

# Pediatric Pharmacotherapy

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## Lamotrigine in the Treatment of Seizures During Childhood Marcia L. Buck, Pharm.D., FCCP

Previous issues of *Pediatric Pharmacotherapy* have focused on phenytoin (August 1996), carbamazepine (November 1996), and valproic acid (March 1997). This issue continues the series on anticonvulsants with a review of lamotrigine. While still approved by the Food and Drug Administration (FDA) only for use in adults, lamotrigine has been found to be useful in a number of pediatric seizure types.

### Mechanism of Action

Lamotrigine is a member of the phenyltriazine class, and is structurally unrelated to anticonvulsants in current use. As with other agents in this therapeutic class, the mechanism of action of lamotrigine is not fully understood. The primary mechanism of action appears to be inhibition of voltage-sensitive sodium channels resulting in the stabilization of neuronal cell membranes and modulation of the activity of excitatory amino acids such as glutamate or aspartate. Unlike most other anticonvulsants, lamotrigine has little or no effect on serotonergic, dopaminergic, or adrenergic receptors.<sup>1-3</sup>

### Indications

Lamotrigine is currently approved by the FDA as adjunctive therapy in the treatment of partial seizures in adults with epilepsy and as monotherapy in selected patients. It has also been found to be effective in some patients with generalized seizures.

### Use in Children

During the last 5 years, there have been several studies of lamotrigine use in children. A wide variety of seizure types have been studied, including generalized seizures such as typical and atypical absence, atonic, myoclonic, and tonic seizures, as well as infantile spasms, Rett and Lennox-Gastaut syndromes.<sup>2-9</sup>

In 1994, Schlumberger and colleagues published the results of treating 120 children with lamotrigine.<sup>4</sup> Their report combined data from three separate studies: a single-blind dosing study

with 60 children, a pharmacokinetic study with 23 children, and patients treated under a compassionate use protocol. The patients ranged in age from 10 months to 16 years. Doses ranged from 1 to 17 mg/kg/day. At 3 months, nearly 40% of the patients receiving lamotrigine had a significant decrease in seizure frequency (i.e. had become seizure-free or had greater than a 50% reduction in events). The 14 patients who were followed for a year showed no decline in response.

The following year, Besag and co-workers published a large multicenter study of lamotrigine as adjunctive therapy.<sup>5</sup> Thirty-seven centers in 11 countries were involved in this open-label study of 285 children between the ages of 1 and 13 years. All patients were considered to have seizures that were resistant to current treatment and all had at least two different seizure types. Seizure frequency and global assessments were made at the end of four successive 12-week treatment periods. Doses ranged from 1 to 5 mg/kg/day in children also taking valproic acid and 5 to 15 mg/kg/day in those not on valproic acid.

Seizure frequency was reduced by at least 50% in one third of the children treated. This level of response continued throughout the entire study period. As in the first study, the patients most likely to respond were those with generalized seizures. Also of note in this study, some of the patients with learning or behavioral disturbances unrelated to their seizure disorders experienced an improvement in function after initiating lamotrigine that was independent of the degree of seizure control.<sup>5</sup>

Since publication of these reports, there have been several other studies of lamotrigine use in children with refractory seizures. These studies have shown similar results, with a 30 to 40% response rate lasting from 6 months to 3 years. The improvement noted in behavior and learning found in earlier studies has also been documented in these smaller scale trials.<sup>6,7</sup>

In 1997, a double-blind, placebo-controlled trial of lamotrigine as add-on therapy was conducted in 169 patients with Lennox-Gastaut syndrome.<sup>8</sup> The patients ranged in age from 3 to 25 years. At the end of the 16 week treatment period, a significant decrease in seizure frequency was noted with lamotrigine. There was at least a 50% decrease in seizures in 33% of the patients receiving lamotrigine, but in only 16% of the patients in the placebo group.

#### Pharmacokinetics

Lamotrigine is rapidly and completely absorbed from the gastrointestinal tract after oral administration. Bioavailability is estimated at 98%. Administration with food does not affect absorption. Peak serum lamotrigine concentrations occur from 1 to 5 hours after a dose. The drug is approximately 50 to 60% protein bound and has an average volume of distribution of 1.2 to 1.5 L/kg.<sup>2,3</sup>

Lamotrigine exhibits first-order linear elimination. It is metabolized in the liver by conjugation with glucuronic acid. The resulting metabolite has no pharmacologic activity and is excreted in the urine. Less than 10% of a dose is excreted unchanged.<sup>2,3</sup> The average elimination half-life in adults is 20 to 35 hours. In children, limited information on elimination suggests a shorter half-life of 7 to 10 hours. Children less than 6 years of age may clear lamotrigine faster than older children.<sup>6</sup>

