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Recent Literature on Pediatric Antiepileptic Drugs

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With the addition of over a dozen new antiepileptic drugs (AEDs) in the United States over the past 20 years, there has been a steady increase in the number of papers published describing alternatives to traditional therapy with phenobarbital, phenytoin, carbamazepine, and valproic acid. Among them are papers addressing the use of newer AEDs in the prevention and treatment of seizures in infants, children, and adolescents. This issue of Pediatric Pharmacotherapy provides an overview of pediatric AED research published during 2012.

Open-Label Extension Studies of Levetiracetam

Many of the papers published this year describe the use of levetiracetam in different settings. An effective therapy for partial-onset, generalized tonic-clonic, and myoclonic seizures, levetiracetam also offers the advantages of a mild adverse effect profile, few drug interactions, and no requirement for serum concentration monitoring. The results from several extension studies became available this year which support the safety and efficacy of levetiracetam in pediatric clinical practice.[1,2]

Delanty and colleagues published the findings from a manufacturer-sponsored phase III open-label study which included children and adults who participated in two earlier clinical trials.[1] The study was conducted at 69 institutions in 16 countries over a 5-year period. A total of 217 patients (4-64 years of age) were enrolled, with 125 completing the study. All but one patient were taking one or more concomitant AEDs. The average levetiracetam dose was 2,917.5 mg/day (range 788.2-3,993 mg/day). The median treatment period was 2.1 years, with a maximum of 4.6 years. The median reduction in seizure frequency from baseline was 91.4%. Eighty-five percent of patients achieved a 50% or greater reduction in seizures. Overall, 56.2% of patients experienced at least one seizure-free period lasting at least 6 months. Of those patients, 22.6% had no seizures during the evaluation period. The results were consistent among all seizure types. Adverse effects were reported by 165 patients (76%), most commonly headache, dizziness, or depression.

A second manufacturer-sponsored levetiracetam extension study was conducted in children 4 to 16 years of age.[2] This 48-week study was conducted over a 4-year period at 33 centers in five countries. A total of 103 patients were enrolled, with 89 completing the study. The majority (73.8%) were less than 13 years of age. The mean levetiracetam dose during the study was 50.2 $\pm$ 15.6 mg/kg/day (range 9-85.8 mg/kg/day). The median duration of treatment was 11 months. Mean scores on tests of memory and cognitive functioning remained consistent during treatment, demonstrating no detrimental effects on cognition. Changes in the Child Behavior Checklist syndrome scores showed statistically significant improvement from baseline. The median percentage reduction in seizure frequency from baseline was 86.4% (range 23.2-100%). Sixty-nine percent achieved a 50% or greater reduction in seizure frequency, with 33.4% of patients remaining seizure-free. Adverse effects were reported by 91.3% of patients, with headache, irritability, aggression, and fatigue occurring most often. The authors concluded that levetiracetam provided effective, sustained seizure control in children, with stable cognitive functioning and improved behavior.

Levetiracetam for Status Epilepticus

Based on its safety and efficacy profile and the availability of an injectable formulation, levetiracetam has become an alternative treatment for status epilepticus in many hospitals. A recent paper by Misra and colleagues described the results of a randomized, open-label pilot study comparing levetiracetam to lorazepam for the initial management of children

and adults with status epilepticus.[3] Seventy-nine patients (1-75 years of age) received either levetiracetam 20 mg/kg given IV over 15 minutes or lorazepam 0.1 mg/kg over 2-4 minutes. Those who did not achieve seizure control within 10 minutes were treated with the alternate agent. Seizure control was achieved in a similar percentage of patients, 76.3% of those given levetiracetam and 75.6% of those given lorazepam. Of the patients who failed to respond to the initial drug, the percentage responding to alternate agent was 79.3% for levetiracetam and 88.9% for lorazepam. Seizure control at 24 hours was also comparable between the groups: 79.3% in those given levetiracetam initially and 67.7% in those given lorazepam. The only statistically significant difference between the groups was a higher need for mechanical ventilation in the lorazepam group (10 patients versus 4 in the levetiracetam group, $p = 0.03$).

Additional clinical experience in this setting comes from McTague and colleagues who conducted a 2-year open-label observational study of IV levetiracetam in 51 children with acute repeated seizures or status epilepticus.[4] Patients ranged in age from 0.2 to 18.8 years, with a mean age of 7.1 years. The median starting dose was 14.4 mg/kg (range of 5-30 mg). Twenty-three children with repetitive seizures (59%) became seizure-free and four of five children had termination of their status epilepticus. Forty-two patients (81%) were started on maintenance levetiracetam. Three children developed aggressive behavior, with one child requiring discontinuation of the drug. These two studies, while limited by their small sample size, lend support to the consideration of levetiracetam as an alternative therapy for the management of pediatric status epilepticus.

