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Zonisamide Use in Pediatrics

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Zonisamide was approved by the Food and Drug Administration on March 27, 2000 for the adjunctive treatment of partial seizures in adults.[1] In their 2004 report, the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society concluded that zonisamide was effective in reducing seizure frequency as adjunctive therapy in adult patients with refractory partial seizures, but that there were not enough studies to support a recommendation for its use in children.[2] While there are still relatively few controlled trials, six additional papers have been published in the last two years describing zonisamide use in infants and children, primarily in patients with seizures refractory to traditional antiepileptics (AEDs). This issue of *Pediatric Pharmacotherapy* will review the pharmacology of zonisamide and examine the recent papers describing its efficacy and adverse effects in the pediatric population.

Mechanism of Action

The precise mechanism of zonisamide's antiepileptic effect remains undefined. It has been suggested that zonisamide raises the seizure threshold through action at sodium and calcium channels, stabilizing neuronal membranes and suppressing neuronal hypersynchronization.[1,3]

Clinical Experience in Children

Most of the data on zonisamide use in children has come from Japan, where it has been available since 1989. In 2002, Glauser and Pellock reviewed 20 Japanese pediatric clinical trials.[4] Fourteen of the trials examined the safety and efficacy of zonisamide in the treatment of partial or generalized seizures. The majority were open-label. When studying zonisamide as monotherapy, both newly diagnosed patients and those refractory to other AEDs were enrolled. The overall responder rate (defined as the percentage of patients whose seizure frequency decreased by at least 50%) was 78% for patients with partial seizures and 71% in patients with generalized seizures. When zonisamide was used as adjunctive therapy in patients with refractory seizures, 34% of the patients with partial seizures responded, but only 15% of the patients with generalized seizures.

Glauser and Pellock also reviewed five open-label trials of zonisamide in the treatment of infantile spasms.[4] The percentage of patients who responded ranged between 22% and 36%, although it should be noted that the definition of response varied in the studies from greater than a 50% reduction in seizures to complete cessation of seizures and disappearance of hypsarrhythmia. Three studies conducted in children with Lennox-Gastaut were also reviewed, with response rates ranging from 26% to 50%.

Since that review of the Japanese literature, several other small studies and case series have been conducted in Japan and the United States. Two additional studies from Japan, as well as a postmarketing survey were published in a supplement to the journal *Seizure* in 2004.[5-7] Miura studied zonisamide as monotherapy in 72 children (ages 3 months to 15 years) with partial seizures.[5] Therapy was initiated at a dose of 2 mg/kg/day and titrated to an average maintenance dose of 7.97 ± 0.55 mg/kg/day. Seizure control was achieved in 57 (79%) of patients.

Seki and colleagues conducted another study of zonisamide monotherapy in 77 children (8 months to 15 years of age).[6] Among the 44 patients with cryptogenic partial seizures, 36 (82%) became seizure-free, while four (9%) had a $\geq$ 50% reduction in seizure frequency and four did not respond. Of the 11 children with cryptogenic generalized seizures, 10 (91%) became seizure-free and one experienced no change. All four of the patients with idiopathic partial seizures became seizure-free, as well as eight of the nine patients with idiopathic generalized seizures. Adverse effects were reported in 30 patients (39%), including somnolence (11.7%), decreased spontaneity (7.8%), and anorexia (6.5%).

Four retrospective case reviews conducted in the United States have been published this year which included children with a variety of seizure types.[8-11] Santos and Brotherton from Wake Forest reviewed their experience in 50 children (ages 9 months to 20 years) receiving zonisamide for a variety of seizure types.[8] The majority of patients, 66%, were treated for complex partial seizures, with the remainder having simple partial, generalized, absence seizures, or infantile spasms. The average dose used was 15.9 mg/kg/day, with a range of 3.3 to 35 mg/kg/day. Length of follow-up ranged from 4 to 34 months, with a mean of 15.6 months. All but three patients were receiving other AEDs. Eight patients (16%) became seizure-free, while another 11 (22%) experienced a seizure reduction of $\geq$ 50%. Thirty-one patients (62%) reported an adverse effect, most often decreased appetite and weight loss. Fourteen patients discontinued therapy.

Wilfong published a retrospective of zonisamide use in 131 patients (1 to 21 years of age) at Texas Children's Hospital.[9] As in the other reviews, patients with a variety of seizure types were included. The median maintenance dose was 260 mg/day, with a range of 100-800 mg/day. Median duration of therapy at follow-up was 53.4 weeks (range 2-180 weeks). Seventy-seven percent of the children achieved a 50% or greater reduction in seizure frequency, including 39 who became seizure-free. Forty-three patients (33%) experienced an adverse event, but only three patients discontinued therapy: one for sedation and increased seizures, one for failure to gain weight, and one for behavioral changes.

