Simvastatin, Pravastatin May Lower Blood Pressure

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW ORLEANS — Statins produce a small but significant blood pressure reduction that might explain some of the benefits that these drugs provide.

Treatment with either simvastatin or pravastatin led to significant reductions of both systolic and diastolic BP 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.

The modest BP reduction (2.5 mm Hg) may explain the ability of statin therapy to cut the risk of stroke, a finding hard to attribute to its lipid-lowering effects.

"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 BP 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). This study enrolled more than 19,000 patients with hypertension but without known coronary artery disease to an intervention trial that was primarily designed to compare the effects of different antihypertensive regimens. The study also randomized a 10,305-patient subgroup to treatment with either 10 mg of atorvastatin daily or placebo. The blood pressures recorded in this subset were evaluated in a posthoc analysis to explore whether atorvastatin had any effect on blood pressure.

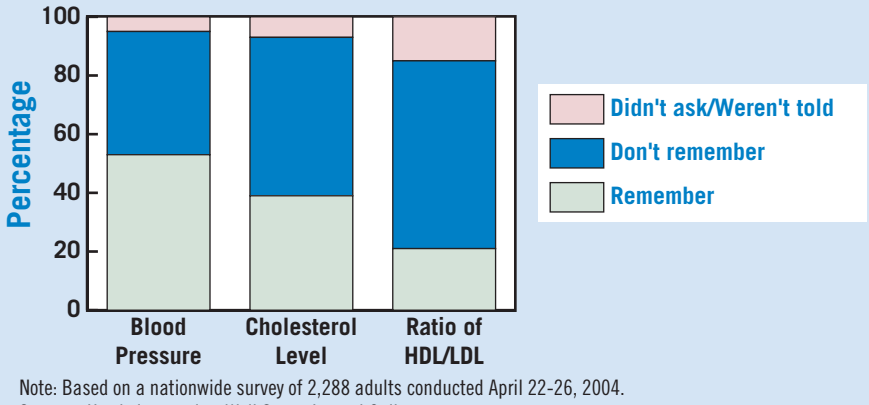
Although all patients in the study were on combined regimens of antihypertensive drugs, those who also received atorvastatin had small but consistently lower systolic and diastolic BPs than the patients who did not receive statin therapy, reported Bjorn Dahlof, M.D., professor of medicine at the University 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. Although these differences in pressure were very small, they were statistically significant because the study involved so many people, Dr. Dahlof said.

A further analysis was then done to see if there was a correlation between the blood pressure–lowering effect of atorvastatin and patients' levels of total or LDL cholesterol. This assessment showed virtually no link between the two effects. Lipid lowering "explained perhaps 1%" of the effect of atorvastatin on blood pressure, Dr. Dahlof reported.

Statins probably have other effects that lower blood pressure, such as activating nitric oxide synthetase, down-regulating angiotensin II, and enhancing flow-mediated vasodilation, Dr. Golomb said. ■

DATA WATCH

Many Americans Don't Remember Results of BP, Cholesterol Tests



Note: Based on a nationwide survey of 2,288 adults conducted April 22-26, 2004.
Sources: Harris Interactive, Wall Street Journal Online

KEVIN FOLEY, RESEARCH/ANGIE RIES, DESIGN

When Bosentan Treatment Fails, Sitaxsentan May Help

BY NANCY WALSH
New York Bureau

SAN ANTONIO — Pulmonary arterial hypertension patients treated with bosentan whose condition deteriorates or who can't tolerate the drug may respond to a related medicine, sitaxsentan, a preliminary study suggests.

Like bosentan, sitaxsentan is an endothelin receptor antagonist, but it is much more selective for endothelin A. Bosentan blocks the activity of both endothelin A and endothelin B.

Endothelin is a potent endogenous peptide with vasoconstricting, mitogenic, and profibrotic effects. It appears to play a role in the pathology of pulmonary arterial hypertension associated with connective tissue disease.

"Although the relative importance of endothelin A versus endothelin B in pulmonary arterial hypertension remains unclear, selective antagonism of endothelin A may be advantageous in blocking the deleterious endothelin A vasoconstriction in the pulmonary vasculature while maintaining the vasodilator and clearance functions of the endothelin B receptor," Adaani Frost, M.D., said in a poster session at the annual meeting of the American College of Rheumatology.

Although bosentan (Tracleer) has proven beneficial in this condition, many patients develop liver function abnormalities during treatment. Bosentan is metabolized by the liver, and the elevations in liver enzymes are thought to relate to an accumulation of bile salts. Sitaxsentan undergoes both hepatic and renal metabolism, and has no effect on bile salts or bilirubin, Dr. Frost explained.

In an effort to determine if the selective endothelin antagonist would provide an effective alternative to bosentan, 11 patients were enrolled in an open-label study. Of these, three had developed liver function abnormalities, and eight experienced clinical deterioration during bosentan treatment.One patient who was New York Heart Association functional class IV at study entry died after 5 weeks of treatment with sitaxsentan and was not included in the analysis.

The remaining 10 have now been followed for 12 weeks. The mean improvement in 6-minute walk time with sitaxsentan was 36.5 meters. Although the condition of four patients improved, five stabilized, and one's condition deteriorated, said Dr. Frost, professor of medicine, Baylor College of Medicine, Houston.

None of the patients who experienced liver function abnormalities on bosentan did so on sitaxsentan. One patient whose condition had deteriorated clinically experienced transient liver function abnormalities that resolved spontaneously and did not require cessation of the drug.

Ongoing studies should provide further information on using sitaxsentan in this population, Dr. Frost said.

The study was undertaken with a research grant from Encysive Pharmaceuticals, Bellaire, Tex. ■

Inhaled Iloprost Approved for Pulmonary Arterial Hypertension

The Food and Drug Administration approved the first inhaled therapy for pulmonary arterial hypertension in December.

Iloprost, a stable synthetic analogue of prostacyclin, causes selective pulmonary vasodilation, improving exercise capacity and hemodynamics in patients with PAH.

The drug is a strong vasodilator and inhibitor of platelet aggregation. The inhalation formulation (Ventavis Inhalant Solution) was developed to replace continuous infusion prostacyclin, which was the first therapy shown to reduce mortality in patients with severe pulmonary hypertension. In nature, prostacyclin is a local hormone; intravenous introduction can result in systemic side effects and progressive tolerance, requiring more and more of the drug.

The randomized clinical trial reported for approval was conducted on 203 adult patients with PAH; 101 received inhaled iloprost, and 102 received placebo. The response rate in the iloprost group (6-9 inhalations per day) was 19%, compared with 4% for the placebo group. The response rate was determined using a primary composite end point that incorporated improvement in exercise capacity, improvement in at least one New York Heart Association PAH class, and no death or deterioration. Adverse responses with iloprost included flushing, cough, jaw pain, and headache.

Iloprost is dispensed in single-use glass ampules (2 mL) containing 20 mcg iloprost for inhalation via the Prodose Adaptive Aerosol Delivery system. Labeling indicated that iloprost should not be inhaled more than once every 2 hours, and the drug is not effective while a patient is sleeping. Vital signs should be monitored when initiating iloprost because of the risk of syncope.

Iloprost, though not yet commercially available in the United States, will be marketed by CoTherix Inc. as the Ventavis Inhalant Solution under exclusive contract with Schering AG, which markets the drug in Europe and Australia. CoTherix had previously received orphan drug designation for iloprost from the FDA in August 2004.

Clinical trials are underway in the United States to examine its interaction with other drug treatments for PAH, as well as for its potential as a preventive agent for lung cancer in heavy smokers.

—Mark S. Lesney