When used alone, lamotrigine may induce its own metabolism. Some studies have shown up to a 25% decrease in half-life from initiation of therapy until steady state is achieved. This autoinduction has not been demonstrated in all studies and may not occur when lamotrigine is administered to patients already receiving other anticonvulsants.<sup>3</sup>

Patients with renal dysfunction have a prolonged elimination of lamotrigine. In a study of 12 patients with chronic renal failure, the average half-life was 42.9 hours. In another six patients on hemodialysis, the average half-life during dialysis was 13 hours and between dialysis periods was 57.4 hours. Approximately 20% of a lamotrigine dose is cleared by hemodialysis.<sup>1-3</sup> Lamotrigine should be used with caution in patients with hepatic dysfunction. A reduction in metabolic function may lead to drug accumulation, placing the patient at higher risk for adverse effects.<sup>3</sup>

Although clinical trials have not demonstrated a reliable concentration-response relationship, most patients achieve seizure control with lamotrigine serum concentrations between 1 and 5 mcg/ml. At this time, therapeutic drug monitoring of lamotrigine is not routine.<sup>2,6</sup>

#### Drug Interactions

As a result of its reliance on hepatic metabolism, lamotrigine has several significant interactions with other medications (Tables 1 and 2).<sup>3</sup>

Table 1. Drugs that Affect Lamotrigine (LAM)

Folate inhibitors	↑LAM Activity
Valproic Acid	↑LAM Concentrations (decrease dose by 1/2)
Acetaminophen	↓LAM Concentrations
Carbamazepine	↓LAM Concentrations
Phenobarbital	↓LAM Concentrations
Phenytoin	↓LAM Concentrations
Primidone	↓LAM Concentrations

Table 3. Effect of Lamotrigine on Other Drugs

Carbamazepine	↑ Concentrations
Phenytoin	↑ or ↓ Concentrations
Valproic Acid	↓ Concentrations

#### Adverse Effects

The most significant risk of lamotrigine therapy is a severe dermatologic reaction. Ten percent of patients receiving lamotrigine will develop a rash. This rash typically occurs within the first 1 to 2 months of treatment, but has been reported up to 6 months after lamotrigine initiation. Patients receiving multiple anticonvulsants, especially those taking valproic acid, are at greater risk for dermatologic reactions. In the Schlumberger study described previously, 25% of the children already receiving valproic acid developed a rash within the first 2 weeks of starting lamotrigine.<sup>4</sup>

Progression of the rash to Stevens-Johnson syndrome, toxic epidermal necrolysis, and generalized anaphylaxis has been reported in increasing numbers since the drug was first marketed. These serious dermatologic reactions appear to be infrequent in adults, but the true incidence has not been firmly established. In children, these reactions are more common.

**Currently, it is estimated that 1 in 50 to 1 in 100 children receiving lamotrigine will experience a potentially life-threatening rash.**

It is not possible to predict if a rash will progress to a severe reaction based on its appearance or

other patient factors. As a result, lamotrigine should be discontinued at the first sign of any rash. Some authors have suggested that the risk for dermatologic reactions may be lessened by a slow titration of the dose during initiation of therapy.<sup>2</sup>

The mechanism for these dermatologic reactions is not fully understood. Recent research suggests that the rash is likely an immune-mediated hypersensitivity reaction. In a study of 16 children, the two who developed a rash also had an increase in CD4-DR (T-helper) and CD8-DR (T-suppressor) lymphocytes, a slight increase in CD19 (B-cell) lymphocytes, and a significant increase in serum IgE concentrations. The remaining 14 children experienced none of these serologic changes.<sup>10</sup>

While rash clearly stands out as a common and potentially serious adverse effect, other common adverse effects reported with lamotrigine are less severe. Headache, dizziness, somnolence, diplopia, ataxia, blurred vision, nausea and vomiting have been reported in patients taking lamotrigine.<sup>3,5-9</sup> These adverse effects frequently resolve with dosage reduction. A true assessment of the frequency of these adverse effects is difficult because most patients are already taking other anticonvulsants when lamotrigine is initiated. In most adult and pediatric clinical trials, 10 to 15% of subjects withdrew as a result of an adverse effect.<sup>2,4,5</sup>

Photosensitivity is also known to occur in patients taking lamotrigine. Parents of children receiving lamotrigine should be reminded to dress their children in protective clothing and use a proper sunscreen product.

