PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the University of Virginia Children's Hospital

Volume 15 Number 12 December 2009

Vigabatrin: A New Option for Selected Patients with Infantile Spasms or Refractory Complex Partial Seizures

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Vigabatrin was developed as an antiepileptic in 1975. While shown to be effective in early clinical trials, the development of permanent vision impairment, including blindness, in some patients given vigabatrin quickly limited its role as a first-line therapy.[1-4] Despite its potential utility in patients with seizures unresponsive to traditional antiepileptics, there has been reluctance to introduce a drug with this significant of an adverse profile in the United States. However, continued problems with the availability and cost of other treatments for infantile spasms and the completion of studies examining the risk for vision loss led the Food and Drug Administration (FDA) to alter its stance. Vigabatrin was approved on August 21, 2009, nearly 30 years after the new drug application was filed. It is indicated for the treatment of pediatric patients from 1 month to 2 years of age with infantile spasms for whom the potential benefits outweigh the risk of vision loss. It was also approved as an adjunctive therapy for adults with refractory complex partial seizures. This issue of *Pediatric Pharmacotherapy* will describe the clinical trials which supported the FDA approval and review the pharmacology of vigabatrin in children.

Mechanism of Action

Vigabatrin (4-amino-5-hexenoic acid) increases concentrations of gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter of the central nervous system. As a structural analog of GABA, it binds irreversibly to GABA-transaminase (GABA-T), the enzyme which metabolizes GABA, allowing endogenous GABA to accumulate in the brain. The duration of effect is more closely related to re-synthesis of GABA-T rather than plasma or CNS concentrations of vigabatrin.[1-4]

Pharmacokinetics

Vigabatrin is well absorbed after oral administration. Maximum plasma concentrations are achieved within 2.5 hrs in infants and 1 hr in children. Administration with food decreases the maximum concentration by up to 33% and increases the time to achieve maximum concentrations by 1 hr. Vigabatrin is widely distributed throughout the body, with an average volume of distribution of 1.1 L/kg. It does not bind to plasma proteins. Vigabatrin is cleared through renal excretion. It does not undergo hepatic metabolism, but induces cytochrome P450 2C9 activity. The average half-life is 5-6 hrs in infants and 7-8 hrs in adults. Average clearance is 2.4$\pm$0.8 L/hr in infants, 5.7$\pm$2.5 L/hr in children, and 7 L/hr in adults. Renal dysfunction prolongs vigabatrin clearance; lengthening the elimination half-life 3.5-fold in adults with severe impairment.[3,4]

Clinical Trials

Over a dozen studies have been conducted with vigabatrin in patients with infantile spasms.[1,2] The efficacy rate in these trials has ranged from 11 to 76%, reflecting differences in methodology and selection of primary endpoints. Two recent studies formed the basis of the FDA approval.[3-5] The first was a multicenter, randomized, dose-ranging study in 221 infants. Patients with both symptomatic and cryptogenic etiologies were included. The first phase of the study was a 2-3 week trial of low dose (18-36 mg/kg/day) versus high dose (100-148 mg/kg/day) therapy. The dose was titrated as needed over the first week, then held constant for the second week. If patients became spasm-free, they continued on therapy for third week. Seventeen (16%) of the 107 infants in the high-dose group became spasm-free, both by clinical assessment and video EEG monitoring, compared to only 7% (8/114) of the low-dose group ($p=0.0375$). When response was evaluated by etiology, 74% of the infants with tuberous sclerosis became spasm-free as well as 72% of the patients with cryptogenic spasms. Only 50% of the patients with other diagnoses responded. Twenty-three patients eventually relapsed during the open-label follow-up period, but most regained control with a higher vigabatrin dose.

Another 40 patients were enrolled in the second study, a multicenter, randomized, double-blind, placebo-controlled trial. The infants randomized to receive vigabatrin were treated with an initial dose of 50 mg/kg/day, titrated based on response up to 150 mg/kg/day. The primary endpoint of the study was the percent change in spasm frequency as assessed by a 2-hr period at baseline and during the final two study days. No difference was noted in the primary endpoint; however, post-hoc analysis revealed a significant difference in the overall percentage reduction in spasms (68.9% in the treatment group versus 17% in the controls, p=0.03).[3,4]

Other recent studies have confirmed these results. Camposano and colleagues conducted a retrospective study of infants and children treated with vigabatrin over a 5-year period at the Massachusetts General Hospital for Children.[6] Eighty-four children were included, 68 with infantile spasms and 59 with complex partial seizures. Seizure control was achieved in 73% of patients with infantile spasms associated with tuberous sclerosis complex, compared to only 27% of those with infantile spasms of other etiologies. Seizure control was achieved in 34% of children with complex partial seizures, with 17% becoming seizure-free. The authors also noted that shorter time from seizure onset to initiation of therapy and longer duration of treatment were associated with better outcomes in patients with infantile spasms ($p<0.027$ and $p<0.045$, respectively). Vigabatrin was discontinued in only one patient because of abnormal findings on an eye exam.

