Probable Psychosis Associated With Levetiracetam: A Case Report

To the Editor: Levetiracetam is one of the new antiepileptic medications that have been approved for the management of partial epilepsy as an add-on therapy. Although the drug has benign, infrequent, mild side effects, psychiatric adverse effects have also been reported. However, psychosis associated with its use is rarely reported. We report here a case of 20-year-old man who developed psychosis associated with levetiracetam use, and we discuss possible risk factors.

Levetiracetam is an antiepileptic medication similar in chemical structure to piracetam.[1] Levetiracetam has been approved for the add-on treatment of partial epilepsy, and evidence suggests that it is also effective in generalized epilepsies as well as for myoclonus.[2,3] Although its exact mechanism of action is not known, it may entail unique specific binding to a 90-kDa membrane protein restricted to neuronal cell types, blockade of zinc and β-carbolines from interrupting chloride influx in gamma-aminobutyric acid (GABA) and glycine receptors.[4,5] Controlled clinical trials have reported a wide margin of tolerability, with infrequent and mild adverse events. The benefit/side effect ratio seems favorable, with one recent study of 1,422 patients describing a 60% 1-year retention rate, and 38.6% of patients having a 50% reduction in seizure frequency.[6] CNS adverse events include somnolence, asthenia, coordination difficulties, and behavioral abnormalities. In randomized, controlled trials, 13.3% of levetiracetam-treated patients reported behavioral symptoms including agitation, hostility, anxiety, apathy, emotional lability, depersonalization, and depression.[7–9] The majority of behavioral problems were mild or moderate in nature. Psychosis has been reported infrequently with levetiracetam, with a reported frequency of less than 1%.[10,11] Most of the reports have been in the form of case reports.[12,13]

We hereby report a case of a 20-year-old man who developed acute psychotic symptoms after a month of levetiracetam therapy. Although the patient was prescribed olanzapine because of the severity of psychotic symptoms, the dose of levetiracetam was also reduced. The patient reported marked improvement in psychotic symptoms after about 2 days, and he was completely asymptomatic after 1 week. Olanzapine was stopped, and the patient remained well for the next 3 months of follow-up, and also had no seizure activity.

Case Report

A 20-year-old man was brought to the psychiatry outpatient department with complaints of violent abusive behavior, restlessness, muttering and gesticulating to himself, with disturbed physical functioning, for the past 3 days. His history revealed that he had poor school performance since age 11, after he had developed febrile encephalopathy. He was also suffering from generalized tonic–clonic seizures, along with left partial seizures with secondary generalization. The patient also had history of bilateral chronic serous otitis media and had a marked decrease in hearing. He was initially given divalproex up to 2,000 mg per day, but his seizures were not controlled. He had seizures about every 15 days. As a result, about 2 months before his presentation to us, he was started on levetiracetam 500 mg per day. The dose was increased gradually, with increments of 500 mg every 2 weeks, to a dose of 1,500 mg per day. At the time of presentation to us, he was receiving 1,500 mg of levetiracetam, along with 1,000 mg of divalproex. He had had his last seizure 1 month earlier. An MRI brain scan done around 3 years earlier showed altered signal intensity in bilateral parietal, temporal, and occipital lobes, with volume loss. IQ assessment done around that time revealed an IQ of 62. There was no history of any behavioral problems or any other significant history. There was no history of any recent seizures, no history of any urinary/fecal incontinence, or any history of disorientation within the past 3 days. His family history was not significant. Mental status examination revealed a young man with rapport not established, muttering to himself, and having auditory hallucinations, with absent insight.

The was given a physical exam; hematological investigations were all normal. An EEG was also done to rule out any seizure activity and was normal. He was started on olanzapine 5 mg per day, along with lorazepam 3 mg per day. In view of the temporal relationship with levetiracetam, the dose was decreased to 100 mg per day, and divalproex was continued at the same dose. The patient reported

improvement in symptoms by the 2nd day and was asymptomatic by the 7th day. His olanzapine and lorazepam were stopped, and he was maintained on levetiracetam 1,000 mg per day, along with divalproex 1,000 mg per day without any recurrence of seizure or psychosis for the next 3 months of follow up.

Discussion

In our case, the close temporal relationship between psychosis and increase in levetiracetam dose and previous reports of levetiracetam-induced psychosis supported our hypothesis of levetiracetam-induced psychosis. Use of the Naranjo Adverse Drug Scale[14] also revealed a probable relationship between levetiracetam and psychosis. Also, the rapid resolution of symptoms after decrease in the dose of levetiracetam strengthened our hypothesis. Most likely, in our case, the psychosis as a side effect was a dose-related phenomenon, with psychosis occurring at a dose of 1,500 mg per day and resolving completely at 1,000 mg per day. Various risk factors that could have contributed to psychosis in our case were young age, previous cognitive problems, sensory deprivation, history of seizures, and febrile encephalopathy in the past. The possibility of process of rapid "forced normalization" of the EEG was less possible because of the fact that other drugs achieve rapid normalization of the EEG with no such side effects.[15] Other possibilities, such as seizure disorder or postictal psychosis were ruled out on the basis of history and investigations. The mechanism that could explain why some anticonvulsants produce psychosis remains unclear. However, it is possible that the patients who develop such a side effect, may, in fact, have a preexisting psychotic disorder that is not clinically evident. In such cases, the administration of the antiepileptic drug may act as a trigger mechanism. Side effects of levetiracetam include dizziness, fatigue, headache, upper respiratory tract infection, and somnolence. It is well known that levetiracetam can influence behavior. Although there is evidence that the drug may trigger behavioral disorders, there are reports that it may reduce hyperactivity, impulsivity, mood instability, and aggression in autistic children.[16] To conclude, there is no doubt that antiepileptic drugs may lead to various psychiatric adverse effects, including psychosis. At present, there is no evidence to suggest that levetiracetam produces psychosis at significantly higher rates than other antiepileptic drugs. Close clinical monitoring with regard to psychiatric adverse effects is needed when starting treatment with antiepileptic drugs. It is especially important in patients with risk factors for psychiatric adverse effects. Further studies to assess the behavioral profile of levetiracetam in large group of patients are needed.

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