Seizure Aggravation—Evidence That Oxcarbazepine Requires Monitoring

Aggravation of Seizures and/or EEG Features in Children Treated with Oxcarbazepine Monotherapy. Vendrame M, Khurana DS, Cruz M, Melvin J, Valencia I, Legido A, Kothare SV. *Epilepsia* 2007;48(11):2116–2120. Epub 2007 Jul 21. PURPOSE: Exacerbation of epilepsy may occur following initiation of therapy with antiepileptic drugs (AEDs). The aim of this study is to analyze the clinical and EEG characteristics of a group of pediatric patients with worsening of seizures and/or EEG deterioration while on oxcarbazepine (OXC). METHODS: A retrospective analysis of a clinical database was performed to identify patients with epilepsy treated with OXC over the past 3 years. History, neurological examination, and EEG findings were reviewed to identify any who had developed exacerbation of seizures or new abnormalities on EEG. RESULTS: Of 290 patients on OXC, we identified 12 patients with new onset seizures, all with initial normal neurological exam and normal EEG, who developed either worsening of preexisting seizures, new seizure types, and/or EEG deterioration following introduction of OXC monotherapy. EEG changes were primarily characterized by new onset of generalized epileptiform activity not reported on the initial baseline EEG. Following substitution of OXC with a broad spectrum AED, significant improvement of seizure control and improvement in the EEG was observed. CONCLUSIONS: These findings suggest that OXC can aggravate seizures and/or worsen EEG features in children. Following initiation of therapy with OXC, monitoring of patients with follow-up EEGs may be important, especially in patients who do not show adequate response to therapy.

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COMMENTARY

In the article by Vendrame and colleagues, oxcarbazepine is implicated in causing seizure aggravation and eliciting

new seizure types in children ages 4 to 16 years. The most frequent transformation on the EEG in this case series was the appearance of generalized spike and slow wave complexes. Oxcarbazepine is a keto-analog to carbamazepine; therefore, it is not surprising that oxcarbazepine, like carbamazepine, can elicit new seizure types. In carbamazepine case studies, new seizure types have been reported especially in children with partial onset seizures or in seizures that at least initially appear to be partial onset (1). An important point of interest to clinicians is that the Verdrame et al. study investigates oxcarbazepine—the only drug that currently has a Level A classification from the International League Against Epilepsy Guidelines for use in children with partial onset seizures (2,3). These findings now may make the Guideline recommendations questionable. Yet, the frequency of seizure aggravation in this population was only 12 of 290 patients or 4.14 percent. Among the carbamazepine population in similar studies, seizure aggravation is found in up to 44 percent of patients <6 years of age (1).

The weakness of the Verdrame et al. study is that it is retrospective, and therefore the population studied cannot be reliably controlled for all factors. Still, it is a large study, and the patient histories seem to be well documented. Any patient complaining of worsening of seizures or having behavioral changes were reassessed by EEG. If EEG deterioration was seen, the patient was taken off oxcarbazepine and given another drug, most often valproate. The authors assert that the children's parents all kept seizure calendars as well as records of behavioral changes and school performance. If this assertion is correct, then this retrospective analysis could actually be of value for determining the risk of seizure exacerbation with oxcarbazepine, although seizure type or syndrome is never as well defined as in prospective trial. When a pattern of adverse events is detected outside of clinical trials, reports are almost always retrospective. Idiosyncratic side effects are frequently identified in postmarketing studies, as was the case with visual field deficits associated with vigabatrin (4). Therefore, retrospective studies reporting seizure aggravation are an important and valid initial step in determining novel adverse events.

The authors speculate on possible reasons for the seizure aggravation, pointing to the proposed mechanism of action of oxcarbazepine as a sodium-channel blocker and how that mechanism might elicit different seizure types. A recent report by Liu et al. concerning carbamazepine points to the possibility that seizure aggravation of carbamazepine, especially in absence seizures, could be caused by stimulation of a subtype of $GABA_A$ receptors in the ventrobasal nucleus of the thalamus (5). Liu and colleagues studied the effect of carbamazepine on $GABA_A$ stimulation by eliciting absence seizures in the GAERS rat model. Since, as mentioned, oxcarbazepine is a keto-analogue of carbamazepine, this interesting new mechanism may well apply to oxcarbazepine as well.

Seizure aggravation is a problem encountered mainly in GABAergic (e.g., tiagabine, gabapentin, and vigabatrin) and sodium channel blocking drugs (e.g., phenytoin, carbamazepine, and lamotrigine), although anecdotal reports of seizure provocation have been cited for almost all antiepileptic drugs (AEDs) (6). Particularly in patients with idiopathic epilepsies, seizure aggravation is not an uncommon problem, while adult patients with partial onset seizures seem to be more immune to this effect (7). However, children are different in this regard because they have a higher incidence of idiopathic epilepsy syndromes than adults and should be followed with greater care to avoid seizure aggravation, as it may occur when least expected (8).

How can the clinician be sure whether the drug used by a specific patient has elicited a new seizure type or instead has caused an increase in seizures or EEG change? It is possible that a change of seizure type or an increase of seizures could happen anyway—thus, the only way to explicitly demonstrate a correlation is to retest the patient after the drug is first withdrawn and the situation normalized. A retest is, however, not ethically possible so physicians have to rely on evidence of a temporal relationship between the drug use and the appearance of new seizure types.

What are the implications of these findings? It is important for all neurologists to be aware that patients, especially children, can develop a new seizure type or new cognitive and behavioral changes after administration of an untried AED. Changes in these variables might be due to the new AED or to a pharmacodynamic interaction with other AEDs. It is valuable when doctors vigilantly report occurrences in seizure aggravation to health authorities like the Food and Drug Administration and MedWatch in the United States, as patterns of adverse effects can then be detected.

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