Dearth of Data Muddles Choices

Topiramate *from page 1*

place in medicine, with the potential to save patients thousands of dollars per year while providing excellent seizure control and adverse effect profiles. But the lack of extant data makes it difficult to decide which patients might be the best candidates for a generic formulation, and which might face an unacceptable risk of poor outcomes if they switch, said Dr. Privitera, who disclosed that he has served on advisory boards, consulted, and/or received honoraria and research support from a range of companies that manufacture AEDs, including Ortho-McNeil Neurologics, the manufacturer of Topamax.

Dr. Stuart Black, medical director of the Dallas Headache Association, agreed that the lack of evidence clouds the issue of which patients might experience problems if switched to a generic formulation. "We don't have any data at all on the similar comparison of using a generic antiepileptic for migraine as opposed to a nongeneric," said Dr. Black, who is also the medical director of neurology and codirector of the Neuroscience Center at Baylor University Medical Center, Dallas.

However, migraine patients have less at stake in the case of a negative outcome, he said. "The consequences of a poor response would be a migraine as opposed to a grand mal seizure. I would personally recommend prescribing brand name AEDs for a patient with a history of epilepsy. In treating patients with migraine, I would inform the patient of the pros and cons of generic versus brand name and include the patient in the decision making process," said Dr. Black, who said that he has no relevant conflicts of interest.

Migraine patients on antiepileptics have less at stake than epilepsy patients in case of a negative outcome.

DR. BLACK

American Epilepsy Society recommends that generic AEDs should not be substituted for a brand formulation without both physician and patient approval.

The FDA has approved generic topiramate formulations from 17 different companies. Each company has had to show that its formulation is bioequivalent to the original, said Barbara Davit, FDA's acting director of the Division of Bioequivalence 2 in the Office of Generic Drugs. The testing, usually performed in about 40 healthy adult subjects, addresses the new formulations' maximum plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC). Both measurements must be within 20% of the original formula; 90% of all the study's pharmacokinetic ratios of generic to brand name compound must fall within the 80%-125% range, she said.

This doesn't mean, however, that the generic drugs' bioequivalence can vary up to 45% from the reference compound. Instead, the ratio is going to be much lower. "We have shown repeatedly that because we are looking at the confidence interval, and not the mean ratio, it forces the reference ratio to be close to 1," she said in an interview.

In a 2008 review Dr. Privitera wrote on the topic and quoted two FDA reviews of bioequivalence studies, one in 1987 and one in 1997. The papers concluded that the mean difference between the original and generic compounds was 3.5%-4.0% for C_{max} and AUC. That difference may be enough to initiate breakthrough seizures or increased adverse events in sensitive patients, he said, especially if the patient is switching between generics—a distinct possibility. Because pharmacies buy large lots of the least expensive generic, patients aren't assured of getting the same generic with each refill. "You might get a medication one month that's stronger than what you get the next month," he said.

The FDA asserts that there is no conclusive evidence showing that any patient has experienced a lack of seizure control or increased side effects from an AED switch. "That's probably true because if someone has a problem, the doctor is not going to do a full pharmacokinetic study on that one patient. So there is no way of absolutely proving the problem," Dr. Privitera said.

However, reports of such problems do occur in the literature, he said. "More than 60% of physicians in a 2004 survey believed that they have seen patients experience toxicity or breakthrough seizures with a change to generic" (Epilepsy Behav. 2004;5:995-8).

In his review article (Epilepsy Curr. 2008;8:113-7), Dr. Privitera cited several other studies, including case reports, physician surveys, and a study examining switchback rates after the Canadian Health System approved a number of generic drugs. Among 1,354 patients who took generic lamotrigine, 13% switched back to the brand formulation; the switchback rate for other antiepileptics in the study (clobazam and valproate) approached 20% (Epilepsia 2007;48:464-9). Other studies document increased side effects from generic AEDs.

There are no studies that show epilepsy patients will do well within the FDA's bioequivalence range.

DR. PRIVITERA

Although none of these studies examined topiramate, they show that while generic formulations may fulfill the FDA's bioequivalence requirements, they may not be therapeutically equivalent to the original formulation, Dr. Privitera said.