There are relatively few comparison trials with vigabatrin. Earlier this year, Cohen-Sadan and colleagues published the results of a multicenter follow-up of children with infantile spasms associated with West syndrome who were treated with adrenocorticotropic hormone (ACTH) or vigabatrin.[7] Twenty-eight children were evaluated. The average age at disease onset was 5.5 months and the average time between diagnosis and initiation of treatment was 25 days. There were 14 patients in each group. Patients in the vigabatrin group received 100-180 mg/kg/day for 6-12 months. The ACTH group received either an initial dose of 100 units IM every other day, followed by a taper, or a dose of 20-40 units/day for 6-8 weeks. Response rates were 88% in the ACTH group and 80% in the vigabatrin group. Long-term evaluation (mean 9 years) revealed no cognitive deficits in 100% of the ACTH patients treated within 1 month of diagnosis, 67% of the later ACTH group, and 54% of the vigabatrin group (p=0.03). More patients in the vigabatrin group relapsed, but the difference was not statistically significant (21% versus 14%, p=0.62).

Contraindications and Precautions

Vigabatrin-Induced Vision Loss

Vigabatrin carries a prominent black box warning regarding vision loss.[3,4] Accumulated data in adults have revealed a 30% incidence of permanent bilateral concentric visual field constriction, ranging from mild to severe. In some cases, patients have developed tunnel vision to within 10 degrees of visual fixation resulting in significant disability. There are also reports of damage to the central retina resulting in reduced visual acuity. In their 2006 study of 30 children taking vigabatrin, Werth and Schadler reported visual field constriction in 27%,2 similar to the values reported in adults. A recent compilation of the vigabatrin studies conducted in children, however, revealed a wide variation in the rate of visual field defects, ranging from 9-62%.[8]

In February 2009, Gaily and colleagues conducted visual field testing in 16 school-age children who had received vigabatrin as infants.[9] The average age at the start of therapy in these patients was 7.6 months (range 3-20 months) and the average duration of therapy was 21 months (range 9-30 months). The average cumulative dose was 655 grams. At the time of testing, the patients ranged in age from 6 to 12 years. Only one patient (6%) had mild visual field loss. This patient had been treated with vigabatrin for 19 months with a cumulative dose of 572 grams.

In a letter to the editor prompted by the Gaily study, Wohlrab and colleagues described similar results in 15 children who began vigabatrin between 2.5 and 12 months of age.[10] The cumulative dose ranged from 135 to nearly 6,000 grams. The mean treatment duration was 1 year, 8 months. Only one patient (7%) had evidence of vigabatrin-induced visual field constriction by the time of their final exam. While both papers were limited by small sample sizes, they suggest that the incidence of vision loss from treatment during infancy might be lower than that seen in adults.

The mechanisms involved in the vision loss associated with vigabatrin are not known, but may be related to dose and cumulative exposure.[1-4] Vigabatrin is known to accumulate in the retina. A recent paper by an international group of investigators suggests that light exposure and taurine deficiency may also play a role in this toxicity.[11] In a rodent model, treatment with vigabatrin resulted in taurine levels 67% lower than those in controls. Taurine

supplementation reduced all components of the retinal lesions. Retinal damage was also prevented by keeping the animals in darkness during treatment. In follow-up, the authors evaluated taurine levels in six infants treated with vigabatrin. Three had taurine levels below the normal limit and two had undetectable levels. While further studies are needed to substantiate these findings, the authors suggest that minimizing light exposure during treatment and taurine supplementation may be useful.

With a limited ability to assess vision in infants, as well as the gradual onset of symptoms that may go unrecognized, all patients taking vigabatrin are required to undergo scheduled eye exams. Patients are required to undergo baseline assessment prior to or within a month of starting treatment, followed by exams every three months during therapy. An additional exam 3-6 months after completion of therapy is also required, as vision loss can progress after discontinuation. The manufacturer also recommends that vigabatrin be discontinued in patients with infantile spasms who have not achieved significant improvement within 2-4 weeks of starting treatment to avoid unnecessary drug exposure. Adults with complex partial seizures who have not achieved significant benefit within 3 months should be taken off therapy. Vigabatrin should not be used in patients with other risk factors for vision loss, such as retinopathy or glaucoma.[3]

Potential Neurotoxicity

In animal models, vigabatrin exposure has been associated with transient microvacuolization of the myelin laminae and apoptotic neurodegeneration of the brain.[1,2] Abnormal MRI findings have been observed in infants receiving vigabatrin, consisting of hyperintensity on T_2-weighted or fluid-attenuated inversion-recovery sequences in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum. In a recent retrospective study by Pearl and colleagues, 7 of 22 patients treated with vigabatrin had abnormal MRI findings.[11] All of the patients with abnormalities were being treated for infantile spasms, with a median vigabatrin dose of 170 mg/kg/day at the time of the MRI and median length of therapy of 3 months. The abnormalities resolved after discontinuation in all but one patient, who had minimal evidence of change on an MRI obtained 18 days after stopping vigabatrin. To date, there has been no relationship established between the MRI changes observed in infants and the neurotoxicity seen in animals. Prospective MRI studies are currently underway which may clarify these findings.