Wilfong and Schultz also reviewed the use of zonisamide in children with absence seizures.[10] A total of 45 children under 18 years of age were treated. The mean dosage was 9 mg/kg/day (range 2-24 mg/kg/day), and the mean duration of therapy was 64.8 weeks (range 6-154 weeks). Twenty-three children (51%) became seizure-free. Two patients discontinued therapy, one for increased seizure frequency and one for sedation and lack of response.

Kim and colleagues conducted a retrospective review of 68 children (ages 1-18 years) who received zonisamide.[11] The children had a variety of partial and generalized seizure types. In this review, the median dose was 8 mg/kg/day, and the median duration of therapy at follow-up was 11.2 months. Sixteen patients (26%) became seizure free and thirteen (21%) had a greater than 50% reduction in seizures. Among the non-responders, nine patients had an increase in seizure frequency, often associated with alterations in their concomitant AEDs. Adverse effects included behavioral or psychiatric changes (24%), cognitive dysfunction (12%), and sedation (10%). Eleven patients discontinued therapy, including five for adverse effects.

An additional prospective zonisamide study from Japan was reported earlier this year in *Brain & Development*.[12] The authors enrolled 23 infants with West syndrome into an open-label dose-titration study. Patients were randomized to one of three different methods for dose initiation: 1) increasing from 3 to 10 mg/kg every 3 days, 2) increasing from 5 to 10 mg/kg over 3-7 days, and 3) starting with 10 mg/kg. The reduction in seizures was rated as excellent or good in one of the eight patients in group 1, three of the five patients in group 2, and four of the 10 patients in group 3. The period of time required for cessation of seizures was also shorter in group 3 (mean 5.7 days) compared to the other groups (mean 10.3 days). Adverse effects included transient hyperthermia and gastrointestinal symptoms. The authors concluded that starting zonisamide at 10 mg/kg in patients with West syndrome appeared safe and effective and allowed an assessment of response after only 2 weeks of therapy.

Pharmacokinetics

After oral dosing, zonisamide concentrations peak within 2 to 6 hours. Food slows absorption, but does not affect overall bioavailability. In adults, the apparent volume of distribution is 1.45 L/kg. It is approximately 40% bound to plasma proteins, but is extensively bound to erythrocytes. Zonisamide undergoes acetylation to form N-acetyl zonisamide and reduction via cytochrome P450 3A4 (CYP3A4) to form 2-sulfamolacetyl phenol (SMAP). The metabolites, as well as unchanged drug, are excreted in the urine. The average plasma elimination half-life of zonisamide in adults is 63 hours. The elimination half-life in erythrocytes is 105 hours. Renal clearance of zonisamide decreases with decreasing renal function.[1,3]

Drug Interactions

Zonisamide is a substrate for CYP3A4, and is affected by medications which induce or inhibit its activity. Clearance of zonisamide is increased in patients receiving other enzyme-inducing AEDs. Concomitant administration of phenytoin and zonisamide decreases the half-life of zonisamide to 27 hours in adults. Carbamazepine decreases the zonisamide half-life to 38 hours, and valproate decreases it to 46 hours. Zonisamide does not appear to affect the pharmacokinetics of other AEDs.[1,3]

Adverse Effects

The most commonly reported adverse effects associated with zonisamide administration in clinical trials of adults include: somnolence (16-17%), anorexia (13%), dizziness (13%), headache (10%), agitation (9%), nausea (8-9%), fatigue (7%), ataxia, confusion, depression, difficulty concentrating, insomnia, diplopia, and abdominal pain (all 6%), diarrhea (5%), kidney stones (0.1-4%), rash (3%), and anorexia (3-8%).[1,3,13] In an assessment of postmarketing surveillance in Japan, children less than 12 years of age had a significantly lower rate of adverse effects than adults, 24.3% versus 40.1%.[13]

Zonisamide is chemically classified as a sulfonamide and is contraindicated in patients who have a known sensitivity to sulfonamides. Serious dermatologic reactions, including 49 cases of Stevens Johnson syndrome and toxic epidermal necrolysis, have been reported with zonisamide use. In addition, severe hematologic reactions, including agranulocytosis and aplastic anemia, have also been reported. Other rare, but serious, adverse effects with zonisamide have included status epilepticus, fulminant hepatic necrosis, pancreatitis, systemic lupus erythematosus, renal dysfunction, and sudden unexplained death in patients with epilepsy.[1,3,13,14]

Oligohydrosis and hyperthermia have also been associated with zonisamide use, with most of the cases occurring in children during summer months. In the first 11 years of marketing in Japan, 38 cases were reported, all in children, with an estimated incidence of one case per 10,000 patient-years. In the first three years after approval in the United States, 13 cases were reported, giving a much higher estimated incidence of one case per 4,590 patient-years. The mechanism for development of oligohydrosis and hypothermia is not known. It is believed to be mediated by the peripheral nervous system, through inhibition of cholinergic nerves innervating the sweat glands or muscarinic receptors of the epithelial cells of the sweat glands. While some investigators have suggested an association with elevated serum zonisamide concentrations, others have questioned that finding.[1,3,15,16]

