Seizure 2001; **10**: 107–115
doi:10.1053/seiz.2000.0474, available online at http://www.idealibrary.com on IDEAL®

A randomized open-label study of gabapentin and lamotrigine in adults with learning disability and resistant epilepsy

P. CRAWFORD[†], S. BROWN[‡], M. KERR[§] & PARKE DAVIS CLINICAL TRIALS GROUP[¶]

[†]*Department of Neurosciences, York District Hospital, York YO3 7HE, UK;* [‡]*Developmental Disabilities Research and Education Group, University of Plymouth, UK;* [§]*Welsh Centre for Learning Disabilities, Cardiff, UK;* [¶]*Parke Davis, Lambert Court, Chestnut Avenue, Eastleigh, UK*

Correspondence to: Professor Pamela Crawford, Department of Neurosciences, York District Hospital, Wigginton Road, York YO31 8HE, UK

The aim of this study was to evaluate the efficacy and safety of gabapentin in patients with learning disabilities and resistant epilepsy, comparing the effects of gabapentin with lamotrigine on efficacy, behaviour and mood.

An open-label, randomized, parallel group, multicentre add-on study comparing gabapentin with lamotrigine in 109 patients with drug-resistant localization-related epilepsy and learning disabilities was conducted: 39 patients were randomized to gabapentin and 44 to lamotrigine. The study population had a range of learning disabilities and severe partial epilepsy.

The percentage of patients achieving a greater than or equal to 50% reduction in seizure frequency on gabapentin was 50%, (mean reduction in seizures was 51%). Compared to 48.6% of lamotrigine patients, no statistically significant treatment differences could be identified. The safety profile of both drugs was consistent with that seen in previous clinical trials. Carer-rated visual analogue scales detected significant improvements ($P < 0.05$) for the gabapentin-treated patients in seizure severity, attention, general health and sleeping pattern, while for lamotrigine seizure severity improved significantly.

For learning disabled patients with resistant epilepsy, gabapentin and lamotrigine provide safe and effective treatment, with positive benefits on behaviour.

Key words: epilepsy; learning disabilities; mental retardation; gabapentin; lamotrigine.

INTRODUCTION

Epilepsy is common amongst the learning disabled population, especially those with severe or profound degrees of learning disabilities[1]. The risk of developing a seizure disorder increases with the severity of learning disability. Epilepsy occurring in people with learning disabilities can be particularly difficult to treat and assess. A large proportion of patients with learning disabilities continue to have poorly controlled seizures despite the use of two or more antiepileptic drugs (AEDs)[2]. In addition, the common coexistence of behavioural and psychiatric disorders can lead to difficulty in assessing treatment outcome, with such disorders often being attributed to AED treatment. This has lead to recommendations for the assessment of AEDs to include behavioural measures[3].

There have been few well conducted clinical studies investigating the impact of the newer generation of antiepileptic drugs on seizure control and behaviour in people with epilepsy and learning disabilities. Therefore this trial, which involves a significant number of patients with learning disabilities. Therefore this trial, which involves a significant number of patients with learning disabilities and epilepsy, is invaluable in providing real data to assist in the management of this population. Both gabapentin (Neurontin) and lamotrigine (Lamictal) are newer generation AEDs first licensed in the early 1990s. Both are indicated for add-on treatment of partial seizures with or without secondary generalization. Bhaumik *et al.* 1997[4], compared both these AEDs along with vigabatrin as add-on treatment in adults with learning disabilities and epilepsy, in a small retrospective casenote study. The

results of this analysis demonstrated that gabapentin reduced seizure frequency by greater than 50% in 56% of patients compared to 43% of patients taking lamotrigine. However firm conclusions cannot be drawn from this study as it was not a direct prospective comparison and the sample size was too small.

The aim of this study was to evaluate the efficacy and safety of gabapentin, together with its effects on behaviour and mood, in a patient group with learning disabilities whose epilepsy was uncontrolled on current therapy, as part of a randomized controlled trial. Lamotrigine was selected as the comparator drug.

MATERIALS AND METHODS

One hundred and nine learning disabled patients suffering from refractory partial seizures with or without secondary generalization, including a small number of patients who were entered with other seizure types, were recruited into the study. This was a multicentre study conducted with 44 investigators from the UK[†]. Permission for the study was obtained from the local research ethics committees. Consent was obtained either from the patient or from a patient's relative, guardian or carer and an independent witness. The study population comprised either outpatients or inpatients of specialist hospitals, with an identified key worker/carer who was available for the trial, able to complete the carer rating scales, and to keep a record of seizures.

Patients were eligible for the study if they were aged 12 years and over, of either sex, and had a localization-related epilepsy which was not satisfactorily controlled by their existing antiepileptic medication[5]. In order to fulfil study criteria the subjects had to be taking one, two or three standard AEDs (not including gabapentin or lamotrigine) but still not achieving satisfactory seizure control. A minimum of four seizures in each 28 day period and no seizure free 28 day period in the preceding 3 months was required for entry. Patients had to have a degree of learning disability and to meet any level of the DSM-IV criteria for mental retardation[6].

The study exclusion criteria included individuals who had had primary generalized seizures, symptomatic generalized epilepsy or a history of non-epileptic seizures. Concurrent therapy with antacids or a recent participation in any clinical trial was not allowed. Women were ineligible if they were pregnant or lactating or of child-bearing potential and sexually active and not practising a reliable method of contraception. A know hypersensitivity to gabapentin or lamotrigine, or significant renal or hepatic dysfunction, also excluded enrolment. Patients on a stable dose of monoamine oxidase inhibitors or antidepressants were allowed to enter the study, providing that this medication was maintained at a constant dose throughout the study. Intermittent use of benzodiazepines as rescue medication, for example rectal diazepam, was also permitted.

Design

There was an initial baseline period of 8 weeks followed by a titration period of up to 14 weeks. At visit B1 a questionnaire was completed about the seizure disorder in order to prevent patients with generalized epilepsies from being randomized into the study. The treatment was then evaluated for a minimum of 10 weeks (Fig. 1).

Medication was randomized in block sizes of six, with each patient number being unique. Patient numbers were assigned sequentially and this determined the treatment the patient would receive.

Dosing schedule

Patients were randomized to receive either gabapentin or lamotrigine as add-on therapy to their existing AED therapy (between one and three AEDs). The dosages of the study drugs were increased over 14 weeks at the investigator's discretion to a maximum of 3600 mg gabapentin (taken in three divided doses) and 400 mg lamotrigine (taken in two divided doses). For patients taking concurrent sodium valproate the lamotrigine dose was 200 mg.

Assessments

Seizures were recorded in diaries and frequencies per 28 days calculated. The reduction in seizure frequency between the baseline period and the last 8 weeks of the treatment period was assessed using the *R*-ratio (statistical transformation of the seizure frequencies to provide normally distributed data). $R\text{-ratio} = (T - B)/(T + B)$ where T and B are the seizure frequencies per 28 days during treatment and baseline, respectively. Additionally, patients whose seizure frequency was reduced by 50% or more were classified as responders. Patients whose seizure frequency was reduced by less than 50% and those withdrawing for treatment-related reasons were classified as non-responders.

Mood, behaviour and dependency were assessed by:

[†] A complete list of all participating investigators is provided at the end of the paper.