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Cross-Over Trial of Gabapentin and Memantine as Treatment for Acquired Nystagmus

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Abstract

We conducted a masked, cross-over, therapeutic trial of gabapentin (1200mg/day) versus memantine (40mg/day) for acquired nystagmus in 10 patients (28–61 years; 7 female; MS: 3, post-stroke: 6, post-traumatic: 1). Nystagmus was pendular in 6 patients (oculopalatal tremor: 4, MS: 2) and jerk upbeat, hemi-seesaw, torsional, or upbeat-diagonal in each of the others. Both drugs reduced median eye speed ($p < 0.001$), gabapentin by 32.8% and memantine by 27.8%, and improved visual acuity ($p < 0.05$). Each patient improved with one or both drugs. Side-effects included unsteadiness with gabapentin and lethargy with memantine. Both drugs should be considered as treatment for acquired forms of nystagmus.

Keywords

nystagmus; oscillopsia; multiple sclerosis; oculopalatal tremor

Introduction

Acquired forms of nystagmus often produce disabling visual symptoms, such as blurred vision and illusory motion of the visual world (*oscillopsia*),¹ that can be alleviated if the ocular oscillations are reduced or abolished.² Prior studies have identified two drugs – gabapentin and memantine – that are effective in treating nystagmus, especially acquired pendular nystagmus (APN) associated with MS^{3–7} and congenital nystagmus.^{6,8} Gabapentin acts via the calcium channel subunit $\alpha 2\delta$ -19 and memantine is a non-competitive N-methyl-D-aspartate receptor antagonist.¹⁰ We aimed to compare gabapentin and memantine in a double-masked cross-over treatment trial for acquired forms of nystagmus, including jerk nystagmus and oculopalatal tremor (OPT), which have not been previously studied.

Subjects and Methods

Details of the patients studied are summarized in e-Table 1. Details of study design, drug doses, methods of data acquisition, and data analysis are available online (see supplementary information). We recruited adults of either sex complaining of blurred vision or oscillopsia due to acquired forms of nystagmus. All patients gave informed consent in accordance with our Institutional Review Board and the U.S. Food and Drug Administration. Our study conformed to the Consort statement, and was registered at ClinicalTrials.gov (#NCT00928954) and ISRCTN (#57618066).

Patients were evaluated prior to and following treatment with each drug (see Figure 1). At each evaluation, a neuro-ophthalmologic examination was performed, including monocular measurements of best-corrected distance visual acuity (recorded as the logarithm of the minimum angle of resolution, logMAR). Patients estimated the direction and amplitude of their oscillopsia while viewing a stationary target, and were asked about visual improvement and side-effects while receiving the drug treatments.

At each evaluation, eye movements were recorded in three-dimensions using the magnetic search coil technique¹ and median eye speed was determined, for each eye in turn, during attempted fixation of a central visual target at 1.2 m, near target at 20cm, and eccentric targets.

After baseline evaluation, patients were randomly assigned to take one of the two drugs. Each drug was given for two weeks, separated by a 2–3 week wash-out period. Gabapentin began at 1 capsule (300mg) daily for 3 days, then 1 capsule twice daily for 3 days, then 1 capsule thrice daily for 3 days, and finally 1 capsule four times daily (total = 1200mg/day) for the remaining 5 days. Memantine began at 1 capsule (10mg) daily for 3 days, then 1 capsule twice daily for 3 days, then 1 capsule thrice daily for 3 days, and finally 1 capsule four times daily (total = 40mg/day) for the remaining 5 days.

We evaluated our two primary outcome measures, median eye speed and distance visual acuity, by making paired comparisons, for corresponding eyes and fixation conditions, before and during each drug treatment. Since the data were not normally distributed, we used the Wilcoxon rank-sum test for statistical analysis. Finally, we contacted patients after the trial was completed to determine whether they were still taking and benefitting from the drug that suppressed their nystagmus best.

Results

All patients completed the study, but Patient 1 could only tolerate 20mg/day of memantine and remained on this dose until re-evaluation. In Patient 3, it was only possible to record right eye movements and visual acuity, because of left exposure keratopathy.

Representative records of Patient 1's nystagmus prior to and during treatment with each drug are shown in Figure 2; both drugs reduced median eye speed and improved visual acuity. Results of both primary outcome measures are summarized for all patients in Figure 3 and e-Table 1. Both gabapentin and memantine significantly decreased median eye speed ($p < 0.001$), with gabapentin decreasing it by 32.8% and memantine by 27.8%, on average. Comparison of median eye speeds while viewing near and eccentric targets revealed similar and corresponding decreases for each patient. We tested for carry-over effects by comparing the median eye speeds prior to initiation of each drug treatment; there was no overall difference between the pre-treatment values ($p > 0.05$). Only Patient 4 showed a sustained decrease in median eye speed after receiving the first drug (gabapentin, see e-Figure 1). We tested for a priming effect, due to the order in which the drugs were given, but there was no

significant effect ($p>0.05$). In two patients with APN due to MS, neither drug caused a change in nystagmus frequency. In patients with OPT, changes in nystagmus frequency were variable and complex, reflecting the broad spread of the power spectrum of nystagmus in these patients.¹¹

Visual acuity improved significantly with both memantine ($p=0.011$) and gabapentin ($p=0.02$). The mean improvement was 0.084 logMAR with both drugs. Correlations between visual acuity and median eye speed were low ($R^2<0.17$), as were correlations between changes in visual acuity and median eye speed induced by the drugs.

