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Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy

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Abstract

In a multicentre, double-blind trial 150 elderly patients (mean age 77 years) with newly diagnosed epilepsy were randomised in a 2:1 ratio to treatment with lamotrigine (LTG) or carbamazepine (CBZ). Following a short titration period, the dosage was individualised for each patient while maintaining the blind over the next 24 weeks. The main difference between the groups was the rate of drop-out due to adverse events (LTG 18% versus CBZ 42%). This was in part a consequence of the lower rash rate with LTG (LTG 3%, CBZ 19%; 95% CI 7–25%). LTG-treated patients also complained less frequently of somnolence (LTG 12%, CBZ 29%; 95% CI 4–30%). Although there was no difference between the drugs in time to first seizure, a greater percentage of LTG-treated patients remained seizure-free during the last 16 weeks of treatment (LTG 39%, CBZ 21%; $P = 0.027$). Overall, more patients continued on treatment with LTG than CBZ (LTG 71%, CBZ 42%; $P < 0.001$) for the duration of the study. The hazard ratio for withdrawal was 2.4 (95% CI 1.4–4.0) indicating that a patient treated with CBZ was more than twice as likely to come off medication than one taking LTG. In conclusion, LTG can be regarded as an acceptable choice as initial treatment for elderly patients with newly diagnosed epilepsy.

Keywords: Epilepsy; Drug trial; Lamotrigine; Carbamazepine; Elderly; Efficacy; Safety

1. Introduction

Old age is the commonest time to develop a seizure disorder (Tallis et al., 1991; Hauser, 1992; De la Court et al., 1996). More than 1% of 80 year olds and above have epilepsy. Around 25% of new cases of epilepsy occur in people over 60

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years of age (Sander and Shorvon, 1996). No controlled clinical trials of antiepileptic drugs (AEDs) have been conducted in the elderly, despite the differences in drug handling and response in this population compared with younger patients (Willmore, 1998). Epilepsy in the elderly is often complicated by the presence of a range of medical disorders, for which other therapeutic agents may be prescribed. One of the standard treatments for newly diagnosed partial and tonic-clonic seizures is carbamazepine (CBZ) (Brodie and Dichter, 1997). This is also a preferred treatment for the elderly, although phenytoin (PHT) and sodium valproate (VPA) are also commonly used by geriatricians in the UK (Stolarek et al., 1995).

Lamotrigine (LTG), one of the newer AEDs, is licensed widely for partial and generalised seizures as add-on treatment and as monotherapy in adults and children (Dichter and Brodie, 1996). The drug has an elimination half-life exceeding 24 h and is metabolised in the liver largely by glucuronidation (Wilson and Brodie, 1996), a process largely unaffected by ageing (Posner et al., 1991). In a previous randomised double-blind study in adults with recent-onset epilepsy, no difference in efficacy was found between CBZ and LTG, while the latter was better tolerated (Brodie et al., 1995). A similar comparison has now been undertaken between LTG and CBZ in older people with newly diagnosed epilepsy.

2. Methods

2.1. Protocol

Patients aged 65 years and above with newly diagnosed epilepsy were allocated to double-blind treatment with LTG or CBZ, with LTG being allocated twice as often as CBZ. Treatment allocation was determined by a computer-generated random sequence, which was unknown to the investigators during the trial. It was planned to enrol 100 patients on LTG for the study, in keeping with the International Conference on Harmonisation (ICH) guidelines (1993) for studies in the elderly. Fifty additional patients were randomised to CBZ to provide a treatment comparison.

Each patient reported two or more seizures of any type during the previous year with at least one event during the past 6 months. Standard International League against Epilepsy definitions of idiopathic, symptomatic and cryptogenic epilepsies (Commission on Classification and Terminology, 1989) were provided, and investigators invited to indicate at recruitment into which category the patient's epilepsy best fitted. The design and conduct of the study were approved by the ethics committee at each participating centre. Written informed consent was obtained from all patients. Those who met the inclusion criteria were screened and provided with seizure diary cards. Each was assessed during baseline and 2, 4, 6, 12 and 24 weeks after starting treatment. Unscheduled visits were allowed as necessary.