In addition to these common adverse effects, there have also been several rare, but serious, adverse effects reported. Although lamotrigine has only weak antifolate activity, there have been reports of hematologic adverse effects. A small number of megaloblastic anemia cases have been reported, as well as one case of acquired pure red cell aplasia in a patient with heterozygous beta-thalassemia.<sup>2</sup>

Acute hepatic failure has been reported in both adults and children.<sup>2,11</sup> In 1998, Arnon and colleagues described a case involving an 8 year old boy taking lamotrigine who developed jaundice, elevated liver enzymes, and a coagulopathy. Lamotrigine was discontinued and the patient made a full recovery.<sup>11</sup> There has

also been a recent report of two children who developed multiorgan dysfunction and disseminated intravascular coagulation after lamotrigine was initiated. Both children were already receiving valproic acid.<sup>12</sup>

All female patients of child-bearing age taking lamotrigine should be counseled about the potential for a decrease in fetal folate concentrations and an increased risk of neural tube defects. This risk may be lessened by the administration of folic acid prior to and early in the course of pregnancy. Limited experience with lamotrigine to date has not shown teratogenic effects in humans.<sup>2</sup> Glaxo Wellcome maintains a registry of women who become pregnant while taking lamotrigine to monitor the drug's effect on the fetus. Health care professionals may register patients in this program by calling 1-888-233-2334.<sup>3</sup>

#### Dosing Recommendations

In patients 16 years of age or older, the recommended initial regimen for lamotrigine in patients taking other enzyme inducing anticonvulsants (except valproic acid) is 50 mg once a day for two weeks followed by an increase to 50 mg twice daily for two weeks. The dose may then be increased by 100 mg/day increments at weekly intervals until adequate response is achieved. The usual maintenance dose in these patients is 300 to 500 mg/day.

The dose of lamotrigine should be reduced in adult patients taking valproic acid. These patients should start lamotrigine therapy with 25 mg given every other day for two weeks, then 25 mg once daily for two weeks. After this period, the dose may be increased by 25 to 50 mg/day increments every one to two weeks until seizure control is achieved. The usual maintenance dose in adults receiving lamotrigine and valproic acid is 100 to 150 mg/day in two divided doses.

In children not receiving valproic acid, lamotrigine should be initiated at a dose of 2 mg/kg/day in two divided doses for 2 weeks, followed by an increase to 5 mg/kg/day for another 2 weeks, then 10 mg/kg/day for 2 weeks. The usual maintenance dose is between 5 to 15 mg/kg/day. Younger children may need to have the daily dosage divided into 3 doses because of a more rapid elimination.

Children receiving valproic acid, should receive a lower dose of lamotrigine. Therapy should begin at 0.2 mg/kg/day for 2 weeks, then be

increased to 0.5 mg/kg/day, and then 1 mg/kg/day at 2 week intervals. The maximum recommended dose in these patients is 5 mg/kg/day.

Lamotrigine is available from the manufacturer in 25, 100, 150, and 200 mg tablets, as well as 5 and 25 mg chewable, dispersible tablets. An extemporaneous formulation is available to provide an alternative oral liquid dosage form.<sup>13</sup>

### Summary

Lamotrigine offers a new option for increased seizure control in patients not well controlled by conventional anticonvulsants. In children, lamotrigine has been found to be beneficial in treating complex seizure disorders; but, its use must be weighed with the risk of severe adverse drug reactions.

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### Literature Review

#### Erythema multiforme with amoxicillin

A brief case of a 10 month old with erythema multiforme caused by amoxicillin/clavulanic acid is presented, with a color picture of the child during the illness. This case will be interesting to new clinicians who have not yet seen a severe dermatologic drug reaction. It also serves as a reminder to all health care providers of the need to report adverse reactions. Benjamin S, Mueller BA. Erythema multiforme secondary to amoxicillin/clavulanic acid exposure. *Ann Pharmacother* 1999;33:109-10.

#### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 2/26/99:

1. Brimodine (Alphagan®) and timolol/dorzolamide (Cosopt®) ophthalmic solutions were added to the formulary.
2. A long-acting octreotide injectable suspension (Sandostatin LAR® Depot) was added.
3. A combination product containing albuterol and ipratropium (Combivent®) was added.
3. Capecitabine (Xeloda®) was added for the treatment of metastatic breast cancer.
4. Topotecan (Hycamtin®) was added as a second-line agent for the treatment of ovarian or small cell lung cancer.
5. Lepirudin (Refludan®), an anticoagulant, was added as an alternative for patients with heparin-induced thrombocytopenia.
6. The Committee recommended that informed consent be required prior to administration of urokinase. Verbal consent with documentation in the medical record is adequate until a standardized consent form is available.

*Contributing Editor: Marcia L. Buck, Pharm.D.*

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