Stiripentol for Dravet Syndrome: Is It Worth It?

Stiripentol in Dravet Syndrome: Results of a Retrospective U.S. Study.

PURPOSE: To review the efficacy and tolerability of stiripentol in the treatment of U.S. children with Dravet syndrome.
METHODS: U.S. clinicians who had prescribed stiripentol for two or more children with Dravet syndrome between March 2005 and 2012 were contacted to request participation in this retrospective study. Data collected included overall seizure frequency, frequency of prolonged seizures, and use of rescue medications and emergency room (ER)/hospital visits in the year preceding stiripentol initiation, and with stiripentol therapy. We separately assessed efficacy in the following treatment groups: group A, stiripentol without clobazam or valproate; group B, stiripentol with clobazam but without valproate; group C, stiripentol with valproate but without clobazam; and group D, stiripentol with clobazam and valproate. In addition, adverse effects were recorded. KEY FINDINGS: Thirteen of 16 clinicians contacted for study participated and provided data on 82 children. Stiripentol was initiated a median of 6.0 years after seizure onset and 1.2 years after diagnosis of Dravet syndrome. Compared to baseline, overall seizure frequency was reduced in 2/6 in group A, 28/35 in group B, 8/14 in group C, and 30/48 in group D. All children with prolonged seizure frequency greater than quarterly during the baseline period experienced a reduction in this frequency on the various treatment arms with stiripentol. Similarly, 2/4 patients in group A, 25/25 in group B, 5/10 in group C, and 26/33 in group D experienced reduction in frequency of rescue medication use and 1/1 in group A, 12/12 in group B, 3/5 in group C, and 18/19 in group D had reduction in frequency of ER/hospital visits. Adverse effects were reported in 38, most commonly sedation and reduced appetite. Four patients (5%) discontinued stiripentol for adverse effects and two (2%) for lack of efficacy. SIGNIFICANCE: Stiripentol is an effective and well-tolerated therapy that markedly reduced frequency of prolonged seizures in Dravet syndrome.

Commentary
Dravet syndrome is tough. Children with this incurable genetic condition typically face a life dealing with developmental disability, motor impairment, and often intractable epilepsy (1). Antiepileptic drugs (AEDs) are only partially effective, and treatments such as ketogenic diets and vagus nerve stimulation are frequently tried to improve quality of life (2, 3). As is often the case, parents will look for any answer, no matter the cost, to try to help their children.

Stiripentol is an allosteric modulator of the GABA-A receptor, first demonstrated as effective in animal models in the late 1970s and then tried in humans in the early 1980s (4). As often happens, initial trials in partial epilepsy ensued, but in 2000, it was first reported by Chiron and colleagues as helpful for Dravet syndrome (5). Further studies followed, with continued efficacy demonstrated (6). Stiripentol, however, also is a potent cytochrome P450 inhibitor, which decreases the metabolism—hence raising the level of drugs such as clobazam (7). Early trials revealed possible synergistic benefits when stiripentol was combined with clobazam and valproate, raising a question regarding whether stiripentol’s efficacy was primarily related to increased clobazam levels (5).

At this time, stiripentol is available only in Europe, Canada, and Japan, so families in the United States have to pay cash for it to be shipped to their household from abroad. This cost can be as high as $1,000 for a month supply via Caligor in New York City or 1,500 euros per month from Europe directly (Dravet Syndrome Foundation, personal communication). For a family struggling with a devastating disease with comorbidities and a child already receiving (and paying) for multiple other AEDs, the cost-effectiveness of stiripentol is a reasonable concern (8). In 2004, this was addressed by the group at Alberta Children’s Hospital, and stiripentol was deemed worth the cost; however, that was when it was priced at mean $135 per month (9).

The present study was designed to further investigate the value of stiripentol for children with Dravet syndrome, querying child neurologists who obtained this drug for their U.S. patients over a 7-year period. In total, 82 children were identified, most with very severe epilepsy. A median of 7 AEDs were tried, half had been on dietary therapy, and one-quarter...
Why exactly was this study performed? It was funded by Biocodex, the French company that owns and produces stiripentol. Two of the authors are company employees. One has to suspect that Biocodex may be considering either expanding its market to the United States or selling stiripentol to a U.S.-based pharmaceutical company for distribution. Perhaps this study is to test the waters of efficacy and interest here prior to a large scale FDA-mandated prospective clinical trial.

Regardless of the reasons for this study, the results were promising. The authors chose to group patients with sufficient data into those receiving stiripentol alone (n = 6), those on stiripentol with clobazam (n = 35), stiripentol with valproate (n = 14), and stiripentol with both clobazam and valproate (n = 48). One presumes some children were counted twice if they tried stiripentol in different combinations. Overall, 66% (68/103) had a reduction in seizures, with approximately half of those being a “marked” reduction. Most dramatically, every single one of the 35 children with prolonged seizures (and sufficient data to assess response) had improvement, with approximately 80% markedly improved. The best combination identified was stiripentol with clobazam, followed by all three AEDs together. Stiripentol was tolerated well, with sedation seen in 18% and decreased appetite in 8.5%. Quality of life improved in 88%, according to their physicians.

How should we interpret this information? On one hand, it confirms previous reports that stiripentol is helpful for children with Dravet syndrome, especially for those with very prolonged seizures. The value is significant in preventing emergency department visits, need for rescue medications, status epilepticus, and death due to prolonged seizures. On the other hand, the value of stiripentol may at least partially be due to raised clobazam levels. Perhaps it would be more cost-effective to increase the daily clobazam dose to a maximum, and only then consider stiripentol when that approach has failed.

As a U.S.-based pediatric epileptologist treating children with often extremely intractable epilepsy, including those with Dravet syndrome, I would be thrilled to see stiripentol eventually added to the armamentarium of AEDs available. We do need to be cognizant, however, of the high medical costs faced by families of children with severe epilepsy. I hope when it does eventually arrive on the U.S. market, it is priced reasonably and insurance recognizes its value for the select group of children who need it.

by Eric Kossoff, MD

References

Instructions

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