

Andrew Charles
Charles Flippen
Marcela Romero Reyes
Kevin C. Brennan

Memantine for prevention of migraine: a retrospective study of 60 cases

Received: 2 May 2007
Accepted in revised form: 21 June 2007
Published online: 24 September 2007

A. Charles (✉) • C. Flippen •
M. Romero Reyes • K.C. Brennan
Headache Research and Treatment Program,
Department of Neurology,
David Geffen School of Medicine
at UCLA,
635 Charles Young Drive, Suite 575,
Los Angeles, CA 90095, USA
e-mail: acharles@ucla.edu
Tel.: +1-310-794-1870
Fax: +1-310-206-6906

Abstract The objective was to retrospectively characterise the efficacy of memantine as preventive therapy in a series of patients with frequent migraine. Patients in a university headache clinic completed a survey regarding their experience with memantine, and medical records were reviewed. All patients who received memantine as preventive therapy for migraine over a 15-month period were mailed surveys and consent forms for record review. Patients were treated with memantine beginning at a dose of 5 mg/day, increasing if needed by 5 mg/week up to 10 mg twice a day. The majority of

patients (36 out of 54) treated with memantine for at least 2 months reported a significant reduction in estimated headache frequency, and improved function. Side effects were uncommon and generally mild. This limited retrospective case review suggests that memantine may be an effective preventive therapy for patients with frequent migraine. A prospective trial is warranted.

Keywords Migraine • Headache • Prevention • Memantine • Glutamate

Introduction

Despite the existence of multiple well established migraine preventive therapies, there is a significant proportion of migraine patients for whom currently available therapies are either ineffective or poorly tolerated. Migraine is increasingly viewed as an episodic disorder of brain excitability. Signalling by glutamate, the primary excitatory neurotransmitter in the central nervous system, is therefore an appealing target for migraine therapy [1]. NMDA receptor antagonists are known to inhibit cortical spreading depression (CSD), which is believed to be a fundamental mechanism of migraine. Memantine is a low-affinity, open channel blocker of NMDA

receptor channels that is FDA approved in the United States for the treatment of Alzheimer's disease [2, 3]. We have used memantine to treat patients with headache, the majority of whom had failed standard acute and preventive therapy. This report describes the initial experience of our patients with memantine as a treatment for prevention of migraine.

Methods

Patients were independently evaluated and treated by one of three different neurologists (AC, CF or KCB). A diagnosis of migraine was

