Seizure Exacerbation by Antiepileptic Drugs

Worsening of Seizures by Oxcarbazepine in Juvenile Idiopathic Generalized Epilepsies

Gelisse P, Genton P, Kuate C, Pesenti A, Baldy-Moulinier M, Crespel A

Epilepsia 2004;45:1282–1286

PURPOSE: Several studies have shown that carbamazepine (CBZ) may aggravate idiopathic generalized epilepsy (IGE). Oxcarbazepine (OXC) is a new drug chemically related to CBZ. We report six cases of juvenile IGE with a clear aggravation by OXC.

METHODS: We retrospectively studied all patients with IGE first referred to our epilepsy department between January 2001 and June 2003 and treated with OXC.

RESULTS: During this period, six patients were identified. All had an aggravation of their epilepsy in both clinical and EEG activities. OXC had been used because of an incorrect diagnosis of focal epilepsy or generalized tonic–clonic seizures (GTCSs) of undetermined origin (no syndromic classification of the epilepsy). Before OXC, only one patient had experienced a worsening of seizures with an inadequate drug (carbamazepine; CBZ). Four had juvenile myoclonic epilepsy, one had juvenile absence epilepsy, and one had IGE that could not be classified into a precise syndrome. OXC (dosage range, 300–1,200 mg/day) was used in monotherapy in all of them except for one patient. Aggravation consisted of a clear aggravation of myoclonic jerks (five cases) or de novo myoclonic jerks (one case). Three patients had exacerbation of absence seizures. One patient had worsened dramatically and had absence status, and one had de novo absences after OXC treatment. The effects of OXC on GTCSs were less dramatic, with no worsening in frequency in three and a slight increase in three.

CONCLUSIONS: OXC can be added to the list of antiepileptic drugs that can exacerbate myoclonic and absence seizures in IGE.

COMMENTARY

In this article by Gelisse and colleagues, potential exacerbation of idiopathic generalized epilepsy by oxcarbazepine is identified. The strength of their work is that, rather than selecting isolated cases, they reviewed a prospective database spanning 2 years and identified every patient with idiopathic generalized epilepsy who had received oxcarbazepine. Patients were well characterized with a nap video-EEG to assure that the diagnosis of idiopathic generalized epilepsy was correct. Four patients had juvenile myoclonic epilepsy, one had juvenile absence epilepsy, and one had idiopathic generalized epilepsy with photosensitivity. They found that all six patients had experienced an aggravation of seizures after oxcarbazepine was initiated. Removal of oxcarbazepine was effective in correcting the exacerbation; although, in five of six cases, another antiepileptic drug, usually valproic acid, was immediately initiated, which would confound this finding.

Exacerbation of seizures in idiopathic generalized epilepsy has been demonstrated for several commonly used antiepileptic drugs, including vigabatrin, tiagabine, carbamazepine, and possibly gabapentin. The same drugs may exacerbate some seizure types in patients with Lennox–Gastaut syndrome (1). This is not surprising, as both types of epilepsy are associated with generalized spike–wave discharges. Care must be taken when evaluating the literature in regard to potential for exacerbation. Epilepsy, by its very nature, is a waxing and waning condition. Therefore, even if a drug has a neutral effect, some patients will worsen as a result of the natural history of their disease. A few of these patients taken out of the context of a larger sample might give the impression of exacerbation. In addition, it is important not to confuse withdrawal effects, resulting from removal of an old drug, with seizure worsening from addition of a new agent.

Obviously, the best way to determine the likelihood for seizure exacerbation is by applying exactly the same method used to determine improvement. This would involve evaluation of randomized, comparative trial data. Such a method has been used in the past to address whether the new antiepileptic drugs exacerbated seizures in any subset of patients with refractory partial epilepsy (2,3). Only with tiagabine did more patients taking the drug than taking the placebo have seizure worsening. Unfortunately, randomized trials of idiopathic generalized epilepsy syndromes are much less common, and therefore, observational studies are typically the only data available

Epilepsy Currents, Vol. 5, No. 5 (September/October) 2005 pp. 192–193
Blackwell Publishing, Inc.

to address the question of seizure worsening. When evaluating observational studies, reasonable methods should be used. Perucca and colleagues introduced criteria for selecting valid data on seizure exacerbation (1). According to their paradigm, at least one of the following criteria must be present to consider an observational study valid: (a) clear-cut increase in seizure frequency (i.e., above the previously observed range) that is associated with administration of the offending drug and reversible on discontinuation or dose reduction; (b) demonstration of a consistent adverse effect of a given drug in a specific seizure type or syndromic form; (c) identification of any other factor, such as EEG feature, that would be predictive of drug-induced seizure deterioration; and (d) appearance of new seizure types showing a clear-cut temporal association with the change in pharmacologic treatment. Clearly, the case series of Gelisse and colleagues meets these criteria and, therefore, should be taken seriously.

Much speculation has occurred regarding how certain antiepileptic drugs cause seizure exacerbation. The most solid data on mechanism are available for GABA-active drugs. These agents have been shown to exacerbate generalized spike–wave discharges both in humans and in animal models of absence epilepsy, such as the GAERS rat and the lethargic mouse. It is presumed that this effect is a result of activation of $GABA_B$ receptors (4). The mechanism by which carbamazepine and oxcarbazepine, both of which act at least in part by sodium channel blockade, exacerbate seizures is less clear, but may be related to enhancement of neuronal activity within thalamocortical circuitry (5). Again, exacerbation could be predicted based on the effect of carbamazepine on animal models. It, therefore, is not unreasonable to use these animal models to predict the likelihood of exacerbation in humans.

In summary, Gelisse and colleagues provide compelling evidence for seizure exacerbation with oxcarbazepine in patients with idiopathic generalized epilepsy syndromes. Most of the cases that they report were given oxcarbazepine because of an incorrect diagnosis. This study underscores the fact that it is important to make a syndrome diagnosis before selection of an antiepileptic drug.

by Jacqueline A. French, MD

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