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Lamotrigine in trigeminal neuralgia secondary to multiple sclerosis

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Sirs: Lamotrigine (LTG), an antiepileptic drug, has recently been used successfully to treat essential trigeminal neuralgia (TN) [1, 5]. A small number of patients suffering from TN secondary to multiple sclerosis (MS) have also been very successfully treated [5]. LTG has fewer and less severe adverse effects than carbamazepine (CBZ), the traditional drug for treating TN, and is similarly effective in pain relief [5]. LTG is thought to act by blocking sodium (Na^+), thereby preventing anomalous discharges of trigeminal axons [5]. Most of the adverse effects of CBZ are related to functions of the central nervous system, mainly coordination and vigilance. Although not dramatically evident in the large population of young patients who receive CBZ for epilepsy with no obvious neurological deficits, such side effects can be devastating in patients who are neurologically impaired. There are reports of CBZ being responsible for an exacerbation of weakness in MS patients [3] and of a possible correlation between cerebellar atrophy and CBZ side effects in non-MS subjects [8]. The essential form of TN typically affects elderly patients, who suffer from a pseudophysiological decline in some neurological functions (coordination being one of the most relevant). However, the symptomatic form is most common among MS patients, a condition in which coordination is commonly impaired.

We compared LTG to CBZ in the efficacy of relieving TN pain and in effects on the neurological conditions of MS patients. The study included 18 patients (4 men and 14 women) with clinically definite MS [6]. The mean age was 51.1 years, mean disease duration 14.7 years, and mean TN duration 7.1 years. TN had been the presenting symptom of MS in two patients. All patients had previously been treated with CBZ, at doses of 200–800 mg/day. Informed consent was obtained from all patients. It was an open study with evaluation before and after treatment in the same patients. Although the patient was aware of the treatment given, the examining physician was not. The following were evaluated: CBZ and LTG oral intake, pain, Expanded Disability Status Scale (EDSS) [4], ambulation index [2], cerebellar signs [4], brainstem signs [4], and drowsiness. Pain (subjective evaluation) was graded from 0 (no pain) to 3 (most severe pain) according to the scales previously published on trigeminal neuralgia [5]. EDSS, ambulation index, cerebellar functions, and brainstem signs were scored according to scales in the original published papers. Drowsiness was graded as 0=absent, 1=patient experiences mild drowsiness, 2=patient experiences moderate drowsiness, 3=patient sleeps excessively and is sometimes confused upon being awakened.

At the initial evaluation all patients were taking CBZ at doses reported in Table 1. CBZ was tapered until complete suspension over a 1-week period (where indicated clonazepam was allowed as rescue medication). The second evaluation took place after 2 weeks of CBZ suspension. LTG was administered at 25 mg daily, and the dose was gradually increased (25 mg every 3 days) to a maximum dose of 400 mg/day. Patients were instructed to stop increasing LTG when complete pain relief was obtained; they were to notify the treating physician immediately of changes in pain level. The third evaluation took place when complete pain relief was reached or at the dose of 400 mg/day. In addition to the clinical examination which was performed at each visit, plasma levels were now determined by high-pressure liquid chromatography. The fourth and final evaluation followed the third after a mean of 9.6 months (3–22). Statistical analysis was performed using the nonparametric Wilcoxon matched-pairs signed-ranks test by SPSS for Windows (release 5.0.1).

All patients experienced incomplete or poor pain relief with CBZ (Table 1). Pain intensity worsened slightly in six patients with withdrawal of CBZ (Table 1, P=0.005). At the third evaluation LTG had resulted in complete or nearly complete pain relief at doses between 75 and 400 mg/day (Table 1, P=0.0004 vs. evaluation 1; P=0.0003 vs. evaluation 2). Only one patient (no. 7) experienced little or no relief. No variation in pain relief was observed at the final visit, with no increase in dose between visits 3 and 4. Although pain relief was achieved, LTG was discontinued in one patient (no. 8) at the dose 100 mg/day due to adverse event (skin rash). Plasma levels of LTG were proportional to the oral day dose but fairly independent of the occurrence of complete pain relief, which took place within a range from 0.9–3.7 µg/ml (mean 2.3+1.2). Upon withdrawal of CBZ 15 patients showed improvement of at least one point in two of the five measured aspects of neurological condition. Drowsiness was most affected by the change in therapy; since it had been present to some degree in 16 patients, and completely resolved following CBZ withdrawal (P=0.0004). Cere-

Table 1 Subjective evaluation of pain and drowsiness during carbamazepine intake (*CBZ*, evaluation 1), after carbamazepine withdrawal (evaluation 2), and during lamotrigine intake (*LTG*, evaluation 3)

Patient no.	Evaluation 1			Evaluation 2			Evaluation 3		
	CBZ dose (mg/day)	Pain	Drowsiness	Washout (mg/day)	Pain	Drowsiness	LTG dose (mg/day)	Pain	Drowsiness
1	600	2	2	0	2	0	300	0	0
2	600	2	0	0	3	0	200	0	0
3	800	1	2	0	2	0	100	0	0
4	600	1	0	0	2	0	200	0	0
5	600	2	2	0	3	0	200	0	0
6	800	2	1	0	2	0	200	0	0
7	600	2	2	0	3	0	400	3	0
8	600	2	1	0	3	0	100	0	0
9	400	1	3	0	1	0	75	0	0
10	600	2	2	0	2	0	125	0	0
11	600	2	1	0	2	0	200	0	0
12	400	2	2	0	3	0	150	0	0
13	600	2	1	0	3	0	200	0	0
14	600	1	1	0	2	0	150	0	0
15	600	2	1	0	2	0	150	0	0
16	400	2	2	0	2	0	175	0	0
17	400	1	1	0	2	0	75	0	0
18	400	2	2	0	2	0	100	1	0

bellar signs were partially improved in five patients and completely resolved in two (P=0.018). Brainstem signs were partially improved in four patients and completely resolved in three (P=0.018). Eleven patients showed an improvement in ambulation index, and in seven it was unchanged (P=0.003). Introduction of LTG did not affect neurological features, which remained stable at the final evaluation. EDSS was unchanged due to its lack of sensitivity in measuring slight variations in neurological changes [7, 9].

Most of our patients had previously been treated successfully with CBZ although an increased dose resulted in significant adverse neurological effects precluding use of the optimal dose to relief pain. The initial evaluation showed pain relief to be either incomplete or poor, with most patients experiencing neurological impairment as an adverse effect due to CBZ. These considerations made it acceptable to both patients and clinicians to attempt the complete discontinuation of CBZ in order to assess the neurological status without pharmacological interference, and then to attempt controlling their pain with LTG. Pain relief was achieved by LTG with a variable range of daily doses and plasma levels, which appear to be far less homogeneous than those found effective in the similar previous report concerning LTG in TN secondary to MS [5]. The larger number of cases in the present trial may be responsible for this difference, which is probably more realistic than the previous finding. LTG was found to have no relevant adverse effects on the neurological status, which remained stable following withdrawal of CBZ. LTG must be increased gradually to the therapeutic range, which may be a drawback if quick pain control must be achieved. Because of potential interactions between LTG and other antiepileptic drugs currently employed for TG, their use to achieve rapid pain control while slowly increasing the dose of LTG should be carefully monitored. We believe that a brief delay in obtaining pain relief is often acceptable, considering that LTG monotherapy can more quickly suggest the optimal steady state dose with minimal side effects.

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