Seizure Prophylaxis with Levetiracetam

Phenytoin has traditionally been given in the immediate period following head injury to protect against the development of early post-traumatic seizures. The 2012 Guidelines for the Acute Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents give the use of phenytoin prophylaxis a level III recommendation (the lowest category) based on the lack of quality research demonstrating its efficacy.[5] While phenytoin may be beneficial, it has several disadvantages, including the risk for arrhythmias and necrosis after extravasation, as well as potential drug interactions and the need for serum concentration monitoring.

Some hospitals have begun using levetiracetam for prophylaxis of both early and late seizures after trauma, with a variety of treatment protocols ranging from 7 to 30 days. Klein and colleagues recently published the results of an open-label phase II study of levetiracetam added to phenytoin in patients at risk for post-traumatic epilepsy.[6] A total of 126 patients (86 adults and 40 children) completed the study at two level 1 trauma centers. All patients received phenytoin for one week after injury as standard care for prevention of early post-traumatic seizures. Sixty-six patients also received levetiracetam (55 mg/kg/day) for 30 days, while the remainder served as controls. Only two patients stopped treatment due to an adverse effect (somnolence). At 2 years post-injury, 9.1% of the patients given levetiracetam had developed post-traumatic seizures, compared to 13.3% of the controls. Although the study was too small to demonstrate statistical significance, the authors suggest that levetiracetam may be useful addition to phenytoin for the prevention of late post-traumatic epilepsy.

Levetiracetam has also been suggested as an alternative to phenytoin for seizure prophylaxis in patients undergoing craniotomy. A group of investigators from the University Medical Center at Regensburg, Germany recently published a retrospective study of 235 adults and children (9 years of age and older) who received prophylactic perioperative phenytoin or levetiracetam.[7] The primary outcome was the development of seizures during the first week after surgery. Patients treated with phenytoin received 750 mg IV prior to surgery, followed by an infusion of 30 mg/hr for 24 hours. Phenytoin was continued for another 4 days, tapered from 100 mg three times daily down to 50 mg once daily. The levetiracetam group received 1,000 mg IV prior to and following surgery, with 1,000 mg given twice daily on day 2, 500 mg twice daily on day 3, and 500 mg daily on days 4 and 5. The incidence of seizures was no different between the two groups: 7/154 patients (4.5%) treated with phenytoin and 2/81 patients (2.5%) in the levetiracetam group ($p = 0.66$).

While these studies suggest that levetiracetam may be an acceptable alternative to phenytoin for seizure prophylaxis, much more work is needed before it can be adopted as standard practice. Larger multicenter prospective studies, likely requiring the utilization of collaborative research networks, will be necessary to determine the clinical significance of AED prophylaxis in the trauma and postoperative settings.

Levetiracetam Pharmacokinetics in Neonates

Levetiracetam has also become a popular choice for treatment of neonatal seizures that fail to respond to benzodiazepines or phenobarbital. Several studies, both prospective and retrospective, have been published within the past five years describing the safety and efficacy of levetiracetam in the neonatal population. In

the July issue of *Pediatric Research*, Sharpe and colleagues published a study defining the pharmacokinetic profile of IV levetiracetam during the first week of life.[8] Eighteen term neonates with seizures failing to respond to phenobarbital received a 20 or 40 mg/kg loading dose, followed by 5-10 mg/kg/day for one week. The authors identified an increase in clearance, from a mean of 0.7 ± 0.27 mL/min/kg on day 1 to 1.33 ± 0.35 mL/min/kg on day 7. The corresponding half-life decreased from 18.5 ± 7.1 hrs to 9.1 ± 2 hrs. Values at day 7 were similar to those reported by other investigators in neonates up to 1 month of age. This rapid increase in clearance is not easily explained. Levetiracetam is eliminated primarily in the urine as unchanged drug. The reduced glomerular filtration rate of neonates would be expected to result in a slower clearance immediately after birth, with a gradual increase over time. The authors suggest that their findings may be explained by a reduced capacity for tubular reabsorption of levetiracetam in the neonatal kidney and suggest that more frequent dosing may be necessary during the first week of life.

Rufinamide Use in Lennox Gastaut Syndrome

An open-label observational trial of rufinamide was published earlier this year demonstrating the utility of this agent as adjunctive therapy in children with Lennox Gastaut syndrome (LGS).[9] A total of 128 children (1.8-19.9 years) underwent a 4-week titration, beginning at 10 mg/kg/day, followed by a 12-week maintenance phase. The average dose after titration was 31.7 ± 8.7 mg/kg/day. Forty-six of the 112 patients completing the study (35.9%) experienced at least a 50% reduction in seizure frequency. Ten children (7.8%) became seizure-free. Twenty-one children (16.4%) had an increase in seizure frequency. Over a third of patients experienced adverse effects; fatigue was reported by 11.7% and poor appetite by 7% of patients. The 31.7% overall response rate for rufinamide in patients not controlled with an average of 3 other AEDs demonstrates the potential for this agent in the treatment of refractory LGS.