LTG 25 and 50 mg tablets and CBZ 100 mg tablets were formulated to match CBZ 200 mg tablets. Randomisation was stratified by study centre and unused randomisation codes were not made available to the investigators. Dosage regimes are shown in Table 1. After titrating to 100 mg LTG or 400 mg CBZ daily, upward adjustments by 50 mg LTG or 200 mg CBZ increments were made in response to further seizures. Reductions in dosage (25 mg LTG or 100 mg CBZ decrements) were allowed on the emergence of side-effect. All such alterations were undertaken while maintaining the blind. At each hospital visit venous blood was sampled for measurement of AED concentrations which was undertaken in a central laboratory. LTG was

Table 1
Pre-selected dosing schedules for lamotrigine and carbamazepine[a]

	Lamotrigine	Carbamazepine
Weeks 1–2	25 mg	100 mg
Weeks 3–4	25 mg bd	100 mg bd
Weeks 5–6	50 mg bd	200 mg bd
Weeks 7–24	75–500 mg	200–2000 mg

[a] Dosage could be adjusted from week 6 onwards while maintaining the blind.

assayed using a double antibody radioimmunoassay procedure and CBZ by fluorescence polarisation immunoassay as a check on compliance. Results were not made available to the investigators during the study.

2.2. Objectives

As patients were randomised in a 2:1 ratio of LTG: CBZ, the major outcome measures concerned safety, in particular the reporting of adverse events and withdrawal from treatment. Effectiveness was assessed using with-drawal from the study (Mattson et al., 1985), and the proportion of patients remaining seizure-free during the last 16 weeks of treatment. Both parameters can be regarded as a combined measure of efficacy and safety. Secondary efficacy was measured by time to first seizure

2.3. Statistics

The percentage of patients reporting an adverse event was tabulated, and 95% confidence intervals for the difference between treatments calculated based on the normal approximation to the binomial distribution. Withdrawal from the study and the proportion of patients remaining seizure-free after 6 weeks of dosing were compared using the proportional hazard survival method adjusting for the pre-treatment seizure frequency. Kaplan Meier curves were constructed for both. In the seizure freedom analysis, patients were censored upon withdrawal from the study. An additional measure of global effectiveness, the proportion of patients who were both seizure-free in the last 16 weeks of the study and did not discontinue treatment, was compared using Fisher's Exact Test.

3. Results

A total of 150 patients were recruited (Table 2). Similar numbers were classified by the investigators as having idiopathic (LTG 41%, CBZ 31%), symptomatic (LTG 38%, CBZ 44%) and cryptogenic (LTG 21%, CBZ 25%) epilepsy. Thirty percent of the LTG and 38% of the CBZ group had had a previous cerebrovascular accident. The consort table for the study is illustrated in Table 3. The two patients who died while taking CBZ succumbed to a cerebrovascular accident and pneumonia respectively, neither of which was regarded as drug-related. The median daily doses of LTG (79%) and CBZ (82%) in patients completing the study were l00 mg (range 75–300 mg) and 400 mg (range 200–800 mg) respectively. Median AED concentrations at the end (week 24) of the study were 2.3 mg/l for LTG and 6.9 mg/l for CBZ.

Table 2
Demographic data in patients randomised to lamotrigine or carbamazepine

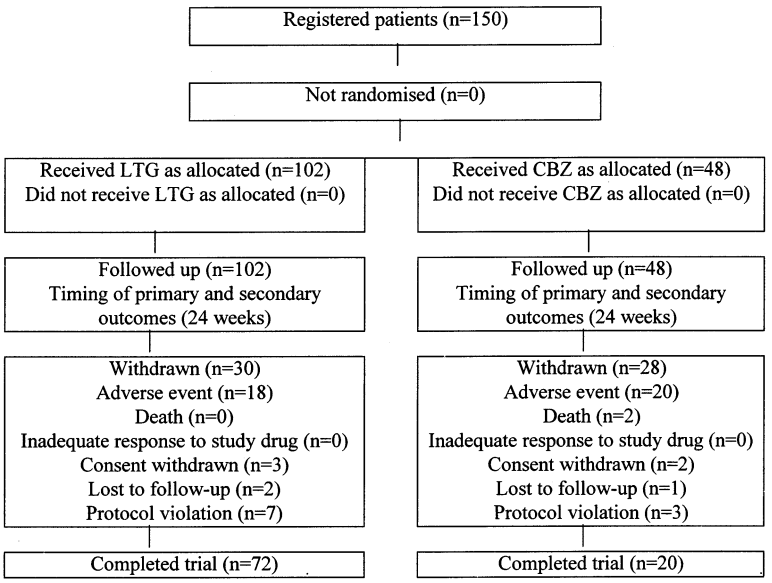
	Lamotrigine	Carbamazepine
Patients	102	48
Mean age (years)	77	76
Age range (years)	65–94	66–88
Male/female (%)	54/46	58/42
Weight (kg)	68	68
Height (cm)	164	164
Baseline seizures (median)	4	5
Range[a]	1–276	1–108

[a] One patient in each group experienced just one seizure.