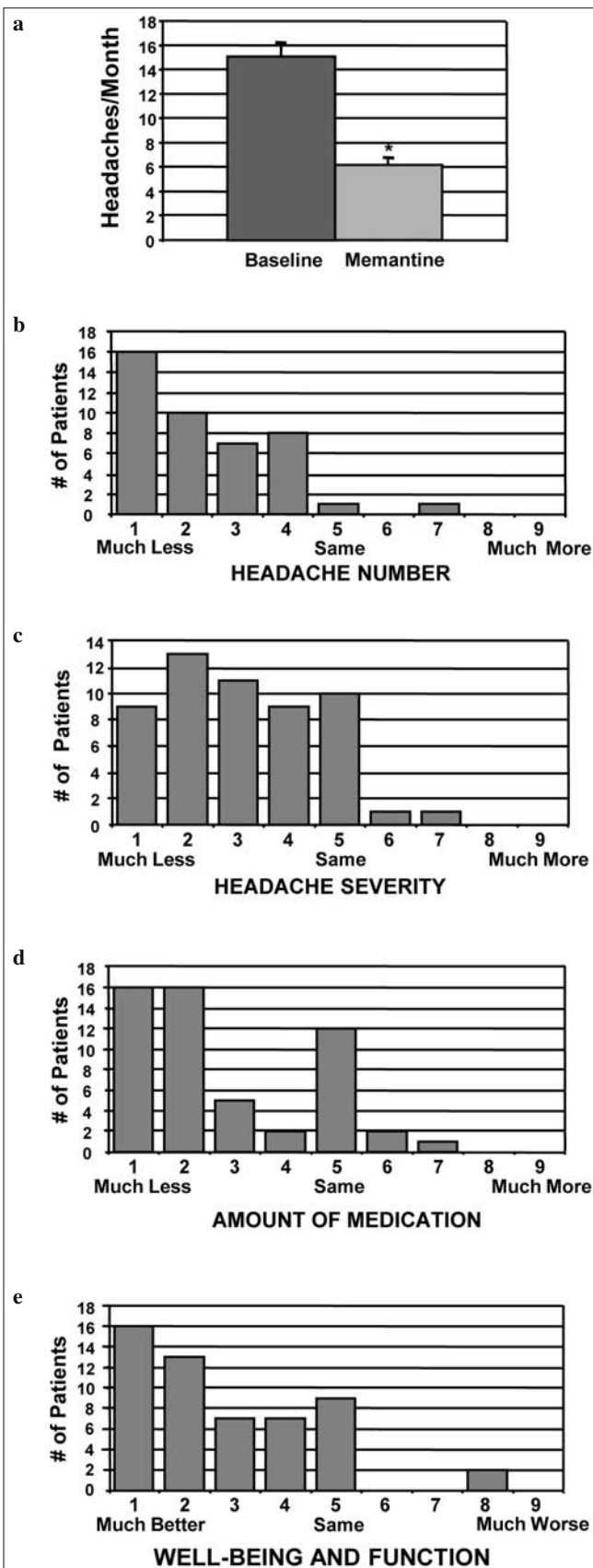
made based on ICDH-II criteria. A significant number had additional diagnoses of chronic migraine or medication overuse headache that were not considered independently of the migraine diagnosis. Patients were treated with memantine beginning at a dose of 5 mg once a day, increasing by 5 mg/week to as much as 10 mg twice a day. Patients were maintained at the lowest dose at which they were satisfied with the reduction in headache frequency. Most patients were provided medication samples to initiate therapy; some patients whose health insurance covered the cost of the medication were written a prescription to obtain the medication at a pharmacy. UCLA IRB approval was obtained to perform a retrospective case review. All migraine patients who had received memantine for at least 2 months were mailed a one-page survey, as well as a consent form to authorize review of medical records and anonymous reporting of their experience. Most patients based their responses on a headache diary, but these were not required for inclusion in the case review; headache frequencies are therefore estimates that may be significantly confounded by recall bias.

Results

Surveys and consents were mailed to 71 migraine patients who had been treated with memantine – of these 60 responded. Patient ages ranged from 14 to 78 years (mean age 49, median age 52); 49 were females and 11 were males. Twenty had migraine with aura and 40 had migraine without aura according to ICDH-II criteria. All patients had previously tried multiple approaches to migraine treatment without success. Out of 60 patients, 56 had tried other standard preventive therapies, and 51 had tried at least 2 different classes of preventive therapy.

Out of 60 patients, 54 continued therapy with memantine for at least 2 months, with ultimate doses of 5 mg, 10 mg, 15

Fig. 1 Patient experience with memantine for migraine prevention based on completed surveys. **a** Average headache frequency. Left bar indicates average estimated headache frequency for 3 months preceding memantine therapy. Right bar indicates average estimated headache frequency for at least two months during memantine therapy. Error bars indicate SEM. Memantine therapy was associated with a significant reduction in average headache frequency ($n=54$, $p<10^{-5}$ using paired sample t -test). **b** Histogram of patient responses to the 1–9 numerical analogue scale of “Overall number of headaches while taking memantine as compared with before you took it.” **c** Histogram of patient responses to the analogue scale of “Overall severity of headaches while taking memantine as compared with before you took it.” **d** Histogram of patient responses to the analogue scale of “The overall amount of medication you took for your headaches since you started taking memantine as compared with before you took it.” **e** Histogram of patient responses to the analogue scale of “How you felt and how well you functioned overall while taking memantine as compared with before you took it.”



