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Preliminary efficacy of levetiracetam in children

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ABSTRACT – Treatment of seizures in pediatric patients is complicated by the fact that the etiology of the disorder and the pharmacokinetics, efficacy, and safety of antiepileptic drugs (AEDs) may differ from that in adults. With few controlled clinical trials of AEDs in children, the selection of agents to treat pediatric patients must be made on the basis of information from small uncontrolled studies or the extrapolation of clinical trial results in adults. Data from a large number of children with a wide range of seizure disorders who were treated in small-scale prospective studies, or whose records were retrospectively evaluated, indicate that levetiracetam reduces the frequency of seizures in pediatric patients. Available data also indicate that levetiracetam is well tolerated in pediatric patients, with a safety profile similar to that in adults, a low potential for behavioral disturbances, and no reported idiosyncratic adverse reactions. As with other AEDs, children metabolize and clear levetiracetam more rapidly than adults, and somewhat higher doses (based on body weight) are needed to achieve desired plasma concentrations. Several ongoing studies will provide further information on the pharmacokinetics, efficacy, and safety of levetiracetam in this patient population.

KEY WORDS: levetiracetam, efficacy, pharmacokinetics, pediatric, safety, seizure

Introduction

Although existing antiepileptic drugs (AEDs) provide effective seizure control in a majority of children, more than 25% of pediatric patients treated with these AEDs experience treatment-resistant seizures or intolerable adverse events [1]. The clinical consequences of intractable or poorly controlled epilepsy can be significant; for example, growth and cognitive development may become impaired [2].

Selecting appropriate AED therapy for pediatric patients may not be easy, however. Few well-controlled studies have been carried out to determine AED efficacy in the treatment of childhood epilepsy. Children are often excluded from clinical trials of antiepileptic medications prior to approval, and historically, there has been little incentive to conduct trials in this patient population once a drug has been approved. There also exist methodological problems related to variable response according to various types of epilepsy [3, 4]. However, conclusions about efficacy and safety based on clinical trials in adults may not always be translatable to pediatric patients.

There are numerous differences between pediatric and adult epilepsy; for example, age-related seizure types, etiologic differences in partial seizures between adults and children, and a higher frequency of special age-related epilepsy syndromes [5-7]. Moreover, children with partial epilepsy tend to have frequent comorbidities, including mental retardation and behavioral problems, that may affect the selection of AEDs due to concerns over potential side effects.

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While safety data regarding dose-dependent or titration-related side effects (eg, sedation, cognitive impairment, rash, headache, nausea) in adults with partial seizures are translatable to children, unpredictable/idiosyncratic side effects (eg, hepatic failure, aplastic anemia), reactions to long-term therapy (eg, tolerance/dependence, weight gain/loss), and delayed effects (eg, teratogenicity, carcinogenicity) are not. In children, neurotoxic side effects may be more subtle, and dermatologic reactions more common, possibly because usual comedication is different [7]. Drugs that typically sedate adults may have the opposite effect—increased irritability and hyperactivity [7].

Significant changes in AED pharmacokinetics occur from birth to adolescence [7]. Some pharmacokinetic parameters (eg, percent metabolized, effect on cytochrome P450 enzymes/potential for drug-drug interactions) may be consistent across patient populations, but others may vary. Age affects half-life, time to steady state, bioavailability, and drug elimination.

Thus, when bringing to the market a new compound for children, several sets of data in addition to those drawn from studies in adults are required. Tolerability may be different, including between infants and children. Pharmacokinetics is clearly distinct across age ranges, with major differences between newborns, infants, and children. Efficacy according to seizure types needs to be studied because there are age-specific seizures. However, age-related syndromes are also specific in terms of response to drugs, both for benefit and risk of worsening.

Levetiracetam, a novel AED structurally unrelated to other AEDs, has been shown to be effective as adjunctive treatment in adults with partial seizures with or without secondary generalization, and well tolerated [8]. This paper reviews findings to date on levetiracetam in children.

