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Levetiracetam for the Treatment of Partial Seizures

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Levetiracetam has become one of the most frequently prescribed new drugs for the treatment of partial seizures. It offers several advantages over traditional therapy, including twice daily dosing, a wide margin of safety with no requirements for serum drug concentration monitoring, and no interactions with other anticonvulsants. In addition, levetiracetam appears to be well tolerated by most patients and may have less adverse effects on cognitive function than traditional agents.[1-4]

Mechanism of Action

The mechanism for the anticonvulsant effect of levetiracetam is not well understood. It is not chemically related to other anticonvulsants and does not appear to act through the traditional mechanisms of neurotransmitter modulation. In animal studies, levetiracetam does not prevent acute seizures induced by electroshock or pentylenetetrazol; however, it does appear to attenuate fully kindled seizures and the development of kindling. This suggests that levetiracetam may act by preventing hypersynchronization of epileptiform burst firing, producing an inhibition of the spread of seizure activity. The recent discovery of a specific binding site for levetiracetam in the brain may lead to more information about its mechanism of action in the future. [4-7]

Indications

Levetiracetam was approved by the Food and Drug Administration on November 30, 1999. It is currently indicated as adjunctive treatment for partial seizures in patients 16 years of age and older.[5,6] Although not as well studied, preliminary reports suggest that levetiracetam may also be useful in some patients with generalized, absence, or myoclonic seizures, and in patients with Lennox-Gastaut syndrome.[3]

Clinical Trials

The results of several multicenter studies have demonstrated the safety and efficacy of levetiracetam as adjunctive therapy or monotherapy in adults with refractory partial seizures.[8-10] In 2000, Cereghino and colleagues, reported the results of a double-blind, randomized, placebo-controlled multicenter trial conducted by the United States Levetiracetam Study Group.[8] Patients were randomized to receive placebo or levetiracetam, titrated to final doses of either 1,000 mg/day or 3,000 mg/day (divided into two daily doses), as add-on therapy to their current anticonvulsant regimen. Dose titration was conducted over 4 weeks, with 14 weeks of maintenance, and an 8-week follow-up. A total of 268 patients completed the trial. Both levetiracetam groups had significantly fewer seizures than the controls. A favorable response ($\geq$ 50% reduction in seizure frequency) was reported in 33% of the 1,000 mg/day group and 39.8% of the 3,000 mg/day group, versus 10.8% of the placebo group. Eleven levetiracetam patients (5%) became seizure-free during the study, compared to none of the placebo patients.

Similar results were published that year from the European Levetiracetam Study Group.[9] In this trial, levetiracetam doses of 1,000 mg/day or 2,000 mg/day were compared to placebo in 324 adults. Using a similar design to the US study, there was a 4 week titration and a 12 week maintenance period. Seizure frequency was reduced by $\geq$ 50% in 22.8% of the 1,000 mg/day and 31.6% of the 2,000 mg/day group, versus 10.4% of the placebo group. Five patients in the 1,000 mg/day group, two in the 2,000 mg/day group and one in the placebo group became seizure-fee.

The European group also studied the effects of a 3,000 mg/day add-on regimen versus placebo in 286 patients.[10] The responder rate in this study was 42.1% in the levetiracetam group versus 16.7% in the placebo group. Treatment responders could then enter into a monotherapy trial, in which their standard anticonvulsants were slowly tapered off. The responder rate for

monotherapy was 59.2%, with a median percent reduction in seizure frequency of 73.8%. Nine patients (18.4%) remained seizure-free on levetiracetam monotherapy.

Based on the positive results and favorable adverse effect profile seen in these trials in adults, levetiracetam has been considered as a potential option for children with treatment-resistant partial seizures. In the May issue of *Epilepsia*, Glauser and colleagues published the results of the first clinical efficacy trial with levetiracetam in children.[11] The University of Virginia was one of six centers involved in this open-label study. A total of 24 children between the ages of 6 and 12 years were enrolled. After a 4 week baseline evaluation, levetiracetam was initiated and the dose titrated over a 6 week period. An 8 week evaluation phase followed. All patients were initially given a single 20 mg/kg dose for pharmacokinetic profiling, then started on a regimen of 10 mg/kg/day (5 mg/kg given twice daily). The dose was increased to 20 mg/kg/day at 2 weeks and 40 mg/kg/day at 4 weeks unless the desired result was obtained at a lower dose. Further dose increases were made based on clinical response. The children continued to receive their current anticonvulsant regimen during the study.

Twenty-two children completed the entire study (two withdrew because of lack of response). In the 23 evaluable patients, the levetiracetam doses at the end of titration ranged from 12.8 to 65.2 mg/kg/day. The majority (61%) had a final dose between 30 and 50 mg/kg/day. Twelve patients (52.2%) had a $\geq$ 50% reduction in seizure frequency compared to baseline. A $\geq$ 75% response was seen in 5 (21.7%) of the children. Two patients remained seizure-free.

