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Efficacy and tolerability of levetiracetam in patients with therapy-resistant epilepsy and learning disabilities

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***Introduction*:** The purpose was to evaluate the effects of levetiracetam (LEV) in routine therapy in learning disabled patients with therapy-resistant epilepsy.
***Methods*:** In an open observational add-on study design, 46 patients (residents of the Bethel Epilepsy Centre) with severe therapy-resistant epilepsy and different degrees of learning disabilities, who were treated with LEV between its introduction in Autumn 2000 and February 2002, were evaluated retrospectively. Information on monthly seizure frequencies, seizure severity and psychiatric status was extracted from the current patient case records. A 3 months baseline and a 3 months LEV treatment period (after 3 months of titration) were compared. Responders were defined as having a 50% reduction in seizure frequency and being evaluated as good or very good in an *ad hoc* global clinical efficacy scale. When only one criterion was positive, a careful individual decision was made based on the impact on the patients' daily activities.
***Results*:** The responder rate was 41.3% (34.8 for 50% seizure reduction). It was higher in focal and multifocal epilepsy as compared to symptomatic generalised epilepsy/Lennox Gastaut Syndrome ($P < 0.05$). Antiepileptic response occurred in doses between 500 and 4000 mg/day. Changes in seizure severity were rare. Nine patients experienced positive psychotropic effects (mostly improved vigilance and mood); six of these patients had antiepileptic effects as well. Twelve patients had adverse effects, mostly mild; in three cases, however, more severe effects led to discontinuation.
***Conclusions*:** LEV is an effective and generally well-tolerated drug for this patient group, especially in focal and multifocal epilepsy.

Key words: levetiracetam; antiepileptic drugs; epilepsy; learning disability.

INTRODUCTION

Approximately 20–25% of all people with learning disabilities suffer from epilepsy, a percentage much higher than in the general population. A high seizure frequency, multiple seizure types, frequent complications, such as status epilepticus or injuries, and a high rate of therapy resistance characterise many of the epilepsies in this population. Therefore, the development of each new antiepileptic drug (AED) is a glimmer of hope for these patients.

On the other hand, knowledge about efficacy and tolerability of the new AED in this patient group is limited. Learning disabled patients are often excluded from the regulatory double-blind placebo-controlled trials because of difficulties with consent. The assumption of efficacy of the new AED in this patient group, strictly speaking, is based on the extrapolation of the data of non-disabled patients. Post-marketing studies are needed to evaluate the effects of new drugs in these special populations. There is some literature on the use of lamotrigine (LTG) in learning disabled patients, but only a few articles report on gabapentin (GBP), topiramate (TPM) and the remaining new AEDs.

Levetiracetam (LEV), one of the most recently introduced AED, has been shown to be effective as add-on therapy in treatment-resistant patients with focal (partial) epilepsies. Efficacy proved to be dose-related with

daily doses between 1000 and 3000 mg[1–3], with no additional effect when doses were further increased up to 4000 mg/day[4,5]. Only recently, a report on the use of LEV in six developmentally disabled patients was published. This indicated both a good antiepileptic effect and favourable changes in problem behaviours in some of these patients[6].

The purpose of our study was to examine the efficacy and tolerability of LEV in therapy-resistant epileptic patients with learning disabilities of varying degrees and not excluding those with additional physical handicaps. The ethical and legal restrictions existing in patients, most of whom are not able to give their informed consent, had to be taken into account.

PATIENTS AND METHODS

Inclusion criteria

The Residential Department of the Bethel Epilepsy Centre provides care for approximately 1200 patients with difficult-to-manage therapy-resistant epilepsies, in many cases with accompanying intellectual and/or neurological deficits. Eligibility criteria included: Learning disabled adult and adolescent patients with a confirmed diagnosis of epilepsy, resistant against at least one traditional AED, but in fact the vast majority of all study participants were resistant against several traditional AEDs up to maximum tolerable dosages and in several cases against one or two new AEDs (mostly LTG). The staff physicians of the Bethel Medical Service (mostly neurologists and psychiatrists, all with special experience in the diagnosis and treatment of epilepsy) selected the patients on clinical grounds, preferably patients with frequent and/or disabling seizures. All patients or their legal representatives had given consent to LEV treatment. Forty-eight patients were started on LEV between its introduction in Germany in Autumn 2000 and February 2002. Two patients had to be excluded from the study because seizure documentation was incomplete or unreliable in these cases and so, 46 patients were enrolled in the study.

Methods

The baseline period was defined as the 3 months prior to starting LEV treatment. The first 3 months on LEV were considered to be the titration period, the second 3 (4th–6th) months as treatment or evaluation period. A post-evaluation after 1 year comprises the 10th–12th months on LEV. A second post-evaluation after 2 years is planned, but is not subject of this paper because data are still incomplete.

LEV was added to the pre-existing medication prescribed for each patient. There was no fixed titration scheme. Usually, LEV treatment was started following the manufacturer's recommendations (initial dose 1000 mg/day, divided in two doses), but some physicians preferred to start at lower dosages. Progressive dosage increases followed subject to clinical observations. A maximum dosage of LEV was not pre-set; the aim was to obtain the best possible antiepileptic effects. Clinicians were allowed to adjust the dose of the concomitant AED if it was considered clinically appropriate.

The method of this study is in accordance with the guidelines for observational studies published in Reference 7. According to these guidelines, an observational study is a form of a phase IV post-marketing study which aims to evaluate the benefits and risks of a drug under natural conditions. Therefore, the study should not interfere with routine therapy. For that reason, consent to the new treatment by the patient or his/her legal representative is needed, but not to study participation. The different points of time and the size of data to be raised have to be exactly determined *a priori* in order to obtain valid data despite the shortcomings of an open study[7].

The methods and time frames of this study were very similar to other studies on new AED conducted previously in our institution[8–10]; it was intended to compare the results to those of the previous studies.

Documentation

Data were extracted retrospectively from the continual seizure records kept on all resident patients and entered into data sheets designed for the purpose of this study. As the institution is specialising in epilepsy and most staff are trained in observing and describing seizures, it is believed that the seizure documentation is as complete and accurate as possible. Besides diagnostic data, medication and seizure frequency per seizure type, possible qualitative changes in seizure severity were noted. Information on seizure severity is based upon staff observations and the patients' own experiences, as summarised by the responsible physician. Criteria applied to judge seizure severity were: seizure duration, time and depth of unconsciousness, and time to complete recovery.

Possible psychotropic effects, as judged clinically by the physicians, and adverse effects (defined as any undesirable effects or patients' complaints when considered probably due to LEV) were recorded, too.

The phenomenological seizure classification currently in use in Bethel is similar to the proposal for