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Update on Levetiracetam in Infants and Children

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After nearly two decades on the market, levetiracetam has become one of the most widely used antiepileptic drugs (AEDs) in the United States. It was first approved by the Food and Drug Administration (FDA) in 1999 with the brand name Keppra™, in tablet form only, for adjunctive treatment of partial onset seizures in adults.[1] Approval was extended in 2005 to children 4 years of age and older. In 2007, the manufacturer introduced an intravenous product, followed a year later by an oral solution. The release of the solution coincided with an indication for use as adjunctive therapy for primary generalized seizures in children 6 years of age and older. The indications for levetiracetam for partial onset seizures were later amended to include infants 1 month of age and older to children 4 years of age; and in 2014, it was approved for use in patients 12 years and older with juvenile myoclonic epilepsy. Throughout these advances, research on the efficacy and safety of levetiracetam in infants and children has continued to grow, providing a much richer picture of the drug's role in the treatment of pediatric epilepsy. The issue highlights the publications on pediatric levetiracetam use from the past 2 years.

Frequency of Use

In a 2017 paper in *Pediatric Neurology*, Shellhaas and colleagues analyzed the choice of initial AED in a cohort of 495 newly diagnosed patients from 17 major pediatric epilepsy centers from across the United States.[2] The authors found that levetiracetam was by far the most commonly prescribed AED, regardless of epilepsy type or patient age. Two hundred ninety-one of the 464 patients (63%) initially received levetiracetam as monotherapy, followed by oxcarbazepine (14%), phenobarbital (12%), topiramate (3.4%), and zonisamide (2.8%). Of the children who did not receive levetiracetam initially, 62% were given it as their second AED. Ninety of the 163 patients (55%) diagnosed at less than 6 months of age were treated with levetiracetam as their first AED. Phenobarbital, the traditional agent of choice for neonatal seizures, was prescribed as initial therapy in only 30.7%. The authors suggest this change in practice may reflect both the increasing acceptance of levetiracetam use in the pediatric population and concerns for the potential adverse effects of phenobarbital in the developing brain.

Efficacy and Safety

Two recent meta-analyses have assessed the efficacy of levetiracetam in children. Zhang and colleagues performed a meta-analysis of 13 randomized controlled trials comparing levetiracetam to placebo or other AEDs as monotherapy or adjunctive therapy in 1,013 pediatric patients.[3] Eleven studies enrolled patients between 2 and 16 years of age, while the other two included infants. Levetiracetam was initiated at doses of 5-20 mg/kg/day and titrated to a maximum of 30-60 mg/kg/day. Five of the studies compared levetiracetam to oxcarbazepine, three to valproate, three to placebo, one to carbamazepine, and one to sulthiamine, an AED not available in the United States. Several of the studies included a placebo control group. The primary outcome for the studies was defined as a 50% or greater reduction in seizure frequency.

Levetiracetam was found to produce a response rate similar than that of the comparators (RR 1.08, 95% CI 1.01-1.16), p = 0.35). The percentage of seizure-free patients was also similar among the AEDs studied (RR 1.16, 95% CI 1.03-1.31, p = 0.3). The authors found a lower incidence of adverse effects with levetiracetam, but the difference did not reach statistical significance (RR 0.9, CI 95% 0.77-1.06, p = 0.22). The most commonly reported adverse effects were irritability and somnolence. The majority of adverse effects were classified as mild and did not require discontinuation.

Earlier this year, Rosati and colleagues published a meta-analysis of AED use in children categorized by seizure type.[4] They included 46 randomized clinical trials with a total enrollment of 5,652 children and adolescents. Comparators

included 22 different AEDs as well as placebo. Carbamazepine and lamotrigine were found to produce higher response rates (a seizure frequency of 50% or greater) in the initial treatment of focal seizures, but the differences among the AEDs were not statistically significant. Nine studies of refractory focal epilepsy were included. In these trials, only levetiracetam and perampanel were found to produce a higher response rate than placebo (OR 3.3, 95% CI 1.3-7.6 and OR 2.5, 95% CI 1.1-5.8, respectively).