Long-term evaluation of the patients enrolled in these trials, as well as several others, suggests that levetiracetam is both efficacious and well tolerated by most patients. Based on compiled results, retention rates are estimated to be 60% at one year and 32% at five years. A $\geq$ 50% reduction in seizure frequency has been reported in 39% of patients (512/1,325) overall, and 13% of trial participants (183/1,422) became seizure-free for at least 6 months.[12]

Pharmacokinetics

Levetiracetam is rapidly and completely absorbed after oral administration, with peak serum concentrations occurring approximately one hour following a dose. Bioavailability is 96-100% and is unaffected by the presence of food or antacids. Levetiracetam exhibits minimal protein binding (< 10%) and has a volume of distribution of 0.5-0.7 L/kg in adults. It is eliminated through renal excretion, primarily as unchanged drug. A minor percentage undergoes hepatic metabolism via enzymatic hydrolysis and hydroxylation to inactive byproducts. The average elimination half-life in adults is 7 hours, with a range of 6-8 hours. Average total body clearance is 0.96 ml/min/kg in adults, with a renal clearance of 0.6 ml/min/kg. Levetiracetam clearance is correlated to creatinine clearance, and is reduced in patients with renal dysfunction. In adult patients with severe renal impairment (creatinine clearance < 30 ml/min), levetiracetam clearance is reduced by approximately 60%.[1,2,5,6,13]

The pharmacokinetics of levetiracetam in children were evaluated as part of the open-label study described previously.[11,14] Following a single oral 20 mg/kg levetiracetam dose, plasma concentrations peaked at 2.3$\pm$1.2 hours. Mean volume of distribution was 0.72$\pm$0.12 L/kg, with an elimination half-life of 6.0$\pm$1.1 hours, a total body clearance of 1.43$\pm$0.36 ml/min/kg, and a renal clearance of 0.79$\pm$0.26 ml/min/kg. These results suggest that the pharmacokinetics of levetiracetam in children are similar to those of adults, with the exception of a higher non-renal clearance (approximately 40% greater) which may explain the need for higher mg/kg/day doses in children compared to adults.

Drug Interactions

One of the advantages of levetiracetam is its lack of drug interactions. Levetiracetam does not exhibit any of the characteristics of substances commonly involved in drug interactions. It is not highly protein bound and does not inhibit or induce cytochrome P450 enzymes, nor does it rely on that pathway for elimination. Prior to marketing, potential interactions between levetiracetam and phenytoin, phenobarbital, primidone, carbamazepine, valproic acid, lamotrigine, gabapentin, digoxin, oral contraceptives, and warfarin were evaluated. None of these drugs influenced the pharmacokinetic profile of levetiracetam, and the addition of levetiracetam failed to significantly alter serum concentrations of the other agents. Clinical trials have replicated these findings.[1,2,5,6,13,14]

Adverse Effects

The most commonly reported adverse effects during clinical trials with levetiracetam in adults were somnolence (15% of patients), asthenia (15%), headache (14%), infection (13%), dizziness (9%) and ataxia (3%). These adverse effects were seen most frequently in the first month of therapy and typically lessened or resolved with continued treatment. In clinical

trials, up to 4% of patients have withdrawn because of these effects.[5,6,15,16]

Similar adverse effects, but higher percentages, were reported in the open-label pediatric study. The most frequent adverse effects in the children participating in that study were headache (33%), infection (33%), anorexia (25%), and somnolence (25%).[11]

In premarketing studies of levetiracetam, up to 13% of patients have experienced adverse neuropsychiatric symptoms. In most of these patients, the symptoms have been mild, including agitation, hostility, apathy, anxiety, emotional lability, and depression. Approximately 0.8% of patients have experienced serious neuropsychiatric symptoms (hallucinations, suicidal ideations, or psychosis). In most of these reports, symptoms have occurred within the first month of therapy, but they may develop at any time during treatment. Dose reduction or discontinuation has led to resolution of symptoms in the cases reported.[5,6,15,16]

In *Epilepsia* last year, Kossoff and colleagues described a series of four pediatric and adolescent patients with symptoms of psychosis after beginning levetiracetam at doses of 15-25 mg/kg/day.[17] In this series, a 5 year old girl experienced visual hallucinations, a 13 year old boy had auditory hallucinations, insomnia, and screaming behavior, a 16 year old girl became agitated with persecutory delusions, and a 17 year old girl experienced auditory hallucinations. All four had a history of cognitive deficits (learning disabilities) prior to initiation of levetiracetam. The onset of symptoms ranged from 2 days to 3 months after starting levetiracetam. All four patients had resolution of symptoms following dose reduction (in one patient) or discontinuation (in three patients). The authors suggested that slower dose titration, beginning at 10 mg/kg/day and increasing to 20 mg/kg/day over 4 weeks, may be beneficial in preventing these adverse effects, particularly in children predisposed to neuropsychiatric symptoms.

