dorsal horns, and in rat nerve injury models of hyperalgesia and allodynia.^{12,13} Most recently, trials using medications which share this physiologic effect have demonstrated effectiveness in treating diabetic peripheral neuropathy in humans.¹⁴

Memantine, an NMDA antagonist

In the past, the therapeutic use of NDMA antagonists like ketamine and dextromethorphan in anti-nociceptive doses has been limited by CNS side effects such as hallucinosis. Memantine is a newer, uncompetitive antagonist with moderate affinity for NMDA receptors and a low side effect profile.¹⁵ It is completely absorbed from the GI tract following oral administration (F=100%), reaching a maximum plasma concentration between 3-8 hours after ingestion. Mean terminal half-life is 60-100 hours. Plasma concentrations are linear over therapeutic doses (10-40mg) and not influenced by food. Memantine is renally eliminated with 80% excreted in its unchanged form. Memantine undergoes renal secretion and reabsorption; alkalization of urine will decrease clearance. Otherwise, clearance is correlated with creatinine clearance. It is not metabolized by the P450 system, nor does it seem to have effects on P450 enzymes in vitro. Mean plasma binding is about 45%.¹⁶ In short, the pharmacokinetic profile for memantine is ideal for a maintenance medication such as would be necessary for a migraine prophylaxis drug.

In vitro studies demonstrate that memantine induces an open channel blockade on NMDA receptors in a voltage- and concentration-dependent manner. This effect persists in the presence of high concentrations of glycine. Memantine produces increased intracortical inhibition in healthy volunteers in a dose-dependent fashion. In addition, Memantine protects cultured neurons from excitotoxin-induced and glutamate-induced neuronal cell death. In animal models, memantine exhibited neuroprotective effects in several models of brain injury to include NMDA-induced injury, trauma, ischemia (vascular and focal), and quinolinic acid injury. Memantine also induced production of brain derived neurotrophic factor (BDNF). The long term implications for use in

migraine prevention are unclear, but one could hypothesize a contribution to disease modification over long term use of memantine.

Memantine's faster on/off kinetics and less complete channel blockade (approx 17% of channels) results in a significant reduction in side effects. Measures of motor excitability and membrane excitability were not altered. At recommended dosages, memantine is not associated with any changes in mood, attention, memory, perception or psychomotor functioning. Elderly healthy patients did demonstrate enhanced vigilance.¹⁷ In a double-blind, randomized controlled trial, adverse events for memantine were not greater than placebo except for diarrhea (5.4% vs 4.9%), insomnia (5.4% vs 4.9%), dizziness (5% vs 2.6%), HA (5% vs 3.1%), and hallucination (5% vs 2.1%). This side effect profile compares favorably to most of the widely used migraine preventatives today.

Conclusion

Glutamate antagonism is a current area of investigation as a molecular mechanism for the acute treatment of migraine. The glutamate antagonists, dextromethorphan and ketamine, have a demonstrated anti-nociceptive effect, but cause unacceptable central nervous system adverse events. Memantine is well tolerated in doses currently marketed for the treatment of Alzheimers Disease and its clinical pharmacology would suggest a possible role in the preventive maintenance of migraine. These three successful cases reported here suggest potential for efficacy in the prophylaxis of migraine. Controlled studies of memantine for the preventive treatment of migraine are warranted. The authors would also propose a theory of potential use of the drug in the long-term prevention of the progression of migraine to chronic migraine, based on the drug's known ability to prevent excitotoxicity induced neuronal dysfunction and death. This theory could be further validated if glutamate receptors could be identified in the descending pain inhibition pathways of the brain stem, such as the periaqueductal gray matter.

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