CURRENT LITERATURE

DO ANTIEPILEPTIC DRUGS MAKE SEIZURES WORSE? A META-ANALYSIS

Aggravation of Partial Seizures by Antiepileptic Drugs: Is There Evidence from Clinical Trials?

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OBJECTIVES: To assess clinical trials for evidence that antiepileptic drugs (AEDs) aggravate partial seizures. To determine if the method used to examine drug efficacy can also be used to examine seizure aggravation.

BACKGROUND: It is widely accepted that AEDs aggravate epilepsy in some patients. However, there is little published objective or quantitative evidence. Most reports concern generalized epilepsies.

METHODS: Pharmaceutical companies responsible for the development of five of the new AEDs were asked to provide data concerning seizure increases during randomized placebo-controlled, add-on clinical trials in patients with uncontrolled partial seizures. Seizure frequency in individual patients taking drug or placebo was compared with the baseline pretreatment seizure frequency. The counterpart of the 50% reduction used in efficacy analyses is a 100% increase, because both represent a twofold change. A dose–response relation also was explored.

RESULTS: More than 40% of subjects in clinical trials of tiagabine (TGB), topiramate (TPM), and levetiracetam (LEV) experienced an increase in seizures while taking a placebo. Seizure increases were no more likely to occur when taking any of the three drugs than when taking placebo. A doubling or more of seizure frequency was less likely to occur with TPM or LEV than with placebo but more likely with TGB. However, for TGB, this did not reach significance. There was some evidence for a dose–response effect with TGB but a negative effect with TPM (aggravation less likely with increasing dose). Data on gabapentin and lamotrigine were not provided.

CONCLUSIONS: Many patients with partial seizures have an increase in seizures when a new AED is added to their therapy. However, it occurs no more frequently when taking drug than placebo. It probably represents the spontaneous fluctuation of seizure frequency. When a patient who has started a new AED deteriorates, this is not necessarily a drug effect.

COMMENTARY

This article is a repeated analysis of randomized clinical trial data that explores the likelihood of worsening as a result of initiation of a new antiepileptic drug (AED). As aptly pointed out by the author in his introduction, a trial that was specifically designed to address this question would not differ from a trial designed to demonstrate a beneficial effect on seizures. Therefore although the data are not always presented, they are readily available. Some published reports on randomized placebo-controlled AED trials include incidence of seizure worsening. For example, seizure worsening as measured by a >50% increase, was analyzed and included in the publication of both pivotal lamotrigine (LTG) trials and did not differ a great deal from placebo (1,2). Information on seizure worsening was included in a separate publication of levetiracetam (LEV) (3). However, most clinical trial reports do not include this information. This information is of interest and of clinical importance; however, it would not have been made available without the efforts of the author, who personally contacted the pharmaceutical companies who have developed new AEDs to obtain primary data for this analysis. The analysis included pooled data, leading to a relatively large study population [491 with tiagabine (TGB), 589 with LEV, and 527 with topiramate (TPM)]. This article is a credit to Dr. Somerville as well as the companies that provided the information. It is to be hoped that more such collaborations are forthcoming. A great deal of information is available from these complex and expensive trials that cannot be easily duplicated by other means.

An important part of the analysis was inclusion of patients who had worsening of seizures that caused them to leave the trial. Obviously, if the analysis had not included these dropouts, it would have potentially biased the study. Inclusion was accomplished by extrapolating seizures that had occurred before dropout into a weekly or monthly seizure rate. Unfor-

tunately, seizure worsening, as demonstrated by change in seizure type or increase in individual seizure severity, was not measured. Another limitation of the study is that it includes only patients with partial seizures. Many reports of seizure worsening involve generalized seizure types such as absence and myoclonus (4–6).

The results indicate that seizure aggravation was less common for most drugs at most doses than it was in patients who underwent no change in their therapy (the placebo group). This may come as a surprise to clinicians who have been convinced that patients have worsened as a result of addition of one of the drugs that was examined. Certainly this study cannot rule out rare cases of individual worsening. It does, however, highlight the fact that such worsening is common among patients with uncontrolled refractory seizures; therefore it is often prudent to allow time for observation before deciding to abandon a recently initiated AED.

We are in the fortunate position of having placebo-controlled data in the partial seizure population to assess the impact of new AEDs. In the generalized epilepsy populations, we are often not so fortunate. The results from this study remind us that findings of worsening in open trials should be interpreted with caution.

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