



New AEDs in Practice, Part I: The Clinical Role of Lacosamide

Two new antiseizure medications expand treatment options for patients with epilepsy. Here's a look at one of them.

This year, we've already seen the introduction of two new antiseizure medications, lacosamide (Vimpat, UCB Inc.) and rufinamide (Banzel, Eisai, Inc.), and will likely see the release of an extended release formulation of lamotrigine (Lamictal XR, GlaxoSmithKline was approved in June). It is always exciting to encounter new treatments for people with epilepsy: their approval signals yet more hope that doctors may yet find a cure for this illness. However, newer treatments also present a challenge: neurologists need to quickly understand and be ready to implement these therapies. Although there are several newer therapies, this installment of Epilepsy Essentials will focus on the newest, lacosamide. In the next installment, I will focus on rufinamide.

Background

Lacosamide has been studied for many years. Initial trials and pharmacokinetic and pharmacodynamic studies have shown that lacosamide follows linear kinetics. It has a half-life of 13 hours, and therefore reaches steady-state in 65 hours, or approximately three days. It has a bioavailability of 100 percent, and food does not affect the way that it is absorbed. The drug is either demethylated or is excreted unchanged (40 percent) by the kidneys. It has a low protein binding of 15 percent. There are few if any drug-to-drug interactions (Table 1).

In addition to this, early studies have shown that lacosamide works through a new mechanism of action. Although lacosamide acts on the sodium channel (as do many AEDs), it has a different effect than the "usual" AEDs. Most AEDs delay the repolarization of the sodium channel. Lacosamide enhances the slow inactivation of these ion chan-

nels. This may have clinical implications. Most physicians, when combining AEDs, purposely select medications that have different modes of action. This approach is logical; by selecting two AEDs that act on the neuron differently, the idea is to "attack" the problem from two different "angles." Although there are no randomized trials that prove this theory, many physicians have adopted this idea in order to optimize the treatment of refractory epilepsy.

Lacosamide Randomized Clinical Trials

As with many newer antiseizure medications, lacosamide was first studied in the treatment of refractory localization related (also called partial onset) seizures in adults. There were several randomized placebo-controlled trials, comprised of 1,294 patients. These patients experienced the spectrum of partial seizures: 32 percent reported simple partial seizures, 84 percent had complex partials, and 42 percent had secondarily generalized tonic-clonic seizures. The average age of the patients was 38.6 years, and 51 percent were women (meaning of course that 49% were men). On average, this group had been having unprovoked seizures for 23.7 years. Further, they experienced quite a few seizures each month, averaging 10-17 seizures every 28 days. Sixty-two percent of subjects were on two medications (to which lacosamide was added), and 22 percent were on three antiepileptic drugs (AEDs) when they entered the trial. In addition, nearly 17 percent (the actual number was 16.6 percent) were using the vagus nerve stimulator as well as the listed AEDs. In short, this was a group of people with very refractory and long-standing epilepsy (Table 2).

In all of the randomized clinical trials, a forced titration

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Table 1: Pharmacokinetic and Pharmacodynamic Properties of Lacosamide

lacosamide	Clinical Implications
T _{1/2} = 13 hours	Steady-state in approximately 3 days
Protein binding=15%	Low likelihood of drug-drug interactions
Major metabolism via demethylation	Possible liver problems
Major elimination via kidneys	Lower doses needed in renal disease
100% bioavailability	Food does not affect absorption

Table 2: Pooled Data from the Initial Clinical Trials

Number of patients	1,294
Average age	38.6 years
Average duration of epilepsy	23.7 years
Average monthly number of seizures	10-17
Number if concomitant AEDs	77% had tried >4, and 45% had tried >7

schedule of medication introduction was implemented. This was done, as in many trials, in order to assure that each person was treated in the same manner. In each of the trials, the dose of lacosamide was started at 100mg (divided as 50mg twice a day), and was increased by 100mg every week to the target dose: 200mg per day, 400mg per day, and in one trial 600mg per day.

The Results

When the data were analyzed, lacosamide was found to statistically significantly reduce the number of partial seizures. Compared to placebo, there was a significant difference at both the 200mg dose and the 400mg dose. There was a median reduction of seizures by 33-35 percent at 200mg per day, and 40-46 percent at 400mg per day. Another way of looking at this is by evaluating the responder rate: 35-38 percent were responders at 200mg per day, and 40-49 percent were responders at the 400mg per day dose. At 200mg per day 2.7 percent of patients were seizure-free, and 3.3 percent were seizure-free at 400mg per day. This was in comparison to 0.9 percent who were seizure-free in the placebo arm.

All medications have possible side effects, and lacosamide is no different. Compared to placebo, where seven percent of subjects experienced dizziness, at 200mg per day 10 of treated

patients were dizzy and at 400mg per day 25 percent were dizzy. Headaches were reported in 10 percent of people taking 400mg per day, compared to six percent of those taking placebo. Nausea was reported in nine percent of those taking lacosamide 400mg daily compared to four percent who were given placebo. Diplopia occurred in eight percent of those taking lacosamide (400mg/d), versus one percent of the placebo group. As with most medications, the side effects were related to the dose. Most people reported them as being either "mild" or "moderate."

Dosing

Based on these results, the usual daily dose of lacosamide is 200-400mg per day (divided into two doses, e.g. 100mg po BID to 200mg po BID). The medication comes in 50mg, 100mg, 150mg, and 200mg tablets. It is also available as an intravenous formulation, where the dose compared to the oral is 1:1. In other words, 100mg IV can be used instead of 100mg dosed orally. The availability of an IV formulation increases the flexibility of the medicine: if the person were to temporarily be unable to take medications orally, the intravenous formulation can be substituted

very easily. As many people with epilepsy may at some point require surgery, the IV formulation eliminates the clinical concern that an alternative AED might be needed during or around the procedure itself.

Conclusions

Lacosamide is the newest AED to be approved for use in the United States by the Food and Drug Administration. It is currently approved for use in adults (over 17 years old) as an add-on drug. Lacosamide is approved for use in partial (or localization related) seizures. Lacosamide reaches steady-state in about three days, and has few if any drug-to-drug interactions. It is started gradually, increasing by 100mg per week to 200-400 mg daily. There was a 45 percent median reduction of seizures at 400mg per day; the responder rate was approximately 45 percent at the same dose. The main side effects, common to many of the available AEDs, were dizziness, headache, and nausea. PN

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