Another recent paper has added to our understanding of the efficacy of levetiracetam in pediatric patients with refractory epilepsy. Muramatsu and colleagues analyzed the cases of 49 children and adolescents (mean age 10.6 $\pm$ 5 years) with multidrug refractory epilepsy lasting more than 2 years.[5] Following treatment with a mean levetiracetam dose of 38 mg/kg/day (range 8-87 mg/kg/day) for a minimum of 6 months, eighteen patients (37%) achieved a 50% or greater reduction in seizure frequency, with 13 becoming seizure-free. Nine patients improved on treatment, but had a less than 50% reduction in seizure frequency. Twenty patients (41%) had no response to levetiracetam, and two patients experienced a worsening of their seizure frequency.

The patients were further classified according to the presence of MRI abnormalities, including cerebral atrophy, leukoencephalopathy, congenital malformations, and focal cortical dysplasia, or the diagnosis of intellectual disability, defined as documented neurologic impairment or an IQ < 70. Of the 19 children with MRI abnormalities, 5 (26%) experienced a 50% or greater reduction in seizures. Among the 36 patients with intellectual disability, nine (25%) had a greater than 50% reduction. Levetiracetam was well tolerated, with the majority of patients (78%) having no significant adverse effects. Seven patients (14%) were found to have increased drowsiness, while one experienced irritability. The authors concluded that levetiracetam can be of benefit in children with multidrug refractory seizures, and may be useful even in patients with central nervous system lesions or significant neurologic impairment.

In contrast to these reports, the role for levetiracetam in preventing seizures within the first week after traumatic brain injury (TBI) remains unclear. A recent prospective observational study by Chung and O'Brien found that levetiracetam administration failed to effectively prevent early seizures following moderate to severe traumatic brain injury in children. A total of 34 patients (median age 6 years, range 5 days-16 years) received levetiracetam prophylaxis with a median dose of 20 mg/kg/day. Six patients (17%) had clinical seizures despite prophylaxis, with another two having non-convulsive seizures. The authors found that the prevalence of seizures in this cohort was similar to that reported in patients not receiving an AED, and higher than in previous reports using phenytoin (2-15%). Larger controlled studies are needed to determine the true efficacy of levetiracetam in pediatric TBI.

Use in Infants

Several new papers focus on the use of levetiracetam in infants. A multicenter observational trial was conducted by Arzimanoglou and colleagues in conjunction with UCB Pharma, the manufacturer of Keppra.[6] One hundred and one infants were enrolled, with a mean age of 6 months (range 1-11 months). The majority (68%) had focal seizures, while 41% had generalized seizures, and the remainder were unclassified. The mean duration of observation was 152 $\pm$ 87 days, and the mean levetiracetam dose was 46 $\pm$ 16 mg/kg/day (range 16-88 mg/kg/day). Most patients (80%) received one or more antiepileptics in addition to levetiracetam during the study, including vigabatrin (34%), phenobarbital (26%), valproate sodium (23%), and diazepam (20%).

In the 85 patients with complete data on seizure severity, 72% experienced improvement, another 19% remained stable, and 9% worsened. Fifty-five patients (54%) of the patients had one or more adverse events during the study, but only five were determined to be drug-related. The events included irritability and convulsions in two patients, and one patient each with somnolence and transient hypotonia. All but hypotonia have previously been documented in patients taking levetiracetam and are listed in the prescribing information. None of the drug-related adverse events were considered serious or led to discontinuation. There were no apparent adverse effects on growth. The results of this study supported the FDA's extension of the indication for levetiracetam use to infants.