mg and 20 mg (1, 7, 1 and 45 patients, respectively). In this group, estimated monthly headache frequency prior to memantine therapy ranged from 4 to 30 (median 12.5, mean \pm SD 15.2 \pm 8.8). Estimated monthly headache frequency during memantine therapy ranged from 0 to 22 (median 3.5, mean 6.1 \pm 6.0) (Fig. 1). Out of 54 patients, 36 (67%) reported a greater than 50% reduction in estimated monthly headache frequency. The majority of patients also reported decreased headache severity, reduced amount of medication taken for headache and improved level of function (Fig. 1). Out of 9 patients with daily headache, 6 reported a greater than 50% reduction in headache. Out of 20 patients with migraine with aura, 16 reported that it reduced the frequency of aura as well as headache. Out of 60 patients, 45 reported no side effects. Reported side effects included agitation, confusion, dizziness, weight loss, fatigue, rash and increased headache. Six patients discontinued memantine before 1 month of therapy because of side effects [rash (1), agitation (2), cognitive dysfunction (1), extremity pain (1)] and/or lack of efficacy (4).

Discussion

Our results suggest that memantine can be an effective therapy for prevention of migraine in patients in whom other established migraine preventive therapies have failed. Patients in this study had a high baseline headache frequency, and most had tried at least two standard migraine preven-

tive therapies. Even in this population, the majority of patients had a meaningful reduction in headache frequency and severity. Memantine was generally well tolerated, although side effects resulted in discontinuation of the medication in approximately 10% of patients.

Memantine's pharmacological characteristics suggest that it has the capacity to block excessive activation of NMDA receptors without affecting normal signalling by the receptor [4]. Memantine, like other NMDA antagonists, has been found to modulate CSD [5]. It is therefore possible that memantine could reduce episodic increases in cortical excitability underlying migraine. This potential mechanism is supported by our observation that memantine reduced the frequency of aura as well as headache. Memantine also blocks other ligand gated ion channels, including nicotinic acetylcholine receptors and 5HT₃ receptors [6, 7]. It could therefore have multiple other mechanisms of action that may modulate migraine.

This study is limited by its retrospective observations, lack of control group and lack of blinding. There are multiple biases that could therefore confound these observations, and there could be a highly significant placebo effect. Nonetheless, the results are encouraging because of the patient population that was studied, the overall tolerability of the medication and the scientific rationale for a mechanism of action in migraine prevention. Our patients' experience indicates that a formal prospective study of memantine's efficacy as a migraine preventive agent is warranted. Studies are ongoing in our laboratory to investigate potential cellular and pharmacological mechanisms of memantine in experimental models.

References

1. Sanchez-Del-Rio M, Reuter U et al (2006) New insights into migraine pathophysiology. *Curr Opin Neurol* 19:294–298
2. Chen HS, Pellegrini JW, Aggarwal SK et al (1992) Open-channel block of N-methyl-D-aspartate (NMDA) responses by memantine: therapeutic advantage against NMDA receptor-mediated neurotoxicity. *J Neurosci* 12:4427–4436
3. Winblad B, Poritis N (1999) Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). *Int J Geriatr Psychiatry* 14:135–146
4. Chen HS, Lipton SA (2006) The chemical biology of clinically tolerated NMDA receptor antagonists. *J Neurochem* 97:1611–1626
5. Peeters M, Gunthorpe MJ, Stribos PJ et al (2007) Effects of pan- and subtype-selective NMDA receptor antagonists on cortical spreading depression in the rat: therapeutic potential for migraine. *J Pharmacol Exp Ther* 321:564–572
6. Aracava Y, Pereira EF, Maelicke A et al (2005) Memantine blocks α 7 nicotinic acetylcholine receptors more potently than n-methyl-D-aspartate receptors in rat hippocampal neurons. *J Pharmacol Exp Ther* 312:1195–1205
7. Rammes G, Rupprecht R, Ferrari U et al (2001) The N-methyl-D-aspartate receptor channel blockers memantine, MRZ 2/579 and other amino-alkyl-cyclohexanes antagonise 5-HT₃ receptor currents in cultured HEK-293 and N1E-115 cell systems in a non-competitive manner. *Neurosci Lett* 306:81–84