



Levetiracetam in children with refractory epilepsy: A multicenter open label study in Germany

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We dedicate this study to the memory of our colleague Dr. Hans Erich Boenigk (deceased November 2000) who inspired us to continue the study after he initiated the German Levetiracetam Study Group.

KEYWORDS

Levetiracetam;
Open label add-on
study;
Drug-resistant
epilepsy;
Children;
Efficacy;
Tolerability

Summary

Purpose: To evaluate the efficacy and tolerability of Levetiracetam (LEV) in a large pediatric cohort with drug-resistant epilepsy from a prospective multicenter observational study.

Methods: We report the results of a multicenter observational survey of a cohort of 285 pediatric patients (mean: 9.9 years, range: 0; 6–17; 11) with refractory generalized and focal epilepsy who received Levetiracetam as an add-on open label treatment trial. The average duration of epilepsy was 6.0 years and the patients were treated with a mean of 7.0 antiepileptic drugs (AED) before LEV was introduced.

Results: No serious persistent adverse events were reported. Reversible colitis and an apnoea syndrome in a child with phosphorylase-A-kinase-deficiency were noted. Mild

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to moderate side effects were reported in 128 patients (44.9%), consisting most frequently of somnolence (23.9%), general behavioral changes (15.4%), aggression (10.5%) and sleep disturbances (3.2%).

In 209 patients, efficacy was analyzed over a treatment period of at least 12 weeks compared to a baseline of 2 weeks. Thirteen patients (6.2%) became seizure free, 39 (18.7%) responded with a seizure reduction of more than 50% following introduction of LEV. No response to LEV was reported in 65.1% ($n = 136$). A decrease of initial treatment effect was seen in 37 patients (17.8%) while in 6.7% the seizure frequency doubled to the baseline ($n = 14$). In seven patients (3.3%), the effect of LEV on seizure frequency could not be evaluated. A positive psychotropic effect was observed in 18 patients (8.6%).

Mental retardation was associated with poor response and associated with more side effects and earlier discontinuation of LEV therapy.

Conclusion: LEV is a well-tolerated new AED that may effectively improve seizure control as an add-on drug in resistant epilepsy in childhood with good tolerability. However, neurologically handicapped children appear at increased risk for reversible neurocognitive side effects and have a poorer treatment response.

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Introduction

In the last 10 years, a substantial number of new antiepileptic drugs (AED) have been developed and introduced into clinical epilepsy treatment which include Felbamate (FBM), Gabapentin (GBP), Lamotrigine (LTG), Oxcarbazepine (OCBZ), Tiagabine (TGB), Topiramate (TPM) and Vigabatrin (VGB). All of these new AEDs were first tested in adults and subsequently many of them have proven to be efficacious and safe in children as well.

Levetiracetam (LEV) is a new AED which was well tolerated, safe and efficacious in several phase-III-LEV studies of adult patients.¹⁻³ It has a favourable pharmacological profile: almost complete absorption after oral administration, linear pharmacokinetics, low-protein binding under 10% and no significant drug interactions appear to take place. Data on the pharmacokinetics in children appear to be similar to those reported in adult patients.⁴ In addition, the first clinical studies suggest that LEV may be a valuable drug in the treatment of epilepsy in children; however, the available data to date are either retrospective studies or prospective studies with an open label design in a small number of patients.⁵

In November 2000, LEV was approved as an anticonvulsant for add-on use in Germany to treat adults with partial seizures with or without secondary generalization. Since then it has also been used in individual cases in children with refractory epilepsy. A pediatric study group was coordinated in the year 2000 with 19 child neurology departments participating throughout Germany. The main objective of this study group was to document and evaluate first clinical experiences with LEV in a large group of

pediatric patients. A questionnaire was compiled comprising a number of clinical parameters to analyse effectivity and tolerability of the drug. We were able to survey and document the clinical response with regard to seizure control and side effects and in addition define a number of predictive variables for both in a large group of over 200 children and report the results of this large prospective observational study in this paper.