Further evidence of the value of levetiracetam in infants with seizures comes from two recent studies. In 2017, Venkatesan and colleagues at Cincinnati Children's Hospital conducted a retrospective single-center study of levetiracetam in neonatal hypoxic ischemic encephalopathy (HIE).[7] Of 127 neonates diagnosed with HIE from 2008 to 2015, 83 developed seizures. Eighty infants received phenobarbital as initial therapy, with 51 (61%) having cessation of seizures. Thirty-two neonates received levetiracetam, either as initial therapy or following phenobarbital, with 27 (84%) responding. Therapeutic cooling made no difference in the results. The mean total dose of levetiracetam required to stop seizures was 63 mg/kg. The mean maintenance dose used was 65 mg/kg/day. There were no significant adverse effects noted. The authors suggested that levetiracetam might be useful as a first-line therapy in this setting.

In April 2018, Grinspan and colleagues published the results of the Early Life Epilepsy Study, a multicenter prospective observational cohort study comparing levetiracetam and phenobarbital for the treatment of infantile epilepsy.[8] Seventeen medical centers throughout the United States participated in this study conducted from 2012 to 2015. A total of 155 patients with non-syndromic epilepsy presenting with an afebrile seizure between 1 and 12 months of age were enrolled. The median age of the patients was 4.7 months (IQR 3-7 months). Infants treated with levetiracetam were more likely to be free of seizures within 3 months of treatment and to not require a second AED compared to those treated with phenobarbital, 47/117 (40%) versus 6/38 (16%), p = 0.01. The superiority of levetiracetam remained after adjusting for covariates, observable selection bias, and within-center correlation, with an odds ratio of 4.2 (95% CI 1.1-16) and a number needed to treat of 3.5 (95% CI 1.7-60). In both of these studies, the authors recommend that larger randomized controlled trials be conducted to clarify the relative efficacy of levetiracetam compared to phenobarbital in the management of neonatal seizures.

Adverse Effects

The adverse effect profile of levetiracetam has been developed from multiple studies and case reports.[1,9,10] While generally well tolerated, approximately 20-50% of patients will experience at least one adverse effect after starting treatment. The most commonly reported in children are headache (in 19%), somnolence (13%), abdominal pain or emesis (9-15%), fatigue (11%), aggression (10%), decreased appetite, and abnormal behavior, dizziness, or irritability (7%). Levetiracetam use has also been linked with hostility, depression, and suicidality. Recent case reports describe some of the other rare adverse effects associated with levetiracetam use, including auditory and visual hallucinations in a 10-year-old boy[9] and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in a 9-year-old girl. In both cases, symptoms resolved after discontinuation of the drug.[10]

Pyridoxine to Reduce Behavioral Adverse Effects

The use of pyridoxine (vitamin B_6) to prevent levetiracetam-associated behavioral adverse effects (BAEs) was initially reported more than a decade ago and has become a relatively common practice. In the cohort study by Shellhaas described earlier, 43 of the 291 patients (43%) prescribed levetiracetam as their initial AED were given pyridoxine to reduce the risk of BAEs.[2] The mechanism of pyridoxine's effect has not been determined, and the use of this combination has not been well studied.

A prospective case-control trial evaluating the use of pyridoxine to prevent or mitigate BAEs in children taking levetiracetam was published earlier this year by Marino and colleagues in the *Annals of Pharmacotherapy*.[11] The authors enrolled 50 patients (mean age 10.2 $\pm$ 2.77 years) with focal or generalized epilepsy receiving levetiracetam as monotherapy. After 30 days, the children were randomized to levetiracetam either alone or in combination with pyridoxine 7 mg/kg/day (maximum dose 350 mg/day). Patients were evaluated monthly for 1 year with the Children's Depression Inventory (CDI). This questionnaire evaluates a wide range of BAEs including mood disorders, vegetative functions, self-esteem, social behavior, and ability to feel pleasure. Scores range from 0 to 54, with higher scores indicating greater BAEs. In addition to CDI scores, patients underwent a clinical exam and video EEG testing, as well as measurement of serum levetiracetam and pyridoxal phosphate (PLP), the active metabolite of pyridoxine.

