SHORT REPORT

Gabapentin but not vigabatrin is effective in the treatment of acquired nystagmus in multiple sclerosis: how valid is the GABAergic hypothesis?

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Abstract

Acquired nystagmus occurs frequently in patients with multiple sclerosis and is often the cause of illusory motion of the environment (oscillopsia), and blurring of vision. Based primarily on the beneficial effect of gabapentin on acquired pendular nystagmus (APN), a GABAergic mechanism in controlling nystagmus has been hypothesised. If increasing GABA concentrations in the CNS are critical for the treatment of nystagmus, then a selective GABAergic drug should be highly successful. However, as gabapentin is not a selective GABAergic agent, vigabatrin, a “pure” GABAergic medication, and gabapentin, were compared in a single blind cross over trial in eight patients with definite multiple sclerosis.

Patients were randomly assigned to begin with gabapentin (1200 mg daily) or vigabatrin (2000 mg daily). Neuro-ophthalmological and electro-oculographic (EOG) evaluations were performed four and three times, respectively. Treatment efficacy was based on improving visual acuity and EOG indices (amplitude or frequency of nystagmus, or both) by at least 50% of pretreatment values. Three out of eight patients dropped out due to adverse effects.

In the remaining five patients gabapentin improved symptomatic pendular or gaze evoked jerk nystagmus in four. Three patients decided to continue gabapentin therapy. Importantly, vigabatrin proved useful in only one out of five patients, suggesting that gabapentin effectiveness may be related to additional non-GABAergic mechanisms of action. Interaction with cerebral glutamate transmission by inhibition of NMDA receptor might be an alternative hypothesis for the therapeutic action of gabapentin.

Methods

Eight patients with clinically definite multiple sclerosis, followed up as outpatients at the Multiple Sclerosis Centre of the Department of Neurological Sciences and Vision, University of Genoa, were initially enrolled in this single blind cross over trial. Three patients dropped out of the study due to the occurrence of adverse effects (two patients experienced dizziness with vigabatrin and one patient severe nausea due to gabapentin). Thus, the final group consisted of five patients, two men and three women, two with relapsing-remitting
multiple sclerosis and three with chronic progressive multiple sclerosis. The mean age was 36.5 (range 24–55) years and the mean disease duration was 10.5 (range 5–21) years. At study entry, mean EDSS score was 5.5. All patients experienced a stable, symptomatic, horizontal nystagmus causing oscillopsia, or blurred vision, or both. One (patient 2) had APN with a mild suppression (and a slight improvement in visual acuity) by fixation of a near target. Four patients presented with APN plus gaze evoked jerk nystagmus. No previous symptomatic treatment had been attempted. Clinical details are shown in table 1.

Patients were randomly given either gabapentin or vigabatrin (both available commercially in Italy) at an increasing dosage to 1200 mg/day and 2000 mg/day, respectively, for 21 days. A lapse of 2 weeks between the two treatments served as a wash out period. Both the treating physician and the patients were aware of the nature of the medications. Gabapentin was given at an initial dose of 300 mg daily. After 3 days, dosage was increased to 300 mg twice daily. After 7 days the dosage was titrated to 1200 mg. The dose of vigabatrin was initially 500 mg daily, then was increased to 1200 mg. The dose of vigabatrin was initially 500 mg daily, then was increased to 500 mg twice daily after 3 days, to reach a maximum dosage (2000 mg) after 7 days. No concomitant medications were allowed. All patients provided informed consent to participate.

Four neuro-ophthalmological examinations were performed: (1) before starting therapy (T0); (2) after 3 weeks of treatment (T1); (3) after a 2 week wash out (T2); (4) at the end of the second treatment period (3 weeks) (T3). The examination included an assessment of nystagmus with description of eye movement and a short video recording, and measurement of monocular and binocular visual acuity (decimal values) at near (Parinaud card) and far (Snellen card) distances, in the primary position and in eccentric horizontal gaze.

A DC electrocugraphy (EOG) recording (Nicolet-Nystar) was performed at T0, T1, and T3. Silver-silver chloride electrodes were attached to the inner and outer canthi of the eyes to record horizontal eye movements. Calibration was done before and during the recording session. We recorded nystagmus with or without fixation in the primary position (looking straight ahead) and in eccentric horizontal gaze, horizontal random saccades (6 degrees–32 degrees) and horizontal smooth pursuit movements (0.4, 0.2, and 0.1 Hz and 16 degree amplitude). The EOG amplifier allowed automatic measurements of mean amplitude (degrees) and frequency (Hz) of oscillations from 1 minute recording sessions. Latency, accuracy, and velocity of horizontal saccades and smooth pursuit gain were automatically measured as well. Both neuro-ophthalmological and EOG assessors were blinded to the nature of the drugs.

The efficacy of treatment was determined using three indices: (1) subjective report of decreased oscillopsia; (2) improvement of visual acuity of at least 50% from baseline values; (3) cessation of nystagmus or reduction in either amplitude or frequency of oscillations by at least 50% from baseline values.

**Results**

Table 2 provides a summary of effects of both drugs in each patient. Gabapentin proved effective in four out of five patients tested.
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Although these two types of eye oscillation reflect different pathogenetic mechanisms, both seemed to respond well to gabapentin.

The main result of our study, however, is that vigabatrin was ineffective in improving oscillopsia or blurred vision and in reducing nystagmus; only one patient (4) benefited from vigabatrin (and from gabapentin as well). Vigabatrin is a structural analogue of GABA, with a well known "pure" mechanism of action—that is, an irreversible inhibition of GABA transaminase. This, in turn, produces an increase in GABA concentrations in CNS. Caution is obviously needed to draw any conclusion from a study on only five patients. However, lack of therapeutic success with a selective GABAergic drug such as vigabatrin raises some considerations. Firstly, GABA seems to be just one, and probably not the most important, neurotransmitter involved in coordinating conjugate ocular movements, at least in the horizontal plane. Many other neurotransmitters—such as excitatory aminoacids, acetylcholine, and glycine—have been identified in the ocular motor system and are likely relevant in controlling visual fixation. Secondly, the beneficial action of gabapentin on nystagmus may be exerted through a non-GABAergic mechanism. Gabapentin is a relatively novel antiepileptic drug recently found to be effective for several neurological symptoms including paroxysmal symptoms in patients with multiple sclerosis. Several putative mechanisms of action have been identified for gabapentin. Among them, voltage dependent block of voltage sensitive sodium (Na+) channels, attenuation of voltage sensitive calcium (Ca2+) channels, and antiglutamatergic activity at the NMDA site.

The molecular mechanisms underlying pathological nystagmus are very complex and, whereas the pathophysiology of eccentric gaze holding impairment is well established, little is known about the neuropharmacology of APN. It is tempting to speculate that the multiple pharmacological actions of gabapentin might explain its role in controlling different types of eye oscillation. In particular, a glutamate antagonist effect through inhibition of NMDA receptor at different neuroanatomical sites (decrease of excitatory input either to the motor neurons or to the Purkinje cells?) might be responsible for the therapeutic action. The reported beneficial effect on APN by memantine, another non-
competitive NMDA receptor antagonist, is consistent with this hypothesis.

4 White HS. Comparative anticonvulsant and mechanistic profile of the established and newer antiepileptic drugs. Epilepsia 1999;(suppl 5):S2–10.
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*J Neurol Neurosurg Psychiatry* 2001 71: 107-110
doi: 10.1136/jnnp.71.1.107