Methods

Patient population, data collection and study design

From October 2000 to September 2002, data was collected and documented in a standardized data file from 19 pediatric neurology departments in Germany for an open multicenter retrospective analysis on children treated with LEV. The following clinical variables were recorded: sex, age, AEDs used prior to LEV, comorbidity, epilepsy classification, duration of epilepsy, dose and titration of LEV, concomitant therapies, response to therapy, duration of therapy, side effects, laboratory findings, physical handicap and mental retardation. Mental retardation was classified according to ICD-10 F70.x to F73.x. There was no titration protocol. Tolerability and side-effects were assessed by documenting spontaneously reported side-effects by the carers or by the child.

Patients younger than 18 years at the time of treatment with LEV and an observational period of at least 4 weeks were included in the analysis.

In a first step, we analysed the side effects and tolerability of LEV.

In a second step, we analysed the efficacy of LEV in controlling seizures. In this second analysis, we included some patients with minor changes of the baseline AEDs over a period of at least 2 weeks prior to LEV-treatment and if the follow-up was at least 12 weeks. Outcome analysis was done on the clinical information available from the last visit.

The primary efficacy outcome variable chosen was a 50% responder rate, defined as a >50% reduction in seizure frequency during the evaluation period compared to the baseline. In addition, the participating neurologists were asked to grade the outcome into one of the following categories according to their clinical judgement: seizure free, marked improvement, mild improvement, no change, drug withdrawal due to side effects and drug withdrawal due to worsening of seizures.

Statistical methods

Non-parametric tests (Fisher's exact test, Mann–Whitney test) and logistic regression analyses were

performed. If not mentioned otherwise, two-sided *p*-values are given. SPSS computer package for Windows (version 11.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Patient characteristics

Of the total reports of 357 patients, 69 had to be excluded because of insufficient data, a too short observation period, age over 18 years, and prior LEV treatment with inconclusive outcome in 3.

The data of the remaining 285 patients were included for analysis of tolerability. The clinical patient data (demographics, seizure types, epilepsy syndromes, comorbidity, history of previous and concomitant AEDs) of this group are reported in Table 1.

The majority of patients (92.1%) had mental retardation or a physical handicap (80.1%). Average

Table 1 Demographics.

Number	Analysis of tolerability and side effects	Analysis of efficacy
	285	209
Sex (male/female)	137 boys, 128 girls, 20 n.d.	100 boys, 93 girls, 16 n.d.
Age, median (range)	9.9 years, range: 0–17; 11 years	9.7 years, range: 0.5–17.9 years
Duration of epilepsy, median (range)	6.0 years, range: 0–17.0 years	6.0 years, range: 0–17.0 years
Cognitive impairment	22 (7.7%) no impairment 63 (22.1%) mild retardation 78 (27.4%) moderate retardation 115 (40.4%) severe retardation 7 (2.5%) n.d.	16 (7.7%) no impairment 45 (21.5%) mild retardation 52 (24.9%) moderate retardation 89 (42.5%) severe retardation 7 (3.3%) n.d.
Physical handicap	55 (19.3%) no impairment 84 (29.5%) mild retardation 53 (18.6%) moderate retardation 85 (29.8%) severe retardation 8 (2.8%) n.d.	42 (20.1%) no impairment 55 (26.3%) mild retardation 42 (20.1%) moderate retardation 62 (29.7%) severe retardation 8 (3.8%) n.d.
Epilepsy syndrome	191 (67.0%) focal 49 (17.2%) generalized 45 (15.8%) focal and generalized signs	139 (66.5%) focal 38 (18.2%) generalized 32 (15.3%) focal and generalized signs
Epilepsy etiology	42 (14.7%) idiopathic 58 (20.4%) cryptogenic 144 (50.5%) symptomatic 41 (14.4%) n.d.	28 (13.4%) idiopathic 41 (19.6%) cryptogenic 110 (52.6%) symptomatic 30 (14.4%) n.d.
Previous AED, median	7.0 (range = 0–20), 2 n.d.	7.0 (range = 0–20), 1 n.d.
Concomitant AED	8 (2.8%) none 87 (30.5%) one AED 128 (45.0%) two AED 56 (20.0%) two or more AED 6 (2.1%) n.d.	9 (4.3%) none 69 (33.0%) one AED 95 (45.5%) two AED 36 (17.2%) two or more AED

n.d.: no data, missing values.

duration (\pm standard deviation [S.D.]) of epilepsy was 6.8 ± 4.3 years. Before LEV treatment the patients had received 6.8 (range 0–20) AED on average and only 31 patients (11.0%) had received fewer than 4 previous AED treatments. LEV treatment was started as add-on treatment in most patients and was given in monotherapy in only eight patients (2.9%). The most prevalent comedication was valproic acid (VPA) in 133 patients (47.7%), followed by LTG in 44 patients (15.8%) and OCBZ in 43 patients (15.4%).