Clinical experience

Refractory partial seizures

An open-label study of children with treatment-resistant partial-onset seizures with or without secondary generalization provided preliminary information on the efficacy and safety of levetiracetam in children [9]. Levetiracetam (target dose 40 mg/kg/day) was administered as add-on therapy to one other AED (carbamazepine, felbamate, gabapentin, lamotrigine, primidone, topiramate, or valproic acid) in 24 patients between 6 and 12 years of age. A 4-week baseline period was followed by a 6-week dose-titration phase and an 8-week evaluation phase. Efficacy data were evaluable in 23 patients, and 22 completed the study. Twelve (52.2%) of the evaluable patients experienced a 50% or greater reduction in seizure frequency during the evaluation phase, and two patients remained seizure-free during this period. The median percentage reduction in partial-onset seizures was 53% (N = 23), with a mean group reduction of 29.8% from baseline. The median and mean group percentage reductions by seizure type were simple partial seizures 26.4% and 22.1% (N = 7), respectively; complex partial seizures 46.9% and 13.5% (N = 19), respectively; and partial secondarily generalized seizures 64% and 45.9% (N = 8), respectively.

Adding levetiracetam to the therapeutic regimen did not affect the plasma concentrations of co-administered AEDs. The safety profile of levetiracetam in this small cohort of children was very similar to that in adults [10]. The most commonly reported adverse events were headache, infection, anorexia, and somnolence. The effect on weight was neutral: three patients experienced significant weight gain, while two experienced significant weight loss.

Lennox-Gastaut syndrome and related conditions

Lennox-Gastaut syndrome is characterized by multiple types of intractable seizures, including mainly tonic and atonic seizures. It is one of the most difficult epilepsy syndromes to treat and can have a devastating impact on a child's development [11]. Nosological limits remain, making it often difficult to determine, in clinical practice, the distinction between Lennox-Gastaut syndrome and its so-called myoclonic variant, which is probably related to myoclonic astatic epilepsy [12,13]. De los Reyes and associates identified six patients 2.5 to 16 years of age who received levetiracetam as add-on therapy for the management of these conditions [14]. An initial dose of 10 mg/kg/day was adjusted weekly depending on the patient's clinical response. Patients were followed for 1 to 11 months (mean, 5.6 months). All were taking a minimum of two medications, and one patient was receiving four. A 100% reduction in seizure frequency was observed in four patients with myoclonic seizures and in three of four patients with generalized tonic-clonic seizures. A reduction of ≥ 50% was observed in patients with atonic (N = 2), generalized tonic-clonic (N = 1), and tonic (N = 1) seizures. The most common side effects were somnolence and irritability, which caused levetiracetam to be discontinued in one patient.

Generalized seizures

Most children with epilepsy have partial or generalized seizures, hence the importance of evaluating AEDs in pediatric patients with these conditions [15, 16]. Adjunct levetiracetam therapy was evaluated retrospectively by Barron *et al.* in 18 children with multiple types of generalized seizures (average age, 10.3 years) [17]. Patients were already taking valproate, lamotrigine, topiramate, and/or zonisamide. The average dose of levetiracetam was 29 mg/kg/day (range, 15 to 52 mg/kg/day). Ten patients had at least a 50% decrease in seizure frequency after the addition of levetiracetam and six experienced a ≥ 75% reduction. Three patients became seizure-free. Six patients experienced adverse events (decreased appetite,

asthenia, and behavioral changes); however, these side effects did not lead to the discontinuation of levetiracetam.

Various seizure types

Several recent small-scale studies have looked at the efficacy and tolerability of levetiracetam in pediatric patients. These patients represent a wide range of seizure types.

