Bioequivalent But Still Variable

Antiepileptic *from page 1*

AED blood concentrations when switching from a brand name to a generic formulation.

After several years of sending Freedom of Information Act data requests to the Food and Drug Administration, Dr. Krauss and his associates at Johns Hopkins were eventually able to collaborate on the study with officials at the agency.

The FDA defines a test product to be bioequivalent to a reference product when the 90% confidence intervals for test-to-reference ratios of the area under the plasma concentration time curve (AUC) and the maximum plasma concentration (C_{max}) are within an acceptance range of 80% to 125%. AUC measures how much drug is absorbed in a given time, whereas C_{max} measures the maximum plasma concentration of a drug.

The investigators examined 147 AED formulations, excluding extended-release products, in 251 bioequivalence studies. All 7,125 healthy volunteers in these studies were adults (mean age, 32 years; 79% male) but only 44 were older than 65 years. The participants were tested in a fasting state.

The race and ethnicity of the volunteers in the studies largely reflected where the formulations were tested. Overall, 54% of the participants were white, 26% were Asian, 10% were black, 3% were Hispanic, and 7% were other race/ethnicity. Enrollment included only men in 42% of the studies and only Asians in 21%.

In 99% of the studies, the AUC for both reference and generic formulations varied by less than 15%. In comparison, 89% of C_{max} studies found that measurements between reference and generic formulations varied by less than 15%. The remaining bioequivalence studies evaluated formulations with AUC and C_{max} measurements that varied 15%-25%.

Some generic AEDs had confidence intervals for AUC or C_{max} ratios that were much less or much greater than a ratio of 1, meaning that for some switches one would expect slightly lower blood concentrations of the active ingredient and for other switches one would expect slightly higher blood concentrations.

But when a switch is made from a generic formulation of a drug with a confidence interval completely below 1 to a generic formulation with a confidence interval completely above 1, Dr. Krauss noted that there is likely to be a bigger change in blood concentration than with brand name to generic switches.

In studies of the AUC for carbamazepine, 64% of the generic formulations were within 0%-5% of the reference product, 27% were within 5%-10%, and 9% were within 10%-15%.

Relatively soluble drugs, such as levetiracetam, generally had closer matches in AUC between generic and reference products, whereas for less soluble drugs, such as oxcarbazepine, there was greater variability between generic and reference formulations.

The investigators found generally greater differences in C_{max} between generic and reference formulations than they did for AUC. One of the greatest differences in C_{max} was found in carbamazepine formulations. For instance, only 9% of generic formulations of carbamazepine were within 5% of the reference product, whereas 64% of formulations were within 5%-10% of the reference, 18% were within 10%-15%, and 9% were within 15%-25%.

Even though all of the drugs were within the accepted range for bioequivalence, the C_{max} confidence intervals for some generic and reference formulations of less soluble drugs did not overlap—and thus resulted in significantly different blood concentrations. One exception to this pattern was oxcarbazepine, whose brand name and generic formulations had broad and overlapping confidence intervals in C_{max} but were statistically similar even though they had wide variability in absorption.

Reference drugs did not provide more stable delivery of active ingredients to individuals, compared with generic formulations. The standard deviations between the generic formulations and a reference drug were nearly identical for most drugs.

AUC and C_{max} measurements varied by about 20% across subjects in each of these studies, and "so with this small difference in standard deviations and this relatively small range of changes across subjects, it seems unlikely that initiating treatment with a generic formulation would cause problems in terms of giving you an unpredictable blood level," he said.

Simulations of 595 possible generic to generic switches estimated large changes in AUC and C_{max} for many pair switches, particularly for oxcarbazepine. Many products were estimated to have shifts of greater than 15% in AUC and C_{max}. Although many of the findings from these estimates may be spurious because of large confidence intervals and multiple comparisons, "the overall trend is quite strong," Dr. Krauss said.