Sweat Chloride Concentrations with Topiramate

Oligohidrosis occurs in a small number of patients taking topiramate, but the mechanism underlying this adverse effect is not well understood. Although numerous cases of topiramate-induced hyperthermia and heat stroke have been reported in the literature, only one recent report describes an elevated sweat chloride concentration in the affected patient. To further characterize the mechanism for topiramate-induced oligohidrosis, Guglani and colleagues at the Children's Hospital of Pittsburgh conducted sweat chloride testing in 21 children on therapy for at least 6 months.[10] Twenty-one children (mean age 11.7 ± 4.1 years, range 6 months-18 years) were enrolled, as well as 20 healthy children (mean age 11.3 ± 4.2 years) who served as controls. Sweat chloride concentrations were significantly higher in the topiramate group, with a mean of 37.7 ± 18.8 mmol/L compared to a mean of 15.9 ± 6.9 mmol/L in the controls ($p = 0.0001$). Mean sweat volume was significantly lower in the children receiving topiramate (29.1 ± 17.4 μL compared to 41.2 ± 17.5 μL in the controls, $p = 0.037$). This study demonstrates that not only is sweat production altered in patients taking topiramate, but the chloride concentration of the sweat is abnormal as well. These differences were consistent among patients and occurred in a controlled environment, without the presence of hyperthermia. The authors suggest that future studies of topiramate-induced oligohidrosis include assessment for a dose-response relationship, correlation with topiramate serum concentrations, and evaluation of potential pharmacogenomic differences.

Propylene Glycol-Associated Apoptosis

Although an international survey published earlier this year in *Pediatric Neurology* found that phenobarbital remains the most common choice for management of neonatal seizures among neurologists and neonatologists,[11] there are growing concerns over its potential for toxicity. Phenobarbital injection contains 68% propylene glycol and 10% ethanol as solvents. While the risk for these compounds to produce cardiotoxicity has long been known, new data suggests the potential for neurotoxicity as well.

In a recent study from Washington University, Lau and colleagues examined the effects of phenobarbital and propylene glycol on the developing central nervous system of immature mice.[12] Tissue from mice exposed to propylene glycol demonstrated widespread apoptotic neurodegeneration. After 24 hours, there was evidence of apoptosis, destruction of axons and dendrites, and residual cellular debris. The greatest damage was documented 7 days after exposure. Administration of phenobarbital dissolved in propylene glycol produced greater damage than propylene glycol alone, suggesting a potentiation of apoptosis with the combination. This information, combined with the low efficacy of phenobarbital in terminating neonatal seizures and increasing interest in levetiracetam and topiramate in this population, has the potential to trigger a change in prescribing patterns.

Behavioral Adverse Effects

One of the most important issues when selecting an AED for a pediatric patient is the likelihood for adverse effects on learning and behavior. An in-depth review of the behavioral adverse effects

of AEDs was published in the June issue of the *Journal of Clinical Psychopharmacology*.[13] Eddy and colleagues summarize the literature on 15 AEDs, including both older and newer drugs, with data from children and adults. Tables for the more commonly used AEDs provide a quick summary of the available studies and make this article a useful resource for any health care provider caring for children with seizures. In addition to presenting information on adverse effects, the authors point out studies describing the positive effects of some AEDs on learning and behavior. They also provide recommendations for future research, including the need for better age-based assessment tools.

Efficacy of Perampanel in Adolescents

Two new AEDs, perampanel and ezogabine, were approved by the Food and Drug Administration during 2012. Perampanel, a noncompetitive α–amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist, is indicated for use as adjunctive therapy in patients 12 years of age and older with partial-onset seizures. In the August issue of *Neurology*, French and colleagues published the results of a multicenter, double-blind, placebo-controlled phase III trial in 388 adolescents and adults.[14] Patients received 8 mg or 12 mg perampanel or placebo once daily for 13 weeks, after an initial 6-week titration period. The median percent change in seizure frequency was -21%, -26.3%, and -34.5% for the placebo, 8 mg, and 12 mg perampanel treatment groups ($p = 0.0261$ and $p = 0.0158$ for the 8 mg and 12 mg groups compared to placebo). The percentages of patients achieving a 50% reduction in seizure frequency during the 13-week maintenance period were 26.4%, 37.6%, and 36.1% for the three groups. The most frequent adverse effects were dizziness, somnolence, irritability, headaches, falls, and ataxia. Based on their results, the authors concluded that perampanel is an effective therapy for patients whose epilepsy has not been controlled with other AEDs.

Summary

Several important papers have been published on the use of AEDs in infants, children, and adolescents during the past year, ranging from extension studies assessing long-term efficacy and safety to reports of their use in new patient settings or new descriptions of adverse effects. These papers add a great deal to our understanding of the role these drugs can play in the treatment of seizures in the pediatric population.

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Formulary Update

The Pharmacy and Therapeutics Committee did not meet in November.

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