Separate, Not Equal?

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responded differently when a generic formulation was substituted for a brand name formulation.

"In my practice, [formulation switching] has a tremendous impact. We now regularly ask patients who have a breakthrough seizure when they last filled their prescription" to check whether substitution occurred, he added.

FDA representatives have said the agency will not change its existing policy on how it assesses the bioequivalence of drug formulations for all indications, including epilepsy, based on anecdotal reports like these, Dr. Privitera said. As a result, officials of the American Epilepsy Society have decided to sponsor a study aimed at testing the hypothesis that existing bioequivalence standards are inadequate for antiepileptic drugs.

"The AES is in discussions with the FDA to design a study that, if positive, will change the FDA's policy," he said at the press conference. Until results are available, it's important that pharmacists do not switch the formulation of an epilepsy patient's drug without first alerting the patient and the prescribing physician, he added.

"We just don't know if the FDA's bioequivalence regulations are correct. Some anecdotal evidence suggests that different formulations are not equivalent," said Dr. Michael Berg, director of the epilepsy center at Strong Memorial Hospital in Rochester, N.Y. "For most drugs and diseases, a range [of bioequivalence] doesn't matter, but we think it might matter for epilepsy and that's why a study is important."

Last April, the American Academy of Neurology issued a statement that criticized the practice of generic substitution of epilepsy drugs. The academy called on pharmacists to alert patients and prescribing physicians when generic substitutions occur (Neurology 2007;68:1249-50).

The FDA's standard for bioequivalence is that the 90% confidence interval for three key pharmacokinetic measures of the generic drug falls between 80% and 125% of the values for the brand formulation, said Barry E. Gidal, Pharm.D., in a talk at the meeting. "While statistically valid, does this really answer the important clinical question?" asked Dr. Gidal.

"Bioequivalence studies are performed in young, healthy adults. Can these data always be generalized to young children or elderly patients?" asked Dr. Gidal, professor of pharmacy and neurology at the University of Wisconsin, Madison.

Additional problems have been uncovered for specific antiepileptic drugs. Generic formulations of carbamazepine have shown substantial differences, he said. In addition, methods for testing bioequivalence are probably flawed for assessing a "nonlinear" drug like phenytoin.

Dr. Gidal also cited data reported in 2007 by Canadian researchers on the rates at which patients switched from a generic to a brand formulation, a step that was presumably triggered by problems with the generic drug. Switching rates were high, about 20%, for patients on antiepileptic drugs such as valproic acid (Depakene) and clobazam (Frisium), while the switch rates were much lower, about 2%, for drugs for other disorders—drugs such as fluoxetine (Prozac) and simvastatin (Zocor).

"Therapeutic equivalence and biopharmaceutical equivalence are not necessarily equivalent terms," Dr. Gidal said. "The overwhelming opinion is that generic substitution is a problem with the potential for breakthrough seizures or adverse events."

A different take was presented in another talk by Dr. Torbjörn Tomson, a neurologist at the Karolinska Institute in Stockholm. He cited a 2006 report in which FDA researchers failed to document any cases of therapeutic failure following substitution with an FDA-designated, therapeutically equivalent generic drug. He also cited a 1997 report that failed to find a difference among tested brand and generic formulations of antiepileptic drugs.

Dr. Tomson thinks it makes sense to start newly diagnosed patients on a generic formulation when it's available, and to use generics when a patient is not fully controlled. It did not make sense to do a generic switch on a patient who is fully controlled on a stable regimen, he said. ■

Carisbamate Shows Antiepileptic Efficacy; Phase III Studies Planned

BY MITCHEL L. ZOLER
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PHILADELPHIA — Carisbamate, a new antiepileptic drug, showed safety and efficacy in a phase II study with more than 500 patients.

Carisbamate's ability to cut seizure frequency and boost the response rate, compared with placebo, was notable because the study involved very refractory patients with a history of numerous partial seizures at entry, despite ongoing treatment with as many as three antiepileptic drugs, said Dr. R. Edward Faught Jr. in a poster presentation at the annual meeting of the American Epilepsy Society.

Carisbamate will be assessed in a phase III study for preventing seizures in patients with epilepsy. The drug is also undergoing testing in additional phase III studies in patients with diabetic peripheral neuropathy, essential tremor, and postherpetic neuralgia. The drug's mechanisms of action for all of these indications are not known.

The phase II seizure study enrolled patients aged 8-70 years who had been diagnosed with epilepsy for at least 1 year, had an established pattern of at least three partial-onset seizures per month, and had failed treatment with at least three drugs. At enrollment, patients had to be on treatment with one to three antiepileptic drugs at stable dosages for at least 4 weeks.

The patients who actually entered the study had a history of epilepsy for an average of 19-25 years, and experienced an average of 9-11 seizures per month. About 15% were treated with antiepileptic monotherapy, about 50% were on two drugs, and about 35% were on three drugs. Nearly half of the patients had been treated with seven or more different antiepileptic drugs during the course of their illness.

