Pregabalin: A New Approach to Treatment of the Dysautonomic Crisis
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abstract

Nausea and dysautonomic crises severely limit function and quality of life for a large number of individuals with familial dysautonomia. We treated a small cohort of 15 patients with familial dysautonomia who suffered frequent dysautonomic crises with pregabalin. Nausea and overt crises markedly decreased in 13 (87%) of these patients and the overall assessments of benefit were extremely favorable, suggesting that pregabalin may be a potentially useful therapeutic agent for this disorder. Pediatrics 2009;124:743–746

Familial dysautonomia (FD) is a genetic disorder that has as one of its most debilitating manifestations frequent bouts of nausea that can escalate to the more pervasive dysautonomic crisis.1,2 In addition to severe nausea with retching, the dysautonomic crisis is associated with symptoms that suggest systemic sympathetic storm, because there can be hypertension and tachycardia, as well as facial flushing, bronchorrhea, gastrorrhea, and worsening of oral coordination such that the child has difficulty swallowing secretions and is reluctant to speak. There is also a general overwhelming feeling of discomfort resulting in negative personality changes such as whining or withdrawal. In ~40% of patients with FD, these crises occur with such regularity that there seems to be a link with circadian rhythms. For some patients, the crisis is a daily, morning event that starts with the sympathetic surge accompanying arousal.

Although nausea, a general feeling of discomfort with an urge to vomit, is the predominant symptom during crisis, the cause may not be a result of peripheral gastrointestinal dysfunction. In fact, there is evidence that the trigger emanates from a central locus.3 In addition, to date, the most effective drugs for treating an acute crisis have been centrally acting agents such as diazepam, a benzodiazepine, and clonidine, a direct-acting $\alpha_2$-adrenergic agonist.4,5 Diazepam acts to increase the activity of $\gamma$-amino butyric acid (GABA) in the brain, which results in sedation and decreased anxiety and also makes it useful in controlling convulsions. A question then arises: Might the chronic use of such centrally acting agents prevent a crisis? Thus, we empirically treated a small group of patients with FD with pregabalin, a $3$-isobutyl derivative of GABA that is known to have anticonvulsant, antiepileptic, anxiolytic, and analgesic activities. We assessed the symptomatic responses of the patients before and after treatment to determine if there was perceived benefit.

METHODS

To evaluate the effectiveness of pregabalin in ameliorating symptoms of frequent nausea or crisis, we treated 15 patients with FD (8 female,
7 male). All individuals were homozygous for the splicing mutation in \(IK-BKAP\) (the IKB kinase-associated protein gene) and were being followed with annual evaluations at the New York University Dysautonomia Center. The mean age was 22.2 ± 8.9 years (range: 10.3–40.1 years) and mean length of treatment was 5.1 ± 3.0 months (range: 1 day to 9 months). After 1 month of treatment in those patients who continued on pregabalin, assessment of efficacy was performed.

Although the symptoms and duration of crisis can vary from patient to patient, we defined the crisis as the occurrence of nausea with retching, and we elected to focus on frequency of the crisis episodes as our primary outcome. The frequency of crises is usually characteristic for a particular patient. We defined frequency of crisis according to a scale that was used in an earlier study that assessed long-term effects of fludrocortisone on FD symptoms and used 4 categories as defined in Table 1. A crisis-frequency score was assigned before the start of pregabalin and then after 1 month of treatment. In addition, the patient or the patient’s family was contacted at the end of the follow-up period and requested to provide their impression of pregabalin’s overall effectiveness on symptoms by using a subjective scale: −5, severe worsening; −4, major worsening; −3, moderate worsening; −2, mild worsening; −1, mild worsening; 0, no improvement or change in status; 1, minimal improvement; 2, mild improvement; 3, moderate improvement; 4, major improvement and change in function; 5, complete resolution of crisis and major improvement in overall function.

We considered the outcome to be beneficial if there was at least a 25% decrease in the crisis-frequency scale or if the subjective overall assessment was ≥3 (ie, at least a moderate improvement). Adverse events were noted.

Because of the small size of our patients (average weight: 41.9 ± 10.5 kg), we empirically selected a starting dose of 25 to 50 mg twice daily. Doses were then escalated over 1 month to either achieve greater effectiveness or a maximum of 6 mg/kg per day. We chose to start the doses at a low level to help patients acclimate to the possible effect on alertness and gait. None of the pre-existing routine medications were changed; 14 patients were taking diazepam daily, and 12 were taking clonidine.

**RESULTS**

As noted in Table 2, the majority (12 of 15) of the patients with FD in this series had a pretreatment crisis scale score of 4, indicating that they were experiencing nausea or crises on a daily basis. For 13 (86%) of the 15 patients, there was at least a 25% improvement in symptoms, with 8 (53%) of the 15 having ≥50% decrease in severity. Two patients had no improvement with pregabalin, and 1 of

<table>
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<th>Patient No.</th>
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<th>Gender</th>
<th>Length of Treatment</th>
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M indicates male; F, female.

* Based on a subjective scale from −5 (severe worsening) to 5 (complete resolution of crisis and major improvement in overall function).
these individuals (patient 3) withdrew after 1 day (2 doses) because of the development of marked peripheral/dependent edema. The other patient (patient 8) continued to have daily episodes of nausea and crises, but her parents reported that she became more sensitive to her usual crisis medications because they needed to be administered at lower doses to avoid profound hypotension. The parents considered this to be a negative effect of the drug. The overall impression, based on the subjective scale, was 3 (moderate improvement) or better (Table 2) in 13 (87%) of the 15 individuals with FD.

For those patients who continued on pregabalin over the course of several months, the beneficial effect on nausea and crises continued. Untoward adverse effects included peripheral edema in 1 patient, weight gain in 4 patients, and worsening balance in 7 patients. Except for the patient who experienced peripheral edema, the adverse effects were not considered so untoward that patients requested to stop taking the drug.

**DISCUSSION**

These preliminary data demonstrate that pregabalin, a central acting agent, may be an effective treatment to prevent or ameliorate the symptoms of the dysautonomic crisis. To date, therapies have all been oriented toward treatment of the acute episode, whereas we have assumed that pregabalin would be associated with fewer dose-related adverse events. Also, pregabalin’s plasma concentrations increase linearly with increasing dose, whereas gabapentin concentrations have been found to have a nonlinear relationship to increasing doses. At this point it is not certain if it is the pregabalin alone or its synergistic effect with other existing medications that ameliorates the crisis symptoms.

Many of the patients were already taking clonidine and/or a benzodiazepine, and these medications were not changed when the pregabalin was added. However, in some cases, either the dose or the frequency of other medications was reduced.

**CONCLUSIONS**

The results of this small case series provide preliminary evidence that modification of central excitability by pregabalin may be a reasonable approach to ameliorate or prevent the dysautonomic crisis in some patients with FD. Pregabalin was generally well tolerated, with the most common adverse effects reported being weight gain, mild ataxia, and peripheral edema. Because most of the patients were already routinely using a benzodiazepine and/or clonidine for either anxiety or blood pressure control, it is not clear at this point if pregabalin was of singular benefit or if it was synergistic with any of these preexisting medications. Thus, although the preliminary observations are strongly suggestive, extensive clinical trials are needed to provide more evidence regarding pregabalin’s efficacy as a specific therapeutic agent for the prevention of the dysautonomic crisis in FD. In addition, one might wish to try pregabalin treatment in other patients who suffer from other autonomic disorders associated with cyclical vomiting.

**ACKNOWLEDGMENT**

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