

Memantine for Chronic Migraine Prophylaxis

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ABSTRACT:

We studied the efficacy of a new moderate affinity NMDA-receptor antagonist in the treatment of migraines and tension-type headaches (TTH). The primary endpoint of this open label study was reduction of frequency and severity of migraines. Secondary endpoints included reduction of TTH and pain related to the head and neck in our study patients.

Memantine has recently been introduced in the US for dementing disorders, although has been used in Europe for some time. It blocks NMDA glutamate receptors, thought to be intrinsic to pain transmission, windup, long-term potentiation and central sensitization. Excitatory amino acid systems, like glutamate and its receptor subtypes, play a role in promoting pain mechanisms. Therefore, blockade of NMDA might reduce central barrage of afferent signals that might contribute to maintenance of migraine states. Agents whose activity, in part, impinges on the glutamate system are in use for migraine prophylaxis (topiramate).

20 patients with chronic migraines who had not responded to other prophylaxis measures were studied. They had an average of 9.2 migraines per month. 14/20 (60%) had TTH as well (average of 12.5 days per month). We added memantine 5mg per day with weekly increases of 5 mg, up to a maximum of 20 mg per day, as tolerated.

Patients kept headache diaries for migraines and TTH and pain scores as well. Evaluation were made after 1 month of therapy on 20 mg (or maximally tolerated dose) of memantine.

Migraine frequency fell to an average of 4.1 migraines per month, or almost 56% less than at baseline, in 14 of 20 patients. Remaining migraines were rated as less severe and easier to treat. Acute migraine and rescue medication use dropped by two-thirds. TTH frequency fell by 62%, to 6 headaches per month. 6 patients saw no response of their migraines to memantine. 4 patients reported dizziness and one nausea. 2 of these patients had betterment of their migraines.

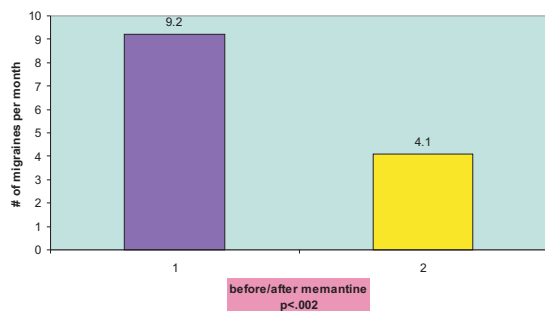
We conclude from this preliminary open-label study that memantine has the ability to offer successful prophylaxis of migraines and TTH in situations where other regimens have not benefited the patient. It speaks to the potential role of NMDA glutamate receptors in the maintenance of migraine and headache states. Memantine should be studied in migraine therapy in a double-blind manner.

RATIONALE/OBJECTIVES:

We wanted to explore the efficacy of blockade of NMDA receptors in the treatment of migraines and chronic tension-type headaches using a low-affinity antagonist, memantine. If one considers that there might be a commonality or overlap of signal barrage to the spinal cord or brainstem in chronic pain and chronic headache states, the glutamate system might be a point of amplification or reinforcement of the pain transmission cascade in these clinical conditions. In particular, memantine blocks excessive NMDA receptor activity without disrupting normal activity. Memantine does this through its action as an uncompetitive, low-affinity, open-channel blocker; it enters the receptor-associated ion channel preferentially when it is excessively open, and, most importantly, its off-rate is relatively fast so that it does not substantially accumulate in the channel to interfere with normal synaptic transmission¹⁻⁴. Numerous studies, both in animal models and in human clinical pain states, have demonstrated the ability of memantine to alter pain behaviors or parameters⁵⁻⁷; some studies failed to demonstrate clinical efficacy. No prior data exists in treating migraine or TTH.

The primary objective in this open-label study was to treat a cohort of refractory clinic patients from our clinic with memantine to see if the migraine and headache patterns would change over time. The primary objective was to look for a reduction in the frequency of migraines per month. The secondary objective consisted of reduction in tension-type headache frequency and severity.

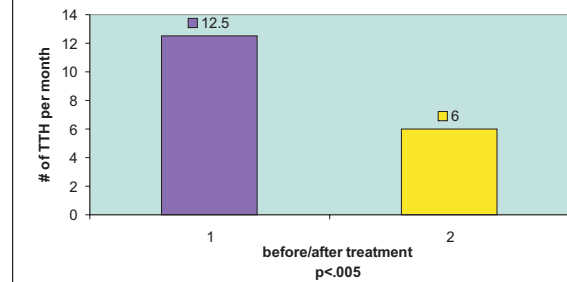
FIG 1--Reduction in Migraine Frequency with memantine



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FIG 2 -- Reduction in TTH with memantine



METHODS:

20 patients (10 females, 10 males) with chronic migraines who had not responded to other prophylaxis measures were studied. The average age of study patients was 49.9 years. All had IHS criteria migraine headaches on a chronic basis (average duration 8.7 years). At baseline, study patients had an average of 9.2 migraines per month. 14/20 (60%) had TTH as well (average of 12.5 days per month). We added memantine 5mg per day with weekly increases of 5 mg, up to a maximum of 20 mg per day, as tolerated. Average dose of memantine was 19.25mg per day across all study patients (range= 10-20mg).

Patients kept headache diaries for migraines and TTH and pain scores as well. Evaluation were made after 1 month of therapy on 20 mg (or maximally tolerated dose) of memantine, typically after at least 2 months' therapy at maximally tolerated doses of memantine. In one case, therapy was discontinued after 1.5 months of therapy before it was discontinued.

RESULTS:

The average length of treatment, including the initial titration of memantine dosage, was 4.6 months, with an average daily dosage of 19.25mg (range= 10-20mg/day).

Migraine frequency fell to an average of 4.1 migraines per month, from a baseline of 9.2 migraines per month, or almost 56% less than at baseline in 14 of 20 patients (p<.002) [See Figure 1]. 6 of 20 patients had no demonstrable change in their migraine frequency. Remaining migraines in responders were rated as less severe and easier to treat. Acute migraine and rescue medication use dropped by two-thirds.

TTH frequency fell by 52%, from a baseline of 12.5 to 6 headaches per month (p<.005) [See Figure 2]. 5 of 14 patients saw no response of their tension-type headaches after memantine treatment. 4 patients reported dizziness, 1 reported dry eyes and 1 nausea. 3 of these patients had betterment of their migraines, despite side effects eventually leading to discontinuation of the study medication.

CONCLUSIONS:

We conclude from this preliminary open-label study that memantine has the ability to offer successful prophylaxis of migraines and TTH in situations where other regimens have not benefited the patient. It speaks to the potential role of NMDA glutamate receptors in the maintenance of migraine and headache states, and its reduction after treatment with an NMDA-type glutamate antagonist. The side effect profile was minimal and the medication was very well tolerated. Memantine should be studied in migraine and headache therapy in a double-blind manner.

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