Bourgeois *et al.* assessed the safety and efficacy of levetiracetam as add-on therapy in 65 patients (mean age, 12.8 years; range, 2 to 34 years, with only nine of the 65 patients older than 18 years of age) with various seizure disorders (54% localization-related, 46% generalized) [18]. This group of patients had treatment-resistant seizures; the mean number of previously tried AEDs was 7.6, and 23.1% had undergone epilepsy surgery. Patients received a mean levetiracetam dose of 35 mg/kg/day and were followed for an average of 5.6 months. Levetiracetam was effective (based on responder rate of 50% or greater decrease in seizure frequency) against focal-onset as well as primarily generalized seizures *(figure 1)*. Four patients became seizure-free. Fifteen patients discontinued treatment because of lack of efficacy, eight because of adverse effects. Adverse events occurred in 16 patients, with behavioral problems most common (10/65, 15% of patients).

Mandelbaum *et al.* treated 26 pediatric patients (median age, 5.3 years) with levetiracetam (mean, 43.6 mg/kg/day) for uncontrolled epilepsy [19]. At the end of 3 months, 24 were still taking levetiracetam. Of these, 12 experienced a ≥ 50% decrease in seizure frequency and six were seizure-free. Three were receiving levetiracetam monotherapy. None of the patients discontinued due to adverse events. The adverse events noted most often in this cohort were mood swings and lethargy.

Ng and Wheless administered levetiracetam as add-on therapy for partial or generalized refractory seizures in a prospective study that included 39 children (mean age, 8.6 years), 28 of whom had developmental delay or mental retardation [20]. Patients received an average maintenance dose of 53.3 mg/kg/day and were followed for an average of 5.9 months. Four (7.7%) of the 39 patients became seizure-free, while eight (15.4%) had > 90% reduction in seizure frequency and six (11.5%) had a 50% reduction in seizure frequency. Eight patients discontinued due to either lack of efficacy or adverse events. The most common adverse events were behavioral (i.e., hyperactivity, agitation, positive psychotropic effects, or sedation).

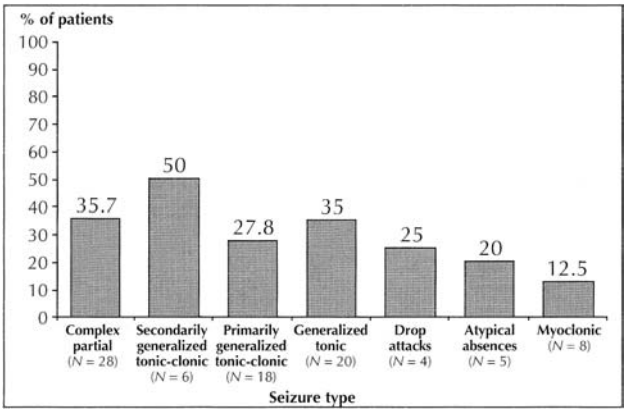

Fig. 1. *Percentages of pediatric patients experiencing a 50% or greater reduction in seizure frequency when levetiracetam was added to their treatment regimen [18].*

The records of 50 children (median age, 6 years) were reviewed by Gustafson *et al.* [21]. Patients received levetiracetam (mean dose, 46 mg/kg/day) as add-on therapy for a variety of seizure disorders and were followed for at least 6 months. All had refractory seizures and had failed to respond to previous therapy (mean, seven AEDs). Eight patients became seizure-free after the addition of levetiracetam, and four were converted to levetiracetam monotherapy. An additional six children had a ≥ 50% decrease in seizure frequency. Improvements were seen in partial-onset seizures, atypical absence, tonic, tonic-clonic, and myoclonic seizures. Ten children discontinued levetiracetam because of adverse events. Nine stopped therapy because of behavioral disturbances; however, six of these had a history of such problems.

Hovinga and colleagues reviewed the records of 27 pediatric patients (median age, 12 years) with various seizure disorders who had levetiracetam (median dose, 35 mg/kg/day) added to their antiepileptic therapy [22]. After the addition of levetiracetam, the median seizure frequency decreased from 12.5 to 7.0 seizures/week, and 22% of patients became seizure-free. Focal seizures decreased by 87%. Physicians were able to reduce the dose of or discontinue the concomitant AED in 52% of patients, and four were converted to monotherapy. Adverse events occurred in 52% of patients and led to the discontinuation of levetiracetam in 11%. Adverse events tended to be CNS-related.

