Seizure (2007) **16**, 185—189

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Retention rate of Levetiracetam in children with intractable epilepsy at 1 year

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Received 9 March 2006; received in revised form 22 November 2006; accepted 4 December 2006

KEYWORDS
Levetiracetam;
Children;
Intractable epilepsies;
Clinical audit

Summary Levetiracetam (LEV) is a novel antiepileptic drug (AED) that has recently obtained marketing authorisation for use in children. The purpose of this study was to assess the efficacy, tolerability and retention rate of LEV in children with refractory epilepsies. It is a retrospective multicentre observational study reporting the use of LEV in 200 children, aged 0.3—19 years (median 9-years-old) over a 4-year period.

All of the patients included in the study had refractory epilepsy with a median age of onset of epilepsy of 3 years (range 0—13 years). The 38% had failed and withdrawn 3 or more AEDs previously and 24% were taking at least 2 other AEDs in addition to LEV. The 47% had focal, and 58% had symptomatic epilepsies. The LEV dose ranged from 8 to 100 mg/kg/day (mean 39 mg/kg). The study comprised 215 person years of LEV exposure.

Results: LEV was well tolerated with a retention rate of 49% at 1 year. No serious adverse events were reported with possibly related adverse events reported in only 24% of patients (mainly emotional or behavioural changes). At more than 2, 6 and 12 months, worthwhile improvement (>50% seizure reduction) was noted in 60, 40 and 32%, including seizure freedom in 14, 14 and 5%, respectively.

Conclusion: Our results confirm the efficacy and tolerability of LEV in children with refractory epilepsies and demonstrate good response and retention rates at

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1059-1311/$ — see front matter
doi:10.1016/j.seizure.2006.12.001

12 months. It represents the largest cohort of paediatric patients published so far on LEV with a 1-year follow-up.

Introduction

Levetiracetam (LEV) is a novel antiepileptic drug with a unique mechanism of action,[1,2] proven efficacy against partial and generalised seizures,[3–8] good tolerability and straight forward pharmacokinetics.[9]

There have been few studies of LEV use in children, and most are retrospective. Although LEV has been shown to be effective against both partial and generalised epilepsy, with a response rate of up to 50% in children with partial epilepsies,[10] most of the studies contain small numbers and have a limited follow-up period. This study reports the use of LEV in 200 paediatric patients with refractory epilepsies, over a 4-year period. Our results confirm the efficacy and tolerability of LEV in this population and demonstrate good response and retention rates at 12 months.

Methods

Children starting treatment with LEV from December 2001 to December 2004 were ascertained retrospectively from hospital pharmacy and from paediatric neurology databases in four tertiary referral paediatric neurology departments in the Midlands, UK. LEV was prescribed as an "add on therapy" for control of refractory epilepsies—partial or generalised, by a Consultant Paediatric Neurologist in each centre.

A retrospective chart review using a standard proforma to assess demographic data, aetiology, epilepsy syndrome, seizure frequency, medication dosage, concomitant AEDs, efficacy and adverse events was recorded at more than 2, 6 and 12 months. Data were analysed using Excel on an intention to treat basis.

Results

Two-hundred children were included in the study. The 59% were male. The majority of our children had early onset epilepsies with a median age of onset of epilepsy of 3 years (range 0–13 years). There was no significant difference between the types of epilepsies treated. The 47% had focal, and 58% had symptomatic epilepsies. Patients commenced on LEV, were aged between 0.3 and 19 years (median 9-years-old).

The intractable nature of the epilepsies treated with LEV is demonstrated by the number of patients who had failed or withdrawn previous AEDs (Table 1). The 76% of children commenced on LEV had been on at least 3 AEDs in the past.

The study comprised 215 person years of LEV exposure. LEV dose ranged from 8 to 100 mg/kg/day (mean 39 mg/kg).

Brain neuroimaging (either MRI or CT) reports were obtained in 185/200 patients. One-hundred and sixteen (58%) were abnormal (20 with cerebral atrophy, 7 neuro-migrational disorders, 6 cortical dysplasias, 5 hippocampal sclerosis, 4 tuberous sclerosis, 74 (37%) with other abnormalities. The 69 (34.5%) scans were reported as normal.

Seven children achieved LEV monotherapy. Of those patients that achieved monotherapy, five had generalised epilepsies and the majority had been on at least two AEDs in the past (mean 3, range 1–5).

Most patients required at least 1 other AED in addition to LEV and there was no particular preference for a specific combination of AEDs across the centres (Table 2).

Possibly LEV related adverse events were reported in 24%. The most frequent adverse-effects involved emotional or behavioural changes (Table 3). Adverse events usually appeared within the first 5 months after treatment initiation. They were not dose-dependent and mostly mild. No serious adverse events (death or events requiring hospital admission or a prolongation of hospital admission) were reported. Adverse events generally resolved without medication withdrawal, but if not, did resolve when the medication was stopped. Only 8 of the 200 patients (4%) withdrew from LEV because of adverse events alone.

Some papers have reported increased behavioural adverse events in children and patients with a history of prior behavioural problems.[11–13] Pre-existing behavioural problems were documented in 8%

Table 1 Previous antiepileptic medication

Number of AEDs	Percent of patients
0–2	24
3–5	56
>5	20

The 76% of children commenced on LEV had been on at least 3 AEDs in the past. This is an indication of the intractable nature of the epilepsies studied in our group.