He and other epilepsy experts are working on the protocol for a controlled trial of patients who have been taking the drugs, which he predicts will include about 50 patients for each AED that has a generic equivalent. "We have a contract with the National Institutes of Health to identify people who have problems with these generic formulations and do a rigorous pharmacokinetic study to see if their levels fall within those FDA goal posts," he said.

The results might lead the FDA to reconsider its requirements for generic AEDs, but might also bolster the use of generics in epilepsy treatment. "A lot of people who might be appropriate candidates for them are not getting them because we don't understand who is and is not at risk when a switch is made." ■

TALK BACK

How have your experiences with the bioequivalence of generic and brand name antiepileptic drugs influenced your prescribing habits for epilepsy patients?

Share your thoughts!
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Lower IQs Seen in Toddlers Exposed to Valproate In Utero

BY MICHELE G. SULLIVAN

Children exposed to valproate in utero have significantly lower IQs at age 3 years than do children exposed to other antiepileptics during gestation, according to findings from the interim analysis of a large international study.

The drug previously had been associated with a higher rate of birth defects in children exposed prenatally. The combination of findings strengthens a recommendation to avoid valproate as a first-line antiepileptic in women who may bear children, Dr. Kimford J. Meador said in an interview.

"Valproate poses a special risk for both congenital malformations and for cognitive impairment," said Dr. Meador, principal investigator on the Neurodevelopmental Effects of Antiepileptics Drugs (NEAD) study. "Since there are other therapeutic options, it would seem prudent to try those first. At a minimum, it is critical that physicians inform women of this risk when prescribing valproate so that they may make an informed choice."

NEAD is an ongoing study of 309 children, including three sets of twins, born in either the United States or the United Kingdom from 1999 to 2004, whose mothers were taking a single antiepileptic drug (AED): carbamazepine, lamotrigine, phenytoin, or valproate. The children are being followed to age 6. Dr. Meador, professor neurology of Emory University, Atlanta, and his associates reported a planned 3-year interim analysis in the New England Journal of Medicine (2009; 360:1597-605).

All of the 303 women in the study were taking the drugs for a seizure disorder. Their mean age at delivery was 30 years. Most of the women were well controlled on their AED, with about 80% having no seizures during their pregnancy.

Most of the children in the study (258) underwent cognitive assessment at either 2 or 3 years of age, or at both ages. Of these, 73 (28%) had been exposed to carbamazepine, 84 (32%) to lamotrigine, 48 (19%) to phenytoin, and 53 (21%) to valproate.

IQ scores were adjusted for factors that could significantly affect cognitive development.

Children exposed to valproate had a mean IQ of 92, the lowest any of the exposure groups and significantly lower than those of any other treatment group. The mean IQ in those exposed to carbamazepine was 98; to lamotrigine, 101; and to phenytoin, 99.

In this analysis, only valproate maintained a significant dose-response relationship. In addition, higher maternal IQs were associated with higher child IQs in all of the treatment groups except valproate.

The results are consistent with several European studies that have found poor cognitive outcomes in children exposed to the drug prenatally, the investigators said.

The findings of both physical and cognitive problems with prenatal exposure show that the drug probably is not safe for use at any time during pregnancy, said Dr. Michael Privitera, director of the Cincinnati Epilepsy Center and another of the NEAD investigators.

"The neural tube defects [with which valproate is associated] occur during the first trimester, so there has been a question whether we might be able to use valproate later in pregnancy. This study shows that the answer is no, because cognitive development in the fetus occurs during the third trimester," Dr. Privitera said in an interview.

"For some patients, valproate is the only medication that adequately controls seizures," Dr. Meador and his colleagues wrote. "Such women should be informed of the potential risks associated with the use of this medication in pregnancy. If a woman taking valproate is already pregnant, it's critical that she not stop valproate without consultation with her physician."

The risk of adverse fetal outcomes holds true for any woman who takes the drug during pregnancy, regardless of the indication, Dr. Meador said in the interview. "One other important point is that less than half of the prescriptions for valproate are for seizures or epilepsy. The majority are for pain or psychiatric indications." ■