Two hundred and nine of 285 patients (73%) had no or only minor changes in concomitant AEDs in a baseline period of at least 2 weeks prior to LEV treatment and the follow up was at least 12 weeks. These 209 patients were subject for further analysis of the efficacy of LEV. The patient data of this group are shown in Table 1. We included seven patients in whom one of the concomitant AEDs was withdrawn during LEV treatment but no change in seizure frequency occurred during or after the drug withdrawal.

Tolerability and side effects

Side effects were reported in 128 of 285 patients (44.9%). After an average treatment duration of 10.5 (range: 1–50, median 6) weeks 49 patients (17.2%) were taken off LEV because of the side effects, although 10 of those had a good treatment response (seizure reduction of more than 50%). There was no relationship between titration schedule and discontinuation due to side effects. Withdrawal due to side effects was more frequent in patients who received LEV in monotherapy (5/10, 50.0%) compared to patients on comedication (44/275, 16%; exact Fisher test, $p = 0.017$).

Only two serious adverse events which reversed completely after drug withdrawal were reported: a 2-year-old girl developed bloody diarrhea and vomiting one day after LEV was started. The diagnosis of hemorrhagic colitis without infectious aetiology was made. LEV was stopped and the gastrointestinal symptoms reversed the following day. Secondly, a severely retarded 8-year-old boy with phosphorylase-A-kinase-deficiency developed reversible apneas that ceased after LEV was stopped.

The reported laboratory findings were within normal range in all patients.

Mild side effects involving neuropsychological functions were frequently reported which reversed once the drug was withdrawn. Increased somnolence was the most common complaint (68/285, 23.9%), and was given as a reason for discontinuing LEV treatment in three patients. In 16 patients,

somnolence occurred transiently only in the titration phase. Mental retardation was a risk factor for somnolence which was reported in 66 of 256 (25.8%; Fisher's exact test, $p = 0.034$) of the retarded patients and only once in 22 patients without mental retardation (4.5%).

Behavioral changes were the next most frequently reported side effect and included aggressive behavior in 44 patients (15.4%) and prompted discontinuation of the drug in 23 cases (8.1%). Behavioural changes were observed slightly more frequently in patients with mental retardation (42/256, 16.4% versus 1/22, 4.5%; Fisher's exact test, $p = 0.11$) and physical handicap (39/222 17.6% versus 4/55, 7.3%; Fisher's exact test, $p = 0.063$) compared to neurologically normal patients but the differences did not reach statistic significance.

The most common behavioral adverse event was aggression, which was seen in 30 patients (10.5%) and was often severe. Two patients attacked others violently, which they had never done before. Aggression was observed more frequently in mentally retarded (28/256, 10.9% versus 1/22, 4.5%) and physically handicapped patients (26/222, 11.7% versus 3/55, 5.5%), but again the differences were not statistically significant (Fisher's exact $p > 0.1$).

Severe mental retardation was however a significant risk factor for sleep disturbances which were observed in nine patients (3.2%), all of whom were severely retarded (exact Fisher test; $p = 0.006$).

Seven patients (2.5%) had a tremor and six of these patients had a comedication with VPA.

For a summary of side effects see Table 2. Rare side effects which are not listed were weight gain ($n = 1$), weight loss ($n = 2$), hypersalivation ($n = 2$), ataxia ($n = 2$), abdominal pain ($n = 2$), headache ($n = 2$), encopresis ($n = 1$), hyperpnoea in

Table 2 Side effects in 285 patients.