Dr. Krauss said neither he nor any of his colleagues had relevant disclosures to report. ∎

At-Risk Population Was Not Studied

MY TAKE

The data presented by Dr. Krauss give us a deeper understanding of the variability among generic AED products. It is important to note that this study is based on data generated from people who will never take an AED. These normal subjects received only a single dose of the drug and were not taking any concomitant medications. There are large potential differences between this population and patients with epilepsy who are taking two or three other AEDs or non-AEDs and who might be older and taking the AED daily for many years. Those are the people in whom I'm most concerned about therapeutic equivalence.

There may be subsets of individuals who are at increased risk for seizures with small changes in bioequivalence, such as those who have had life-threatening status epilepticus in the past, pregnant women, people with epilepsy who have been seizure free for many years, and people with other serious medical conditions.

We don't really know what percentage change in AUC or C_{max} between products is actually safe—that is, which ranges of bioequivalence translate to therapeutic equivalence and which do not. In his study, Dr. Krauss is suggesting that certain ranges of difference between products should be safe and others perhaps not so safe. Unfortunately, we have no data to support that inference. There are no data providing evidence that 90% confidence intervals in the 80%-125% range, which are the current FDA standard, translate to therapeutic equivalence. The FDA created this range based on expert opinion.

A recent advisory committee convened by the FDA indicated that the range for generic AED confidence intervals may not be optimal for patients with epilepsy, but the committee did not agree upon any specific recommendations.

The FDA states that all brand name–to-generic or generic-to-generic switches are safe for all people with epilepsy. I believe the only way to test this is to perform a prospective, randomized study of people with epilepsy like the one that our group of expert investigators has proposed to the FDA and the NIH.

MICHAEL PRIVITERA, M.D., *is a professor of neurology at the University of Cincinnati and is director of the Cincinnati Epilepsy Center. In the past year, he has received research funding and honoraria for speaking or consulting from UCB, Johnson & Johnson, Pfizer, Eisai, the National Institutes of Health, and the American Epilepsy Society. His comments derive from an interview.*

FDA Panel Votes on Safety, Efficacy of Infantile Spasms Drug

BY ELIZABETH MECHCATIE

ADELPHI, MD. — The majority of a Food and Drug Administration advisory panel agreed that the data on H.P. Acthar gel, an injectable formulation of adrenocorticotropin hormone, provided sufficient evidence that it was a safe and effective treatment for infantile spasms.

In early May, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee panel voted 22 to 1 that the data on Acthar provided "substantial" evidence that it was an effective treatment of infantile spasms (IS). The panel also voted 20 to 1, with 2 abstentions, that the manufacturer, Questcor Pharmaceuticals Inc., had provided enough evidence that Acthar was safe at a dosing regimen that was considered effective. However, they noted that there were significant risks associated with treatment and that some re-

maining issues about the treatment needed further study, including whether dosing regimens other than the one proposed by the company should be investigated. The panel was not specifically asked to vote on whether to recommend approval for the IS indication.

If approved, Acthar (repository corticotropin injection) would join vigabatrin (Sabril) as the second FDA-approved treatment for IS, a severe, rare form of epilepsy that affects about 2,000 children in the United States every year, usually appearing at age 3-7 months. Acthar has been used off-label to treat IS since the late 1950s and is recognized as a treatment for IS by the American Academy of Neurology. Prednisone is also used off-label to treat IS.

Questcor reanalyzed data from three published randomized controlled studies, using the end points of complete cessation of spasms and resolution of hypsarrhythmia on a prolonged video EEG (overall re-

sponse) to evaluate the efficacy of Acthar at a dosage regimen of 150 U/m², divided into two daily injections of 75 U/m² for 2 weeks, then tapered gradually over 2 weeks.

In the primary study, published in 1996, 13 of the 15 (87%) infants treated with Acthar had an overall response, compared with 4 of the 14 (29%) treated with prednisone (2 mg/kg per day in two divided doses), a significant difference.

The panel recommended making it clear to clinicians that the main study was small and that patients treated should be closely monitored for adverse effects of treatment, particularly adrenal insufficiency. The company also should analyze the relapse rate in patients who respond to treatment, for which there are scant data.

The FDA usually follows the recommendations of its advisory panels. One panelist with a conflict of interest was granted a waiver by the FDA. ∎