There were no significant differences in age, seizure type, or CDI scores between the pyridoxine and control groups at baseline. All patients had normal results on MRI imaging. The mean daily levetiracetam dose was also similar between the groups: 38.6 $\pm$ 2.12 mg/kg/day in the levetiracetam patients and 39.2 $\pm$ 7.4 mg/kg/day in those receiving levetiracetam plus pyridoxine. Behavioral adverse effects were frequent in both groups, with the most common being irritability and aggression, followed by depression and confusion. Only 25% of the levetiracetam plus pyridoxine group and 20% of the levetiracetam group remained free of BAEs for the duration of the study. The average time to development of a BAE was 7.4 $\pm$ 2.8 days and 7.68 $\pm$ 2.86 days in the two groups, respectively. Seventy-six percent of the patients in the levetiracetam group discontinued treatment as the result of BAEs, compared to only 8% in the levetiracetam plus pyridoxine group ($p < 0.001$). Mean CDI scores at 12 months were also significantly better in the levetiracetam plus pyridoxine group, with 82% of patients having scores less than 19, compared to just 29% of the levetiracetam patients ($p < 0.001$). The mean length of time to resolution of BAEs after the addition of pyridoxine was 9 $\pm$ 3 days. All serum levetiracetam and PLP levels were within the target range, and no adverse effects from pyridoxine were noted.

Toxicity Profile

Levetiracetam has been shown to be effective over a relatively wide range of doses, with a usual recommended dosing range of 20-60 mg/kg/day. A maximum dose has not been established, but several reports suggest that significant toxicity is rare even with doses well above the recommended range. A 2014 review of 74 children 6 years of age or younger with an accidental levetiracetam overdose found no cases of serious adverse effects.[13] A second retrospective study of 11 years of levetiracetam overdoses in children found just two cases requiring hospitalization, with only one patient having moderate adverse effects.[14]

In a 2017 issue of *Clinical Neuropharmacology*, Kartal described an unusual case of a 7-year-old girl with refractory seizures accidentally given high-dose levetiracetam for an extended period.[14] She had been prescribed a dose of 40 mg/kg/day, but a misunderstanding by her parent in how to give the medication resulted in her receiving 200 mg/kg/day for 55 days. Upon recognition of the error, she was immediately hospitalized for observation. Vital signs and laboratory testing remained within normal limits, and there was no evidence of any neurologic toxicity. She was observed for a period of 5 days while treatment with the correct dose was started. She remained seizure-free and without evidence of adverse effects at 1-year follow-up.

Future Studies

The protocols for two randomized controlled phase IV trials of the use of levetiracetam in children have been recently published on-line. Lyttle and colleagues described the EcLiPSE study, which will compare levetiracetam and phenytoin for the treatment of pediatric status epilepticus.[15] In this multicenter open-label comparator trial, at least 308 children 6 months of age and older will be randomized to receive intravenous doses of either phenytoin (20 mg/kg) or levetiracetam (40 mg/kg). The primary outcome will be time to cessation of seizures, with secondary outcomes including the need for additional AEDs and the presence of continued seizures resulting in the need for intubation.

Dalziel and colleagues, writing for the PREDICT research network, described their convulsive status epilepticus pediatric trial (ConSEPT).[16] This study will enroll 200 children 3 months to 16 years of age in Australia and New Zealand with status unresponsive to benzodiazepines. Patients will receive either phenytoin or levetiracetam using the same doses as the EcLiPSE trial. The primary outcome will be clinical cessation of seizures within 5 minutes of dose administration. Secondary outcomes will be seizure activity at two hours, time to seizure cessation, need for intubation, and need for intensive care unit admission.

Summary

Levetiracetam has become a common choice for the prevention or treatment of seizures for infants and children in a variety of clinical settings. It offers several advantages over traditional antiepileptics, most notably a relatively mild adverse effect profile and a lack of significant drug interactions. Within the past two years, a number of papers have been published supporting its use and defining its safety profile. These papers add to our understanding of the drug, while serving as a reminder of the need for continued study to optimize its use and identify rare adverse effects.

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