	Number of patients	Percent
Somnolence/fatigue	52	18.2
Somnolence only initially	16	5.6
Sleeping disturbance	9	3.1
Behavioral changes	44	15.4
Aggression	30	10.5
Altered mood	8	2.8
Loss of appetite	10	3.5
Vomiting	6	2.1
Tremor	6	2.1
Cognitive disturbance	5	1.8
Severe side effects		
Hemorrhagic colitis	1	0.4
Apneas	1	0.4

Table 3 Effect of LEV on seizure frequency in patients on LEV therapy (total) and in patients still on LEV therapy at last visit available (efficacy analysis).

Seizure frequency	Number of patients included in efficacy analyses	Number of patients still on LEV therapy at last visit available
Seizure free	13 (6.2%)	12 (5.7%)
Reduction of 76–99%	24 (11.5%)	20 (9.6%)
Reduction of 50–75%	15 (7.2%)	11 (5.3%)
No significant change	136 (65.1%)	24 (22.8%)
Increase of >100%	14 (6.7%)	0 (0.0%)
Effect on seizures could not be evaluated	7 (3.3%)	3 (1.4%)
Total	209 (100%)	70 (33.5%)

combination with Sulthiame ($n = 1$), constipation ($n = 1$), itching ($n = 1$), and transitory rash ($n = 1$) (Table 3).

Patients with ongoing LEV treatment at the last visit ($n = 115$, 40.4%) were older (mean \pm S.D.: 10.3 ± 4.4 years versus 8.8 ± 4.7 years; Mann–Whitney test, $p = 0.009$) than patients in whom the drug had been withdrawn ($n = 170$, 59.6%) and had a slightly longer duration of epilepsy (mean \pm S.D.: 7.4 ± 4.3 years versus 6.3 ± 4.3 years, Mann–Whitney test, $p = 0.048$). Patients with ongoing treatment were less mentally retarded than patients in whom LEV had been withdrawn (Mann–Whitney test, $p = 0.012$) and slightly less physically handicapped (Mann–Whitney test, $p = 0.089$). The comedication (number of AED) and number of AEDs before add on LEV therapy was started was not significantly associated with withdrawal of LEV.

Logistic regression analysis of multiple clinical variables to look for predictive outcome variables for responders, discontinuation of treatment and risk factors for side effects demonstrated that mental retardation ($p = 0.006$) was the only significant predictor for discontinuation of LEV treatment. LEV was withdrawn in 66.1% (76/115) of the severely retarded, in 60.3% (47/78) of the moderately and 54% (29/62) of the mildly retarded children and only in 36.5% (8/22) of the children without mental retardation.

Withdrawal of LEV ($n = 170$) provoked seizures in six patients (3.5%) which did not correlate with fast or slower withdrawal. However, two patients developed de novo seizures in series (requiring ICU-care and intravenous phenytoin in one patient) which had never been observed before and were interpreted as drug withdrawal seizures.

LEV was administered in a maximum dosage (\pm S.D.) of 47.7 ± 21.8 mg/kg/day (range: 6–

140 mg/kg/day), which was reached in 1–41 weeks (median 3 weeks). Side effects occurred at a mean dosage (\pm S.D.) of 45.5 ± 20.4 mg/kg/day. The titration speed and the maximum dosage were not significantly different in patients who had LEV withdrawn because of worsening of seizures or side effects.

Efficacy

Two hundred and nine patients were included in the analysis of the efficacy of LEV. At the last visit available 70 patients (33.5%) were still treated with LEV whereas in 139 (66.5%) patients LEV had been stopped. The mean duration of LEV treatment in patients with ongoing LEV therapy was 38.8 weeks (median 33, range: 12–86 weeks) compared to 12.3 weeks (median 8, range: 0.5–75 weeks) in patients in whom LEV had been withdrawn.

Thirteen patients became seizure free (6.2%), 39 patients had a seizure reduction of over 50%—of these 24 patients had a 76–99% seizure reduction (11.5%) and 15 patients had a 50–75% seizure reduction (7.2%). Thus, in all 52 patients (24.9%) were responders and add on LEV stopped or reduced seizure frequency by more than 50%. In 9 of these patients (including one seizure free patient), LEV was discontinued because of side effects so that the remaining 43 (20.6%) patients constitute long term responders who continued on LEV after the last clinical study visit.

