A Case of Seizure Activity Associated With a Therapeutic Dose of Venlafaxine

To the Editor: Seizures associated with venlafaxine overdoses[1–4] and with therapeutic doses[5] have been reported. Several factors may increase the risk of generalized seizure activity, including genetic,[6] neurologic,[7] psychiatric,[7] and drug withdrawal[8] effects and the use of agents that lower seizure threshold, such as antidepressants.[9] We report a case of a patient on anticonvulsant pharmacotherapy who experienced a seizure following an increase in venlafaxine dose.

Case report. Ms A, a 25-year-old white woman with juvenile myoclonic epilepsy, was recently diagnosed with *DSM-IV-TR* major depressive disorder and generalized anxiety disorder.[10] Seizures were well controlled on treatment with lamotrigine (600 mg/d) and clonazepam (2 mg/d), with 1 episode of generalized tonic-clonic seizure reported 2 years prior, following nonadherence to anticonvulsant therapy. Ms A received fluoxetine 80 mg/d for 6 months before it was discontinued, at which time venlafaxine extended release (ER) 37.5 mg daily was started along with hydroxyzine 25–50 mg orally 3 times daily as needed for anxiety. Venlafaxine ER was titrated to 75 mg daily after 1 week and then increased to 150 mg daily after another 3 weeks with moderate mood improvement but minimal anxiety improvement. For anxiety, alprazolam was started 4 weeks after initiation of venlafaxine and hydroxyzine and was titrated to 1 mg twice daily with good adherence. After another 12 weeks, the patient's mood symptoms worsened, and venlafaxine ER was titrated to 225 mg daily. Sixteen days following this dose titration, the patient experienced a generalized tonic-clonic seizure despite adherence to her anticonvulsant regimen and other medications.

Venlafaxine-induced hyponatremia (serum sodium level less than 136 mEq/dL)[11] was considered as a potential cause of seizure in our case, but our patient's sodium level checked on the day of the seizure was 138 mEq/dL.

On the basis of the time course of the generalized tonic-clonic seizure, the Naranjo Adverse Drug Reaction Probability Scale[12] was applied and indicated a probable relationship between the adverse effect of a generalized tonic-clonic seizure and venlafaxine ER in this patient.

Venlafaxine-associated seizure activity at a therapeutic dose has been reported. In the case report identified,[5] a patient demographically similar (25-year-old white woman with chronic depression) to ours experienced a generalized tonic-clonic seizure 11 days following an increase in trimipramine from 50 mg to 100 mg daily; her venlafaxine dose was 150 mg daily. No further seizure episodes were reported (12 months of monitoring) following antidepressant discontinuation. The authors theorized that a pharmacokinetic or pharmacodynamic interaction between the antidepressants may have induced the episode. This potential was not identified in our patient.

Concurrent medication use and the potential for seizure activity were evaluated. The patient in our case report also received benzodiazepines, ie, clonazepam and alprazolam. The potential for benzodiazepine-mediated seizures was deemed noncontributory.

Venlafaxine doses up to 225 mg are included in the recommended dosage range for patients with seizure disorders.[7] However, clinicians should be aware of the epileptogenic effects of venlafaxine even at therapeutic doses, particularly in patients with a previous history of seizure activity. For these patients, clinicians should consider using antiepileptics also indicated for psychiatric disorders, avoiding, if possible, agents known to lower the seizure threshold, starting with low doses, proceeding cautiously, and using the lowest effective dose for maintenance therapy.[13]

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