About 100 patients were randomized to receive each of four carisbamate regimens or placebo, with a total enrollment of 537 patients. The carisbamate dosages tested were 100 mg, 300 mg, 800 mg, and 1,600 mg per day.

Following a baseline observation phase of 4 weeks, patients underwent a dose-escalation phase of 4 weeks until they reached their target dosage. They remained on a stable dose for 12 weeks, when their response rate was assessed.

The three highest carisbamate dosages all led to significant reductions in seizure frequency, versus placebo. The reductions in these groups were 21%-29%, compared with a 6% drop in seizure frequency in the placebo patients, reported Dr. Faught, director of the epilepsy center at the University of Alabama, Birmingham. Patients in the 100 mg/day group had an average 15% cut in seizure frequency, but this was not significantly different from the placebo group.

The percentage of responding patients (those with at least a 50% decrease in their seizure rate) was 24% in the 300 mg/day group and 25% in the 1,600 mg/day group. Both rates of lessening seizure frequency were significantly higher than the 10% rate among placebo patients. The prevalence of responders was 12% in the 100 mg/day group and 19% in the 800 mg/day group; neither was significantly higher than that of placebo.

The incidence of adverse events was similar to placebo in the three lowest carisbamate dosage groups. Patients on the 1,600 mg/day dosage had significantly more adverse events, compared with placebo patients. The most frequent adverse events were headache, somnolence, nasopharyngitis, and nausea. Adverse events led to study discontinuation in 8% of the placebo patients, and in 5%-12% of patients in the three lowest-dosage carisbamate groups. (The discontinuation rate was 19% in the highest-dosage group.) The rate of serious adverse events was similar in the placebo and carisbamate groups. Clinically significant elevation of liver enzymes (at least three times the upper limit of normal) occurred in one patient on the 800 mg/day dosage and in three patients on the 1,600 mg/day dosage; enzyme levels normalized in all four patients once treatment stopped.

A 300 mg/day dosage of carisbamate appears optimal. The study was sponsored by Johnson & Johnson, which is developing the drug. Dr. Faught has received research support and honoraria from Johnson & Johnson. ■

Generic Substitution Boosts Total Cost of Epilepsy Care

BY MITCHEL L. ZOLER
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PHILADELPHIA — Generic substitutions were linked with significantly increased medical care cost and total health care cost in a retrospective study of more than 600 epilepsy patients.

Even though a year's worth of treatment with the brand-name drug Lamictal costs an average of about $360 (Canadian dollars) more than a year's worth of generic lamotrigine, this excess was more than offset by an average 56% increased cost for in-patient hospitalization among those on the generic, as well as increased costs for drugs that were not antiepileptics.

Total health care costs averaged $1,482 (Canadian dollars)/patient-year higher in patients treated with generic lamotrigine, compared with those on Lamictal, a 23% relative increase that was statistically significant, Dr. Jacques LeLorier and his associates reported in a poster at the annual meeting of the American Epilepsy Society.

The study was sponsored by GlaxoSmithKline, which markets Lamictal. Dr. LeLorier has received consultation fees and research support from GlaxoSmithKline.

The study used data obtained by the medical and pharmacy health claims filed with the Quebec provincial health plan during April 1998–July 2006. Patients treated with any one of four different antiepileptic drugs switched from the generic to brand formulation at rates that ranged from 21% (for carbamazepine) to 44% (for clobazam). The switch rate for lamotrigine to Lamictal was 28%. In contrast, the switch rate for drugs for other disorders, such as the β-blocker carvedilol and the lipid drug simvastatin, ranged from 8% to 9%, reported Dr. LeLorier, a professor of medicine and pharmacology at the University of Montreal. Overall, patients treated with a generic antiepileptic drug were about 2.5-fold more likely to switch to a brand formulation than were patients who had other disorders.

A follow-up analysis in a second poster at the meeting attempted to convert the observed economic effects seen in Quebec into equivalent costs in the United States. Two different conversion formulas were used; each formula took into account economic factors that differed between the United States and Canada during the study period, including currency exchange rates, purchasing power, and medication and health care costs.

The extrapolation to U.S. costs showed a much larger cost difference between generic lamotrigine and Lamictal. In one cost-conversion model this difference meant that treatment with Lamictal cost an extra $1,175 (U.S. dollars) more than generic lamotrigine per patient-year. The second model calculated an excess cost for Lamictal of $1,926 (U.S. dollars) per patient-year, reported Mei Sheng Duh, Sc.D., an epidemiologist at the Analysis Group in Boston.

But despite the higher drug cost, patients treated with Lamictal could expect to save a net of $693 (U.S. dollars) per patient-year, based on one conversion formula used, or $787 (U.S. dollars) per patient-year according to the second formula. ■