Positive psychotropic effects were reported in 18 patients (8.6%): 15 were reported to be more bright and alert, 2 patients had improved speech and one patient was in a ‘better mood’ while 1 patient showed lessening of previously observed ataxia.

In 136 patients (65.1%), seizure frequency was neither reduced by more than 50% nor increased to more than double of the baseline frequency. In 24 of these patients, the therapy with LEV was continued for more than 12 weeks and in 19 of these patients the referring physician regarded the effect of LEV as a “mild improvement” (15 patients) or “marked improvement” (4 patients). The reasons to continue LEV treatment were seizure reduction of less than 50% or seizures of shorter duration (13 patients), fewer side effects compared to other AED (2 patients) and/or positive effect on mood and cognition (5 patients).

Fourteen of the 209 patients (6.7%) showed a doubling of seizure frequency and in a further 7 patients an increase of seizure frequency was given as the main reason for discontinuing LEV.

In 9 patients, the good initial response was lost early within 4 weeks with seizure frequency returning to a similar level as before treatment (4.3%) and

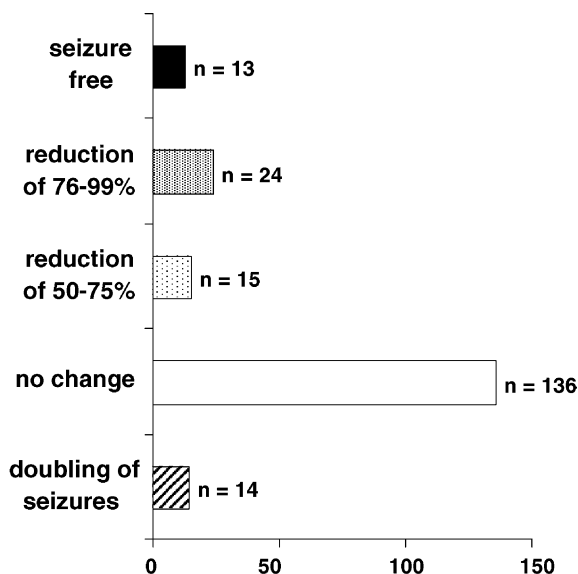


Figure 1 Effect of LEV on seizure frequency (efficacy analysis).

similarly 28 patients (13.4%) showed delayed tolerance with loss of improved seizure control after more than 4 weeks.

In seven patients (3.3%), the effect of LEV on seizure frequency could not be evaluated because side effects lead to a quick withdrawal of LEV in two patients. The remaining five patients had no visible seizures and LEV was given to reduce EEG discharges in CSWS syndrome. None of the five showed a lasting reduction of discharge frequency, but three showed improvement in cognition (classified as “mild improvement” in one patient and “marked improvement” in two patients).

There was no difference in the outcome in different epilepsy syndromes ($p > 0.1$, Fisher's exact test): a seizure reduction of $\geq 50\%$ was seen in 26.1% (35/134) patients with focal epilepsy, in 18.4% (7/38) patients with generalized epilepsy and in 33.3% (10/30) patients with epilepsy with focal and generalized signs. We also found no significant differences in seizure control ($p > 0.1$, Fisher's exact test) based on etiology of the epilepsy syndrome: 29.8% (36/121) with symptomatic epilepsy, 20.0% (5/25) patients with idiopathic epilepsy and 16.7% (9/54) patients with cryptogenic focal epilepsy (Fig. 1).

The 12 patients who became seizure free and had ongoing treatment (mean \pm S.D.: 30 ± 15 weeks) received average daily doses (\pm S.D.) of 35.5 ± 21.5 mg/kg compared to 53.0 ± 23.8 mg/kg/day in all other patients with ongoing treatment.