In another retrospective study, Strunc and Levisohn reviewed the records of 19 children (mean age, 10 years) with either idiopathic generalized epilepsy or symptomatic localization-related epilepsy who had levetiracetam added to their therapy [23]. Five patients (26%) had a > 50% reduction in seizure frequency, and an additional four patients (21%) became seizure-free. Behavioral and cognitive side effects led to a decrease in the dosage of levetiracetam in two patients and to the discontinuation of levetiracetam in two other patients. Improved behavior was reported in one patient.

Faircloth *et al.* focused on refractory focal-onset seizures with or without generalization [24]. Their retrospective review included 27 children (mean age, 9.9 years) who received levetiracetam (mean dose, 32 mg/kg/day) as add-on therapy and were followed for a mean of

6 months. Two children discontinued treatment within 1 month because of side effects. A 50% or greater reduction in seizure frequency was reported in 16 (64%) of the 25 children who continued treatment, while 13 (52%) had a > 75% decrease and seven (28%) became seizure-free. Twelve (44%) children experienced adverse events, which were generally mild. Behavioral/psychiatric symptoms were most common and were reported in six patients; three of these patients had pre-existing behavioral disorders. Four patients discontinued treatment because of behavioral side effects.

Prospective tolerability study

To assess the tolerability of levetiracetam, Wannag and colleagues prospectively evaluated 45 children (mean age, 10 years) whose epilepsy was treatment-resistant despite having tried an average of nine AEDs [25]. Approximately half of the patients achieved significant seizure reduction (50% or greater) on levetiracetam doses of 10 to 20 mg/kg/day. Over 3 to 5 months of follow-up, adverse events (ataxia, dizziness, lethargy, and 'forced normalization') were reported in four patients. At the end of the observation period, 27 (60%) remained on levetiracetam therapy. Doses > 30 mg/kg/day were less effective than doses < 30 mg/kg/day and were associated with increased seizure frequency.

Psychosis in children

Recently, Kossof *et al.* reported the development of acute psychosis in four patients aged 5 to 17 years [26]. Symptoms occurred within 2 days to 3 months of the initiation of levetiracetam therapy and resolved rapidly when levetiracetam was discontinued. All four patients had cognitive deficits, and the three adolescents had mild behavioral abnormalities prior to receiving levetiracetam.

Dosing guidelines

The pharmacokinetics for any given drug are likely to be more variable and less predictable in children than in adults. When treating pediatric epilepsy patients, drug dosing is complicated by age-related changes in drug metabolism and pharmacokinetics and the need to minimize interference with normal development.

Pellock and associates evaluated the pharmacokinetics of levetiracetam in 24 children (mean age, 9.4 ± 2.2 years; range, 6 to 12 years of age) with partial seizures in a multicenter, open-label, single-dose (20 mg/kg) study [27]. Their findings are shown in *table 1*. The maximum plasma concentration and area under the curve, equated for a 1mg/kg dose (1.33 µg/mL and 12.4 µg/h/mL, respectively) is comparable to that reported for adults (1.38 µg/mL and 11.5 µg/h/mL, respectively) [28, 29]. Apparent total body clearance of levetiracetam in children was approximately 30% to 40% higher than in adults. The variability in the elimination half-life (4.0 to 8.2 hours) could not be explained by interpatient differences in age or creatinine clearance.

Table 1. Pharmacokinetics of levetiracetam after a single dose of 20 mg/kg [27]

Parameter	Mean ± SD (n = 24)
Dose (mg/kg)	19.6 ± 4.6
CL_{CR} (mL/min/1.73 m^2)	80.6 ± 27.2
C_{max} (µg/mL)	25.8 ± 8.6
T_{max} (h)	2.3 ± 1.2
AUC (µg/h/mL)	241 ± 76
λ_z (h^{-1})	0.120 ± 0.022
$t_{1/2}$ (h)	6.0 ± 1.1
CL/f	
(mL/min/kg)	1.43 ± 0.36
(mL/min/1.73 m^2)	72.7 ± 18.1
Fe ($_{0\text{-}24h}$) (%)	51.9 ± 13.8
CLR_R	
(mL/min/kg)	0.79 ± 0.26
(mL/min/1.73 m^2)	39.5 ± 12.8
CL_{NR}	
(mL/min/kg)	0.64 ± 0.32
(mL/min/1.73 m^2)	32.3 ± 16.5
V_Z/f (L/kg)	0.72 ± 0.12

