Lennox-Gastaut Syndrome (LGS) is a devastating form of epilepsy that usually starts in childhood (Table 1). It is not a common form of epilepsy, accounting for one to four percent of childhood epilepsies. It is fortunate that it is not so common: when a child has LGS, he or she often has very frequent seizures. They can experience a combination of many kinds of seizures, including tonic-clonic (also known as convulsions), partial seizures, myoclonic seizures, atypical absence seizures, and tonic or atonic seizures. The last type mentioned is the most injurious: when a person has this seizure type, they often fall and injure themselves since they lack the ability to protect themselves from the fall. Unfortunately, LGS rarely responds to medications, and up to 96 percent of people with LGS will continue to have seizures despite multiple medications.

The treatments for LGS fall within the same categories as those for other types of epilepsy. The mainstay is anti-seizure medication. Valproate is probably the most recommended medication for LGS. Though very effective, there is a higher incidence of liver failure in children younger than five years old. Felbamate, lamotrigine, and topiramate have all been studied in randomized clinical trials as add-on treatments for LGS; All are effective. The vagus nerve stimulator has never been studied in a randomized clinical trial; however, there are many case series that suggest very strongly that this is a very effective treatment for this refractory epilepsy syndrome. The most recent therapy to be studied is rufinamide (Banzel, Eisai, Inc.).

The Rufinamide Study
The rufinamide study was performed from March 1998 to September 2000. It took place in 36 centers in nine countries (Table 2). Although 139 patients were enrolled in the trial, one decided to withdraw, and 138 were therefore randomized to treatment or placebo (Table 3). There were 74 patients in the rufinamide group and 64 in the placebo arm of the study. There was a 28-day baseline phase, where seizures were carefully counted. Following this, there was an 84-day double-blind, placebo controlled, parallel group treatment period. Of the 84 days, 14 days were used to titrate the drug to the target dose, and the patient maintained that dose for the remaining 70 days. The number of seizures in the treatment phase were then compared to the frequency that had been calculated during the 28-day observation period before treatment had begun.

The study group, before the study began, had agreed on criteria for LGS based on the International League Against Epilepsy (ILAE) criteria. This way, since many centers were involved, there would be uniformity in the accuracy of diagnosis. As per the ILAE criteria, they defined LGS as a pediatric epilepsy syndrome, which caused many seizure types as well as developmental delay. Slow spike-and-wave, which is a generalized pattern of less than 2.5Hz on electroencephalogram, had to be present on the EEG. The studied patients all underwent at least six hours of video-EEG to confirm this. In addition, video-EEG assisted the families in identifying the different seizure types that occurred. Since most people with LGS have many seizure types, it was important for...
the families to be as accurate as possible when reporting the occurrence of seizures.

Because LGS is so resistant to medications, it is not surprising that all patients were taking other anti-seizure drugs. The study allowed persons who were taking up to three other seizure medications. To be certain that there was no serious, progressive underlying neurological problem, all patients had a computed tomogram or magnetic resonance image of the brain. Finally, dosing was calculated based on weight: it was agreed that children had to be at least 18 kilograms in weight in order to be in the study.

**The Results**

Rufinamide statistically reduced the number of seizures compared to placebo (Table 4). For the most injurious of seizures—tonic or atonic—there was a responder rate of 42.5 percent versus 16.7 percent in the placebo group (p=0.002). Although no patients became seizure-free, 4.1 percent in the rufinamide group stopped having tonic-atonic seizures (compared to 3.3 percent in the placebo group). When looking at all seizure types, the responder rate was 31.1 percent versus 10.9 percent in the placebo group (p=0.0045). Caregivers reported a reduction in seizure severity of 53.4 percent in the rufinamide group, versus 30.6 percent for placebo (p=0.0041).

The most common side effects were somnolence and vomiting. Six people in the rufinamide group stopped taking the drug because of side effects. One half of this group stopped taking the drug within two to three weeks of initiation. Cognitive side effects were reported in 17.6 percent of the rufinamide group compared to 23.4 percent in the placebo group. Three patients in the rufinamide group developed status epilepticus; none in the placebo group had status epilepticus.

**More About Rufinamide**

The way that rufinamide works is unclear. Rufinamide, whether taken with food or without, reaches a peak plasma concentration in four to six hours. It has a plasma half-life of six to 10 hours. Thirty-four percent is serum protein bound. It is mainly broken down by hydrolysis, which is not dependent on the cytochrome P450 system. However, rufinamide is a weak inducer of the CYP3A4 system and therefore weakly influences the metabolism of...
other drugs that are broken down by this pathway. P450 enzyme-inducing medications increase the clearance of rufinamide by up to 45 percent. Since rufinamide does not go through the P450 system, the mechanism by which this occurs is still unclear. Women seem to clear the drug up to 14 percent less than men do, though the difference has so far not been reported to result in a clinical difference. Co-administration of rufinamide with oral contraceptives reduced the serum concentration of the estradiol by 22 percent. Although the clinical significance of this is unclear, women taking oral contraceptives should be told of this possible interaction and counseled about appropriate birth control.

Other Important Information about Rufinamide

Rufinamide has been observed to shorten the QT interval on the electrocardiogram by up to 20 milliseconds (msec). However, this does not seem to cause a clinical effect. The concern, however, is in patients with familial short QT. When QT becomes shorter than 300msec, there is a greater concern for ventricular cardiac arrhythmias, including death. As such, people with known short QT should not receive rufinamide. If the prescribing physician does not know, a pre-treatment ECG should identify this, if present.

Conclusions

Rufinamide is an important and effective addition to the class of antiseizure medications. It reduced tonic and atonic seizures strongly. Given the injurious nature of these seizures, this makes rufinamide an important medication to consider in patients with LGS. Given its effectiveness in Lennox-Gastaut Syndrome, it is likely to have a broad spectrum of action in many epilepsy syndromes; Future studies may confirm this. It is well-tolerated, and although sleepiness and vomiting were the most common side effects in the study, most people self-reported side effects as either mild or moderate. Rufinamide is a weak inducer of the CYP3A4 system and therefore can reduce the serum concentration of drugs that are broken down this way. Enzyme inducers of the P450 system, like phenytoin and phenobarbital, increase the clearance of rufinamide, though for reasons that have not yet been explained.


Table 4: Efficacy and Safety Results from Trial of Rufinamide in LGS

<table>
<thead>
<tr>
<th></th>
<th>Rufinamide</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% change in all seizures</td>
<td>-32.7</td>
<td>-11.7</td>
<td>0.0015</td>
</tr>
<tr>
<td>% change in tonic/atactic seizures</td>
<td>-22.5</td>
<td>+1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% change in myoclonic seizures</td>
<td>-30.4</td>
<td>-13.6</td>
<td>0.5711</td>
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<tr>
<td>% change in tonic-clonic seizures</td>
<td>-41.6</td>
<td>-18.1</td>
<td>0.3306</td>
</tr>
<tr>
<td>% change in absence/atypical absence</td>
<td>-50.6</td>
<td>-29.8</td>
<td>0.0222</td>
</tr>
<tr>
<td>Responders: 50% or greater decrease in seizures</td>
<td>31.1%</td>
<td>10.9%</td>
<td>0.0045</td>
</tr>
<tr>
<td>Somnolence</td>
<td>24.3%</td>
<td>12.5%</td>
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</tr>
<tr>
<td>Vomiting</td>
<td>21.6%</td>
<td>6.3%</td>
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</tbody>
</table>

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