Seizure types

The results show that the outcome was dependent on seizure type (Kruskal–Wallis test, $p = 0.004$) with

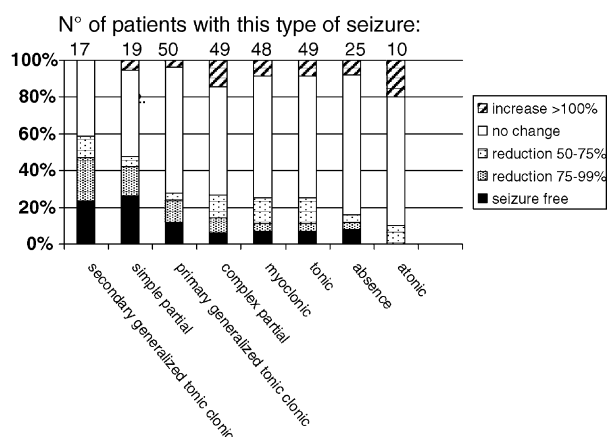


Figure 2 Effect of LEV on different types of seizures (often more than one type in a single patient).

a most favourable outcome in secondarily generalized tonic seizures and simple partial seizures, followed by generalized tonic–clonic seizures, complex partial seizures, myoclonic and tonic seizures. Improved seizure control was least likely with absences and atonic seizure (see Fig. 2). However, as a whole when considering the most frequent seizures types ($n > 40$) the outcome did not differ significantly (Kruskal–Wallis test, $p = 0.439$).

Discussion

Drug-resistant epilepsy remains a challenging clinical issue in pediatric neurology.

New treatment paradigms that have gained increasing prominence in optimizing patient management include early resective surgery, the ketogenic diet and vagal nerve stimulation. A number of new drugs have been added to the clinical repertoire in recent years to improve seizure control and reduce drug-related comorbidities in the pediatric population. Of these LEV promises to be a potent and well-tolerated drug based on adult studies and the first clinical pediatric studies. The group of very drug-resistant children with high rates of coexisting comorbidities stand to benefit from the early use of a well-tolerated potent new drug such as LEV.

In our study, we report on the observed seizure control and side effects in 285 pediatric patients with drug-resistant epilepsy treated with LEV as part of a multicenter observational survey. In this large sample, LEV was generally well tolerated and there were no reports of significant drug interactions and or idiosyncratic side effects. Although side effects were documented quite frequently (in 128 (44.9%) patients), they were often limited to the titration period, did not invariably lead to drug withdrawal and were reversible on cessation of treatment.

Somnolence was the most common complaint. Mental retardation and physical handicap appeared as a risk factor for experiencing somnolence during LEV treatment which was seen in 25.8% of mentally retarded patients and in only 4.5% of normal developed patients.

Behavioural changes that occurred with the introduction of LEV were seen in 15.4% of our patients. They were considered clinically relevant and disturbing in some patients and led to discontinuation of LEV treatment in 8.1% of our patients. Comparing these data to a number of adult studies where the incidence of aggression was no higher than with placebo¹⁻³ or appeared in only 9 of 118 patients (7.6%) in a recent study of a subgroup of learning disabled adults,⁵ behavioural side effects appear to be more frequent in the pediatric patient population. Weyrheter et al. reported of withdrawal of LEV due to irritability and aggression in a third of 28 pediatric patients.⁶

Similarly, Kugler et al. reported irritability, increased aggressiveness, mood changes and attentional disturbances in 23/79 patients⁷ and aggressive, oppositional behaviour was also observed in 36 of 115 patients in data of Gustafson et al.⁸ Of the neuropsychological side effects reported in our patients somnolence, sleep disturbances and behaviour disorders were most frequent in patients with physical handicap or mental retardation so that this patient group needs to be monitored carefully for these adverse events under LEV treatment. As yet there is no data available on the effects of titration rate on these side effects or dose related issues.

The single most severe adverse event observed in our study was an acute bout of hemorrhagic colitis in a two-year-old girl which was rapidly reversible on immediate drug withdrawal and has been recently also reported in two adult cases.⁹

A number of pediatric studies usually on small selected patient groups report on seizure control with LEV.¹⁰⁻²² With regard to the effectiveness of LEV in improving seizure control in this cohort of drug-resistant epilepsy we found a 50% responder rate in 20.6% while 6% still became seizure free. This rate is lower than the response rates found in the large phase III-studies with adult patients¹⁻³ and lower than the rates in most previous studies with pediatric patients. Responder rates of 33.3% were reported by Coppola¹⁰ and up to 40-50% were reported separately by Bourgois et al.,¹¹ Gustafson et al.,⁸ Lagae et al.,¹² Nieto-Barrera,¹³ and Veendrick-Meeke et al.¹⁴ Responder rates of more than 50% have been reported by Garcia-Peñas et al.,¹⁵ Glauser et al.,¹⁶ Herranz et al.,¹⁷ Mordekar,¹⁸ Papavasiliou,¹⁹ and Tan and Appelton.²⁰ This wide range of response of seizure control to LEV most likely

represents the heterogeneous patient populations studied showing variable effectiveness of the drug.