CL_{CR}, creatinine clearance; C_{max}, maximal plasma concentration; t_{max}, time to reach maximal concentration; AUC, area under the plasma concentration-time curve extrapolated to infinite; λ_z, elimination rate constant; $t_{1/2}$, half-life; CL/f, apparent total body clearance; $Fe_{(0\text{-}24\ h)}$, 24-h cumulative urinary excretion; CL_R, renal clearance, CL_{NR}, non-renal clearance; V_Z/f, volume of distribution.

These findings suggest that pediatric patients may require a daily maintenance dose equivalent to 130% to 140% of the usual adult daily maintenance dose (1000 to 3000 mg/day). However, it is likely that the increase, compared with adults, is even higher in infants, for whom the data remain insufficient. As when administering any AED, a key principle is to 'start low and go slow' (*table 2*).

Discussion

When prescribing AED therapy for pediatric patients, the clinician must carefully balance both drug efficacy and safety. While adverse events in pediatric patients are similar to those that occur in adults, the incidence may differ,

Table 2. Dosing suggested for levetiracetam in pediatric patients*

- Initial dose: 10 mg/kg/day
- Titration rate: increase by 10 to 20 mg/kg/week

*Authors' recommendations.

and normal development is a concern over the long term. Some AED-related adverse events are particular to children and may not be predicted on the basis of safety data obtained from adults. For example, the risk of a severe dermatologic reaction to lamotrigine is significantly higher in children than in adults [4]. Neurobehavioral changes have been observed with virtually all agents [29] and are a particular concern for the developing child [4]. Levetiracetam is generally well tolerated in pediatric patients. Adverse behavioral or psychological reactions may occur but appear to resolve quickly when treatment is discontinued. The full side effect profile of levetiracetam is still being determined.

Several ongoing studies of levetiracetam will provide further information on the pharmacokinetics, efficacy, and tolerability of levetiracetam in pediatric patients. A multiple-dose study in children 4 to 12 years of age with treatment-resistant partial-onset seizures will further study pharmacokinetics, including potential drug-drug interactions. Efficacy and safety will be assessed in a large randomized, double-blind, placebo-controlled multicenter trial of patients 4 to 16 years of age with uncontrolled partial-onset seizures and on a stable AED regimen.

Both children and adults will participate in another large randomized, double-blind, placebo-controlled multicenter study. The study population will include patients experiencing idiopathic generalized epilepsy with primary generalized tonic-clonic seizures that are uncontrolled despite treatment with other AEDs.

These new data should be very helpful. However, some additional pharmacokinetic data in infants and young children will be required. As with all newly marketed AEDs, physicians will need to be vigilent to identify idiosyncratic age-related side effects, and determine whether some types of epilepsy worsen.

Conclusions

The goal of AED therapy is to produce the best quality of life with complete control of seizures without causing untoward side effects. Results from small prospective and retrospective studies provide strong support for the efficacy and safety of levetiracetam in pediatric patients with a wide range of seizure disorders. Data from these and other studies will help determine whether levetiracetam can be considered as a first-line treatment option or monotherapy in children with epilepsy. In the absence of sufficient data, certain criteria can help assess suitability as first-line therapy: effectiveness in two or more randomized, double-blind controlled trials, a favorable safety profile, no idiosyncratic adverse reactions, and ease of use [30]. In the meantime, clinical findings suggest that levetiracetam could be an effective and well-tolerated treatment option in children with refractory epilepsy. The need exists for additional pediatric clinical data regarding levetiracetam's efficacy, pharmacokinetics, and tolerability.

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