The most common adverse events reported in both groups are listed in Table 4. LTG was significantly less likely than CBZ to produce somnolence (LTG 12%, CBZ 29%, 95% CI 4–30%). Premature discontinuations are shown in Table 5. Fewer patients dropped out due to adverse events with LTG (18%) than CBZ (42%). Reasons for withdrawal in the majority of patients are listed in Table 6. Significantly fewer LTG than CBZ-treated patients withdrew due to rash (LTG 3%, CBZ 19%; 95% CI 7–25%). There were no reports of Stevens–Johnson syndrome or toxic epidermal necrolysis with either drug, although three patients with CBZ-induced rash were hospitalised for observation.

In terms of global effectiveness, 71% of patients remained on treatment for the duration of the

Table 3
Consort table defining patient accountability



study with LTG compared with 42% on CBZ (Fig. 1). The hazard ratio from the analysis of withdrawal rates was 2.4 (95% CI 1.4–4.0) indicating that, at any time, a patient treated with CBZ was more than twice as likely to withdraw from treatment than one taking LTG ($P < 0.001$). Forty patients on LTG (39%) remained seizure-free during the final 16 weeks and did not discontinue drug treatment compared with 10 (21%) patients taking CBZ ($P = 0.027$). Interestingly, 35 of the 40 patients on LTG took 100 mg daily (range 75–200 mg), while all 10 seizure-free patients in the CBZ group received 400 mg of the drug daily. Fig. 2 shows the proportion of patients who remained seizure-free as a proportion of those patients remaining in the study. No differences were detected between treatments on this outcome measure. The hazard ratio was 0.86 (95% CI 0.42–1.77, $P = 0.68$). The wide confidence intervals indicate that the study had a low power to detect a difference between treatments in terms of this outcome measure.

Table 4
Adverse events (>6%) reported by lamotrigine and carbamazepine-treated patients

	LTG ($n = 102$) (%)	CBZ ($n = 48$) (%)	95% CI (%)
Poor co-ordination	13	17	NS
Somnolence	12	29	4–30
Dizziness	10	17	NS
Rash	9	25	4–28
Headache	9	17	NS
Constipation	9	6	NS
Vomiting	9	6	NS
Diarrhoea	7	8	NS

Table 5
Premature discontinuations from lamotrigine or carbamazepine treatment

	Lamotrigine	Carbamazepine
Adverse events	18 (18%)	20 (42%)
Protocol violation	7	3
Consent withdrawn	3	2
Intercurrent death	0	2
Lost to follow-up	2	1
Total	30 (29%)	28 (58%)