The effects of the drugs were idiosyncratic and unrelated to the etiology or waveform of nystagmus. The most common nystagmus form in our study, OPT following brainstem stroke, improved with both gabapentin and memantine (see Figure 2 and e-Figure 1). APN due to MS improved with both drugs; superimposed upbeat nystagmus in one patient was suppressed with memantine (e-Figure 2). Patients with jerk nystagmus all showed some improvement with one or the other drug: upbeat, upbeat-diagonal, and hemi-seesaw nystagmus all improved most with memantine, while torsional nystagmus improved most with gabapentin (e-Figure 3).

Reported side-effects are summarized in e-Table 1. In general, gabapentin was most likely to cause unsteadiness (especially in patients with pre-existing ataxia), while memantine was most likely to cause lethargy and drowsiness. However, both drugs were generally well-tolerated and no exacerbation of symptoms was reported with memantine in the patients with MS.

Seven patients continued to take their preferred drug following the trial, with ongoing beneficial effects (follow-up after exam 4 ranged from 1–34 months, median 19); some preferred a reduced dose, to minimize side-effects. One patient could not afford treatment, one spontaneously improved, and one with MS preferred gabapentin due to side-effects with memantine (e-Table 1).

Discussion

We compared the effectiveness of gabapentin and memantine in suppressing acquired forms of nystagmus and improving vision. We found that both drugs were effective, with an equal number of patients gaining a better response with one or the other drug.

How do our results compare with previous controlled trials? Anticholinergic agents, such as trihexyphenidyl¹² and transdermal scopolamine,¹³ are not effective treatments. The GABA_B agonist baclofen was reported to reduce upbeat and downbeat nystagmus,¹⁴ but a trial of baclofen versus gabapentin in 21 patients with acquired nystagmus demonstrated little effect of either drug on jerk nystagmus; gabapentin, but not baclofen, suppressed APN in 10/15 patients.³ Memantine has been reported to suppress APN in patients with MS.^{4,7} It was possible to abolish nystagmus in some patients when giving 60mg/day, but this also produced fatigue and dizziness.⁷ Additionally, memantine is reported to exacerbate MS symptoms.¹⁵ In our study, every patient demonstrated decreased median eye speed due to one or the other drug, and both were generally well-tolerated. Our other primary outcome measure, visual acuity, also improved with both drugs. Pendular nystagmus, due to MS or OPT, was improved by both drugs, while jerk nystagmus improved most with memantine. At the doses we gave, neither drug abolished the nystagmus in any patient, but symptomatic improvement with one or the other was the rule.

Do our results suggest that one drug is better for a specific form of nystagmus? Four of our patients had pendular nystagmus due to OPT, with three showing a greater improvement

with gabapentin than with memantine. Nystagmus in OPT is thought to be due to synchronized discharge of neurons in the inferior olivary nucleus (IO) at ~2 Hz; the IO pacemaker then induces maladaptive learning by the cerebellar cortex, which variably causes oscillations of the eyes and branchial muscles.¹¹ Although gabapentin and memantine might have their effect on the IO pacemaker, a more likely site is within the cerebellum. Systematic analysis of changes in power spectra of the nystagmus of OPT may provide further insights into pathogenesis.

Currently, APN associated with MS is thought to arise from instability in the brainstem-cerebellar neural network that normally ensures steady eccentric gaze (the *neural integrator*),¹ to which both GABAergic and glutamatergic mechanisms contribute.^{16,17} Our two patients with APN associated with MS improved with both drugs, with memantine also suppressing a superimposed upbeat component in one patient (e-Figure 2).

Both memantine and gabapentin had effects on jerk forms of nystagmus. Memantine was more effective in suppressing upbeat, upbeat-diagonal, and hemi-seesaw nystagmus, whereas gabapentin was superior for a patient with torsional nystagmus. Since each of these forms of nystagmus has a different pathogenesis,¹ further studies of larger patient groups are required to confirm our results.

In summary, we have demonstrated that both gabapentin and memantine can suppress nystagmus and improve vision in patients with a variety of acquired forms of nystagmus. Whether one drug or the other was more effective was idiosyncratic, but both drugs were generally well-tolerated. Thus, the neurologist should consider both gabapentin and memantine as therapy for patients with acquired nystagmus. However, gabapentin may be preferable in MS, since memantine is reported to cause worsening of MS symptoms.¹⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow diagram summarizing study design; see Methods for details.

Figure 2.

Representative records of vertical gaze prior to and during treatment with gabapentin and memantine from Patient 1; positive values indicate upward movements. Note that this patient was only able to tolerate 20mg/day of memantine.

Figure 3.

Summary of changes in median eye speed (in deg/second) (A and B) and distance visual acuity (expressed as logMAR) (C and D) for all ten subjects. In A and B, each point is a comparison of the dimension of each patient's nystagmus with the fastest component, measured during either right or left eye viewing of a stationary target. Data points lying below the diagonal indicate a reduction of median eye speed during treatment. In C and D, each point compares visual acuity of each eye prior to and during treatment in each patient. Data points lying below the diagonal indicate an improvement in visual acuity during treatment. Comparisons were performed using the Wilcoxon rank-sum test and significance values are indicated.