Levetiracetam has also been associated with minor changes in hematologic studies in some patients. Decreases in red blood cell counts, hemoglobin, hematocrit, white blood cell count, and neutrophil count have been reported in up to 3% of patients in premarketing trials, but have been considered clinically significant only in rare cases. These effects were transient in most subjects and did not require discontinuation of levetiracetam.[1,5,6,15,16]

Lack of Adverse Cognitive Effects

One of the most undesirable characteristics of the traditional anticonvulsants, such as phenobarbital and phenytoin, has been their adverse effects on cognitive function. In children, the decreased attention span, difficulty concentrating, and memory loss associated with these drugs may significantly impair school performance. Although the effects of levetiracetam on cognition have not been assessed in a pediatric population, in adult trials it appears to have no adverse effects.[1,2,16,18] In a study of 10 adults given levetiracetam for two weeks as an adjunct to phenytoin or carbamazepine (with or without valproic acid), no significant changes were found on neuropsychological tests of psychomotor functioning, memory performances, or information processing.[18]

Dosing Recommendations

Levetiracetam (Keppra; UCB Pharma) is available in 250, 500, and 750 mg scored tablets.[5,6] An oral liquid formulation is currently under investigation.[2] In adults, dosing should be initiated at 500 mg twice daily. The dose may be titrated based on patient response with 1,000 mg/day increments every 2 weeks, up to 3,000 mg/day. Higher doses have been used in clinical trials, but may not provide additional therapeutic benefit in all patients. Levetiracetam may be taken with or without food.[1,2,5,6]

In children, levetiracetam should be initiated at a dose of 10 mg/kg/day divided and given twice daily. The dose may be increased by 5 to 10 mg/kg/day increments every 2 weeks as needed, up to 40 mg/kg/day.[11,14,17] Higher doses, up to 60 mg/kg/day, may be necessary in some patients to achieve full benefit. A maximum weight-based dose for pediatric patients has not been established.

In patients with moderate to severe renal dysfunction, the dose of levetiracetam should be reduced by 50%, still given twice daily. Hemodialysis removes approximately 50% of a levetiracetam dose in one 4-hour session. Patients undergoing hemodialysis should receive a supplemental dose of half their standard maintenance dose after dialysis. No dosage adjustment is needed for patients with hepatic dysfunction.[1,5,6]

Patients requiring discontinuation of therapy should have their levetiracetam dose slowly tapered over the course of 2-4 weeks to prevent withdrawal seizures.[3,5,6]

Summary

Levetiracetam offers a number of advantages over the traditional anticonvulsants used for the

management of partial seizures, including a wide margin of safety, no drug interactions, and a relatively benign adverse effect profile. New studies have demonstrated the utility of levetiracetam in the pediatric population, but more research is needed to identify a safe maximum dose, further define the adverse effect profile, and evaluate its long-term effects on growth and development.

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Pharmacology Literature Review

Ceftriaxone review

An extensive review of ceftriaxone has been published to highlight new data on its antimicrobial activity, pharmacokinetics, efficacy, and adverse effects. This review is highly recommended for pediatric health care providers who use ceftriaxone in their practice. Lamb HM, et al. Ceftriaxone: an update of its use in the management of community-acquired and nosocomial infections. **Drugs 2002;62:1041-89.**

Fetal pharmacotherapy

The role of drug therapy given during pregnancy to treat the unborn infant is the focus of this new review. In addition to a discussion of the drugs currently in use, the authors also address the pharmacokinetic considerations of drug delivery through the placenta and the ethics of providing this form of treatment. Koren G, et al. Fetal pharmacotherapy. **Drugs 2002;62:757-73.**

Lansoprazole kinetics in children

Lansoprazole, a proton pump inhibitor, is a useful therapy for children at risk for gastrointestinal erosions. Forty children (ages 18 days to 14 years) were given single oral lansoprazole doses (17 mg/m^2) or multiple doses for up to 2 weeks. Single dose pharmacokinetics were: volume of distribution 0.61$\pm$0.36 L/kg, half-life 1.5$\pm$2 hours, and clearance 0.57$\pm$0.47 L/hr/kg. Similar results were seen with multiple dosing. Although no significant differences were seen with age, there was a trend for infants to have a more rapid clearance than adults. Antisecretory effect was greatest in the youngest patients, falling to adult values at 6 months. Tran A, et al. Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. **Clin Pharmacol Ther 2002;71:359-67.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 6/28/02:

1. Lansoprazole compounded oral suspension was added to the Formulary. The dose for lansoprazole in children $\leq$ 14 years of age is 0.5-1.6 mg/kg PO given once daily. The recommended dose for gastrointestinal reflux or duodenal ulcers in adults is 15 mg PO given once daily. Omeprazole compounded oral suspension was deleted.

2. The remainder of the meeting was used to discuss issues related to the restructuring of the committee.

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