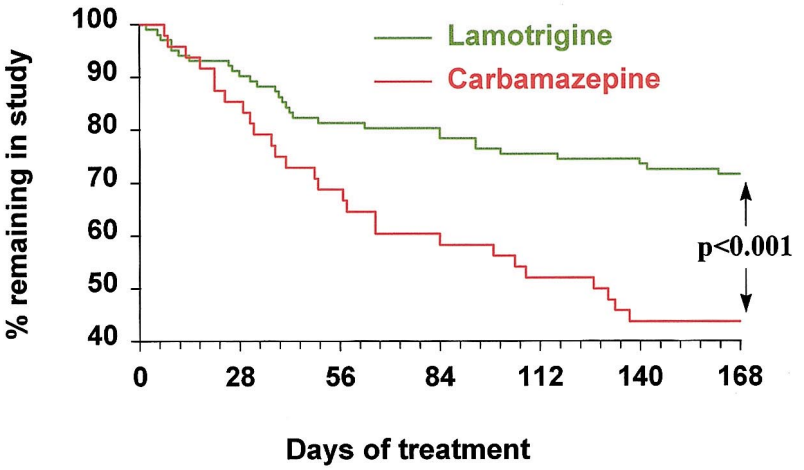


Fig. 1

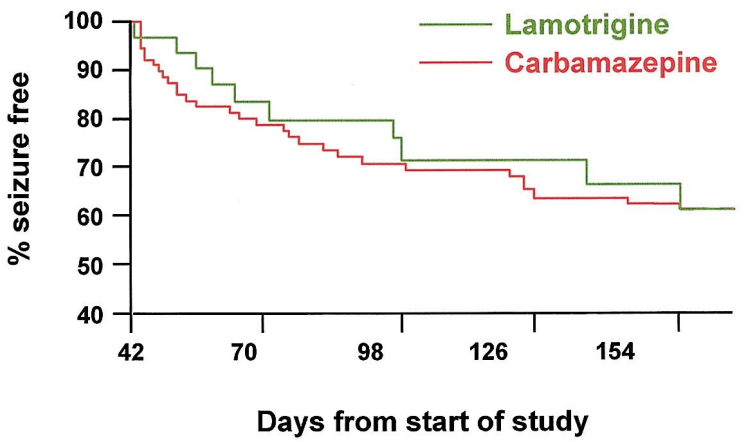


Fig. 2

Fig. 1. Kaplan–Meier distribution curves for patients remaining in the study.
Fig. 2. Kaplan–Meier distribution curves for time to first seizure.

Table 6
Withdrawal (> 3%) due to adverse events in lamotrigine or carbamazepine-treated patients

	Lamotrigine	Carbamazepine
Rash	3 (3%)	9 (19%)
Somnolence	2 (2%)	3 (6%)
Asthenia	1 (1%)	3 (6%)
Nausea	3 (3%)	1 (2%)
Incoordination	3 (3%)	1 (2%)
All withdrawals	18 (18%)	20 (42%)

4. Discussion

No controlled trials of AED therapy have been undertaken in an elderly patient population, despite the differences in drug handling and response between older and younger people (O'Mahoney and Woodhouse, 1994). There are a number of reasons why established AEDs, such as CBZ, PHT and VPA, might not be an ideal choice in the elderly, relating in particular to their propensity to cause neurotoxicity, idiosyncratic

reactions, and pharmacokinetic interactions (Brodie and Dichter, 1996). In terms of tolerability, there appears little to choose between them (Craig and Tallis 1994; Read et al., 1998). In this study, one of the standard treatments for partial and tonic-clonic seizures, CBZ, was compared in a double-blind, randomised study with LTG, one of the newer agents, which has been shown to be more effective on an overall measure of efficacy and safety in a similar comparison in younger adult patients (Brodie et al., 1995).

Because both drugs are known to be effective, patients were randomised in a 2:1 ratio to LTG or CBZ. The primary objective, therefore, was to explore tolerability differences in an older patient population with overall effectiveness and efficacy being secondary outcome measures. As in the previous comparative study (Brodie et al., 1995), significantly fewer patients reported somnolence with LTG than CBZ. In that study too, more patients withdrew prematurely due to adverse events with CBZ, although the difference between the drugs was more marked in the current trial. The commonest side-effect resulting in discontinuation of medication was, as expected, skin rash, the likelihood of which seems to be related to the starting dose with both drugs (Chadwick et al., 1984; Brodie et al., 1997). In the starting doses used in this study (LTG 25 mg versus CBZ 100 mg), significantly fewer patients withdrew due to rash with LTG than with CBZ.

No difference in efficacy between the two drugs was found using time to first seizure. This analysis, however, only included patients who remained in the study. Because of the higher dropout rate with CBZ, a much higher percentage of patients taking LTG remained seizure-free for the last 16 weeks of the trial compared those treated with CBZ. This was achieved at modest doses and concentrations of both drugs. Overall, significantly more patients continued on treatment with LTG than with CBZ for the duration of the study. Indeed, patients randomised to CBZ were more than twice as likely to have their treatment changed than those taking LTG.

LTG has a number of other credentials that would support a useful role as monotherapy in elderly people with newly diagnosed epilepsy (Wilson and Brodie, 1996). Its range is broad covering all seizure types. It has a long elimination half-life allowing once or twice daily dosing. It does not inhibit or induce the hepatic metabolism of other lipid soluble drugs and will not, therefore, interact with concomitant medication. Drugs with central effects have been linked with an increased risk of falls in elderly patients and the low rate of somnolence with LTG might prove advantageous in this respect. The one potential drawback, namely rash leading to discontinuation of treatment, appeared less frequently with LTG than CBZ and was limited to around 3% of patients by starting with 25 mg LTG daily. LTG seems, therefore, an acceptable choice as initial treatment for elderly patients with newly diagnosed epilepsy.

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