Patients receiving zonisamide, particularly children, should be monitored for early signs of heat stroke. Clinicians should use caution when prescribing other therapies which might further predispose patients to this adverse effect, including anticholinergic agents and carbonic anhydrase inhibitors.[1,3,15,16]

Zonisamide has also been associated with adverse cognitive and neuropsychiatric adverse effects, including depression and psychosis, psychomotor slowing, difficulty concentrating, and speech problems, particularly word-finding difficulty. The manufacturer reports that 2.2% of patients receiving zonisamide in placebo-controlled trials discontinued treatment or were hospitalized for depression, compared to 0.4% of placebo patients. Difficulty thinking or concentrating is most often seen within the first month of therapy and is associated with doses above 300 mg/day in adults.[1,3,13]

In a review of Japanese children treated with zonisamide, Glauser and Pellock found that somnolence had been reported in 12-50% of the patients, sluggishness in 7-17%, irritability in 6-14%, decreased spontaneity in 6-8%, psychotic symptoms in 6%, and insomnia in 6%.[4,17] Irritability was reported more frequently in children with mental impairments.[17] Akman and colleagues reported three case of visual hallucinations associated with zonisamide use.[18] Two of the patients were children, one 7-year-old and one 13-year-old. In both cases, the hallucination resolved with discontinuation of the drug. In the third case, a 21-year-old woman, the hallucinations resolved with a reduction in dose. In a series of 27 children treated with zonisamide, Hirai and colleagues reported two cases of adverse psychiatric effects with zonisamide.[19] The first was a 14-year-old who developed selective mutism, violent behavior, and inability to concentrate after 4 years of therapy. In the second case, a 15-year-old girl developed obsessive compulsive disorder after 3 years of treatment. Both patients had resolution of symptoms with dose reduction.

Dosing Recommendations

The recommended dosing regimen for zonisamide in patients over 16 years of age is 100 mg/day. The dose may be increased by 100 mg/day at 2 week intervals. It may be administered in one or two daily doses. In most of the pediatric studies published to date, zonisamide has been initiated at a dose of 1 to 2 mg/kg/day, with titration in increments of 0.5 to 1 mg/kg/day every two weeks. Maintenance doses have been in the range of 5 to 10 mg/kg/day, with a suggested maximum dose of 12 mg/kg/day. In cases of infantile spasms or refractory seizures, doses up to 20 mg/kg/day have been used. Zonisamide doses should be reduced in patients with renal or hepatic dysfunction.[1,3]

Zonisamide may be taken with or without food. Patients and their families should be informed to

avoid abrupt discontinuation of zonisamide, which could precipitate increased seizures or status epilepticus. If treatment must be discontinued, the drug should be slowly tapered while the patient is closely monitored for changes in seizure frequency or pattern. In addition, families should be aware of the need to monitor for potential decreased sweating and inability to tolerate hot weather.[1,3]

Availability and Cost

Zonisamide (Zonegran®; Elan Pharma International) is available in 25 mg, 50 mg, and 100 mg capsules.[3] The average wholesale price for a bottle of 100 tablets is $61.00 for the 25 mg capsules, $121.91 for the 50 mg capsules, and $243.83 for the 100 capsules.

Summary

The role of zonisamide in the treatment of seizures in children remains to be determined. While several small studies and case series have shown benefit, use of the drug may be limited by its adverse effect profile. In particular, adverse cognitive and neuropsychiatric effects, and the potential for oligohydrosis and hyperthermia, may limit its role in children to those with seizures refractory to traditional antiepileptic drugs.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 10/28/05:

1. Azithromycin extended-release microspheres (Zmax™) was added to the Inpatient and Outpatient Formularies. It is given as a single 2 gram dose in adults with acute bacterial sinusitis or community-acquired pneumonia.
2. Human secretin (Secretin®) was added as a diagnostic aid to stimulate pancreatic secretions. Porcine secretin was deleted.
3. A subcutaneous formulation of medroxyprogesterone (Depo-SubQ Provera 104) was also added to the Formulary.
4. Tigecycline (Tigacyl™), a gylcylcycline antibiotic, was added to the Inpatient Formulary.
5. Ciprofloxacin 0.3% ophthalmic ointment (Cilaxan™) and moxifloxacin 0.5% ophthalmic solution (Vigamox™) were added to the Inpatient Formulary for the treatment of bacterial conjunctivitis, with restriction to Ophthalmology.
6. Tipranavir (Aptivus®), a non-peptidic protease inhibitor for HIV-1 infection, was added to the Inpatient and Outpatient Formularies.
7. Ultralente® and Lente® insulins were removed from the Formulary. Both products have been discontinued by the manufacturer.

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