Drug Interaction Complicates Lipid Lowering

BY BRUCE JANCIN
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BRECKENRIDGE, COLO. — Carbamazepine and certain other older antiepileptic drugs accelerate hepatic metabolism of statins to such a degree that either their joint use should be avoided or the statin dose must be increased to often impractical levels, Jose E. Cavazos, M.D., said at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

This was the key conclusion of a recent pharmacokinetic study by investigators at Varnamo (Sweden) Hospital.

"This is a study that has really changed my practice," commented Dr. Cavazos of the university's South Texas Comprehensive Epilepsy Center. One implication of the Swedish study is that it makes a great deal of sense for many statin users requiring antiepileptic drug (AED) therapy to turn to one of the newer AEDs that don't induce liver enzymes.

Intrigued by case reports of unexpectedly low serum levels of simvastatin in patients on selected AEDs, investigators decided to study the phenomenon in a randomized two-phase crossover study. They put 12 healthy volunteers on carbamazepine at 600 mg/day or no drug for 2 weeks. On day 15 everyone took 80 mg of simvastatin (Zocor). After a 2-week washout period, participants switched to the opposite study arm and repeated the protocol.

The central study finding was that carbamazepine resulted in a 75% reduction in the mean total area under the 24-hour serum concentration-time curve of simvastatin. The reduction for simvastatin acid, the drug's active metabolite, was 82%.

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Mean peak concentrations of both simvastatin and simvastatin acid were decreased by 68%. The half-life of simvastatin fell from a mean of 5.9 hours on placebo to 3.7 hours with carbamazepine (Eur. J. Clin. Pharmacol. 2004;59:879-82).

What this means is that a patient whose hyperlipidemia would ordinarily warrant 20 mg/day of simvastatin will require 80 mg/day to achieve comparable serum levels if carbamazepine is on board. And to achieve the equivalent of 40 mg/day of simvastatin—a common dosage for secondary cardiovascular prevention—a patient would actually need to take considerably more than the approved maximum dose.

This drug interaction is a class effect that also applies to the other statins, since they too undergo hepatic metabolism.

The phenomenon has also been shown to occur with phenytoin and phenobarbital, which, like carbamazepine, are older, less expensive antiepileptic drugs—as well as potent inducers of liver enzymes, Dr. Cavazos explained.

"If you think that you're going to save some money by prescribing an older antiepileptic over one of the newer ones, that may be an ill-advised strategy in statin users because of these [drug] interactions," he said.

One newer AED that induces liver enzymes, albeit to a lesser degree than carbamazepine, is oxcarbazepine (Trileptal).

The extent to which oxcarbazepine alters hepatic metabolism of statins is unclear. ■

Simvastatin, Pravastatin May Also Lower Blood Pressure

BY MITCHEL L. ZOLER
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NEW ORLEANS — Treatment with either simvastatin or pravastatin led to significant reductions of both systolic and diastolic blood pressure that averaged about 2.5 mm Hg in a controlled study with 1,016 patients, Beatrice A. Golomb, M.D., reported at the annual scientific sessions of the American Heart Association.

"Some patients who are on the cusp of having hypertension and are not on antihypertensive therapy may benefit from the statin effect," which may help them continue to avoid needing a blood pressure–lowering drug, said Dr. Golomb, a cardiologist at the University of California, San Diego. This modest degree of blood pressure reduction may explain the ability of statin therapy to cut the risk of stroke, a finding that has been hard to attribute to lipid-lowering effects.

The study enrolled men and postmenopausal women who did not have heart disease, diabetes, or hypertension, and whose LDL-cholesterol level was 115-190 mg/dL. These people were randomized to treatment with 20 mg/day simvastatin, 40 mg/day pravastatin, or placebo, and treatment continued for 6 months.

After 6 months of treatment, systolic BP had fallen by an average of 2.8 mm Hg in the simvastatin group and by 2.5 mm Hg in the pravastatin group, compared with baseline. Diastolic pressures had dropped by an average of 2.7 mm Hg and 2.5 mm Hg, compared with baseline in the simvastatin and pravastatin groups, respectively. Once patients were off statin treatment for 2 months, these BP reductions largely disappeared.

The results of a second study presented at the meeting suggested that the blood pressure–lowering effect of a statin is independent of the drug's lipid-lowering effect. This analysis used data collected from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).

One part of the study randomized a 10,305-patient subgroup to treatment with either 10 mg of atorvastatin daily or placebo. BPs recorded in this subset were evaluated in a post hoc analysis to explore whether atorvastatin had any effect.

Although all patients in the study were on combined regimens of antihypertensive drugs, those who also received atorvastatin had small but consistently lower systolic and diastolic BPs than the patients who did not receive statin therapy, reported Bjorn Dahlof, M.D., professor of medicine at the University of Göteborg (Sweden).

The 5,168 patients treated with atorvastatin had an average systolic pressure that was about 1 mm Hg lower than that among 5,137 patients treated with placebo at several times during 3 years of follow-up. Diastolic BP averaged about 0.6 mm Hg lower in the atorvastatin group, compared with those on placebo. ■