As with all antiepileptics, vigabatrin carries a warning for suicidal behavior and ideation in adult patients. Patients should be closely monitored for symptoms of depression or changes in mood or behavior.[3,4]

Adverse Effects

In placebo-controlled trials of vigabatrin in patients with infantile spasms, the most common adverse effects were somnolence (45%), bronchitis (30%), ear infection (10%), and acute otitis media (10%). In a dose-ranging study, the adverse effects occurring in 10% or more of infants included: vomiting, diarrhea, and constipation (reported in 13-14% of patients), fever (29%), infections (20-51%), sedation and somnolence (17-19%), irritability (16%), pneumonia (13%), nasal congestion (13%), insomnia (10%), and rash (8%). Studies in older children and adults have produced similar results, with the most commonly reported adverse effects including headache (18%), somnolence and fatigue (16-17%), dizziness (15%), convulsions (11%), and nasopharyngitis, weight gain, and upper respiratory tract infection (all in 10%). Adverse effects related to vision included visual field defects in 9% of patients, nystagmus in 7%, and blurred vision or diplopia in 6%.[3-5]

Drug Interactions

Vigabatrin interacts with several other antiepileptic drugs. When administered with phenytoin, plasma phenytoin concentrations decrease by approximately 20%. Administration of vigabatrin with phenobarbital or primidone decreases phenobarbital concentrations by 8-16%. Giving vigabatrin with sodium valproate decreases valproate levels by 8%, and use with carbamazepine decreases its levels by 10%. The interactions with barbiturates, valproate, and carbamazepine are generally not clinically significant. Administration of vigabatrin with clonazepam increases clonazepam maximum concentrations by up to 30% and decreases the time to maximum concentration by 45%.[1,3,4]

Dosing Recommendations

Patients with infantile spasms should begin vigabatrin at a dose of 50 mg/kg/day, divided and given by mouth twice daily. Therapy may be titrated by 25-50 mg/kg/day increments every 3 days up to a maximum recommended dose of 150 mg/kg/day. For adolescents and adults with refractory complex partial seizures, therapy should be initiated at 500 mg twice daily, and titrated as needed to a maximum of 1,500 mg twice daily. If therapy is to be discontinued, vigabatrin should be tapered by decreasing the dose 25-50 mg/kg/day every 3 to 4 days.

Vigabatrin doses should be reduced in patients with renal dysfunction. In patients with mild renal impairment (creatinine clearance of 50-80 mL/min) vigabatrin doses should be reduced by 25%. In patients with moderate renal impairment (creatinine clearance 30-50 mL/min), doses should be reduced by 50%, and in patients with severe renal impairment (creatinine clearance < 30 mL/min), doses should be reduced by 75%.[3,4]

Vigabatrin is available in 500 mg tablets and as powder packets to be made into a 50 mg/mL oral solution. Each packet contains 500 mg of vigabatrin and should be mixed with 10 mL of water. Multiple packets may be used for larger doses. No other liquid than water should be used. The solution should be administered immediately after mixing. Any remaining solution should be discarded. Oral syringes are supplied with the powder packets. A medication guide and detailed written instructions for preparing the oral solution are available on the manufacturer's website at www.sabril.net.[3,4]

Availability and Cost

Vigabatrin (Sabril®, Lundbeck, Inc.) is currently marketed in bottles of 100 tablets and boxes of 50 powder packets to be made into an oral solution. In the United States, vigabatrin distribution is coordinated by the manufacturer through its SHARE program (Support, Help and Resources for Epilepsy). This program was developed to comply with the FDA requirement for an ongoing Risk Evaluation and Mitigation Strategy (REMS) program to assess and minimize the risk of vision loss. To obtain more information, or to enroll a patient and begin treatment, go to www.LundbeckSHARE.com or call 1-888-45-SHARE.[3,4]

The manufacturer does not provide pricing information for vigabatrin in the United States outside of the patient registration process. In Canada, the current price for a bottle of vigabatrin tablets ranges from $90 to $110. The price of a box of 50 powder packets is $50 to $75. A patient assistance program is available for uninsured families or those unable to meet their insurance co-payment requirements.[3,4]

Summary

Vigabatrin provides an alternative therapy for infantile spasms, especially in patients with tuberous sclerosis, or complex partial seizures in patients who have failed other antiepileptics. While effective in many cases, vigabatrin use comes with a significant risk for permanent loss of vision. The decision to use vigabatrin should be based on a careful evaluation of each patient's risk to benefit profile.

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The editors wish to thank Dr. Howard Goodkin for his review of the article prior to publication.

Formulary Update

The following actions were taken by the P&T Committee at their meeting on 11/19/09:

1. Recombinant human thrombin (Recothrom®) replaced bovine derived topical thrombin.
2. Artemether/lumefantrine (Coartem®) was added to the Inpatient Formulary for acute, uncomplicated malaria in patients > 5 kg.
3. Zanamivir (Relenza®) was added for the treatment or prophylaxis of influenza A or B.

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