As LEV is a new AED, which is not yet approved for the use in children, there is a strong selection bias for patients with very difficult to treat epilepsies. This bias is enhanced in our data which is made up of pooled data of the first experiences with LEV collected from 19 child neurology departments in Germany.

The patients investigated in our study had highly refractory epilepsies. They were treated with a high number of AEDs before LEV was added on (mean: 7 AED), had a long duration of epilepsy (mean: 6.0 years) compared to the age of the patients (9.9 years) and were frequently mentally retarded (92.1%).

The phenomenon of increased seizure frequency under new AED drug treatment which was seen in 10% of our patients with doubling in 6.7% of these raises the interesting issue of idiosyncratic seizure activation by LEV. This has also been reported by other authors: Nakken et al.²¹ observed an increase in seizure frequency in 19/44 (43%) pediatric patients, Veendrick-Meeke et al.¹⁴ reported an increase in seizure frequency in 5/59 (8.5%) children and adolescents and Wannag and Ng noted what they felt to be a dosage related increase: after an initial good response to LEV the seizure frequency again increased with doses of 30 mg/kg/day or higher in 19 of 45 patients (42%).²² However, this phenomenon may reflect early seizure breakthrough and therefore the natural history of the epilepsy rather than true activation.

In addition to responder rates, the retention rate is an important measure of the overall drug effectiveness as this represents a reliable composite measure of adverse events and efficacy over time.²³ At the last visit available, 70 of the 209 patients (33.5%) were still on medication with LEV. This means that in addition to the 43 responders who had a seizure reduction of more than 50%, there were 27 other patients who continued LEV. Reasons for this were a seizure reduction of less than 50% which apparently still was regarded as a benefit to the patient, seizures were of shorter duration and a positive effect was observed on mood and cognition. Thus, one-third of patients benefited from LEV treatment. Prospective comparative studies will be necessary to further elucidate these parameters for the use of LEV in children.

Can we at this point make a general statement about which patients should be treated with LEV? Our data do not show any significant differences in the responder rates dependent on epilepsy syndromes, but the responder rates differ between seizure types. Focal seizures (simple and complex partial, secondary generalized tonic-clo-

nic seizures) responded better than generalized seizures (primary generalized tonic-clonic seizures, absences). This is in accordance with the data of Wheless and Ng²⁴ in 39 pediatric patients.

Regarding LEV dosing LEV was administered in maximum dosages of 47.7 ± 21.8 mg/kg/day in our survey. In the 13 patients who became seizure free, the mean dosage was lower -35.8 ± 20.6 mg/kg/day (range: 10–93 mg/kg/day). This reflects the practice of increasing the daily dosage till seizure control is achieved or the maximal tolerated dosage is attained. Our data do not permit conclusions about daily recommended dosages but suggest that most treatable patients will respond in the 30–40 mg/kg/day range.

Although our study includes a large number of patients there are a number of limitations in our study design. Principally these include the heterogeneous and highly refractory patient group with various seizure types, epilepsy syndromes and additional neurological deficits. The study was not designed with a set protocol defining the handling of comedication, LEV dosages, titration schedules and study endpoint.

Nevertheless valuable new information was gained from the statistical analysis of the pooled data of the largest cohort of pediatric patient reported in a single study to date.

In conclusion, our study supports the available data to date that LEV is an effective and well-tolerated AED in children with refractory epilepsy. Severe side effects were rare but patients with additional comorbidities are more likely to have side effects which need to be monitored. Besides its value as a new add-on drug in resistant epilepsy, further studies are required to determine the value of LEV as a first line drug by defining its comparative efficacy and tolerability over other established AEDs.

The neurotoxic side effects observed in our study and reported on by other authors in the literature need to be monitored in the long-term treatment paradigms of pediatric patients and may limit its use in at risk subgroups of children with mental and physical handicaps.

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