ASCOT at Odds With JNC Recommendations

BY BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — Combination antihypertensive therapy with a calcium channel blocker and angiotensin-converting enzyme inhibitor provides important clinical outcome advantages over the traditional β-blocker/diuretic combination, Peter S. Sever, Ph.D., said at the annual meeting of the American College of Cardiology.

He reported on 19,257 hypertensive patients free of coronary heart disease (CHD) who participated in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure-Lowering Arm (ASCOT-BPLA) who were randomized to amlodipine/perindopril or atenolol/bendroflumethiazide. The study was halted early, after a mean 5.4 years, due to a highly significant 14% relative risk reduction in all-cause mortality favoring the amlodipine/perindopril group.

Preliminary ASCOT results indicate that at the 5-year mark a total of 1,178 cardiovascular events and procedures had occurred in the amlodipine/perindopril group, compared with 1,376 in the atenolol/bendroflumethiazide arm, said Dr. Sever, professor of clinical pharmacology and therapeutics at Imperial College, London.

Other significant differences in end points—all favoring the calcium channel blocker/ACE inhibitor combination—included:

► A 32% reduction in new-onset diabetes.

► A 23% decrease in the incidence of fatal and nonfatal stroke.

► A 24% reduction in cardiovascular mortality.

► More favorable HDL and triglyceride levels.

Blood pressures were an average of 2.9/1.8 mm Hg lower in the amlodipine/perindopril group. But that's sufficient to account for only part of the observed benefit, according to Dr. Sever. Additional possible explanations include a suspected adverse interaction between atenolol/bendroflumethiazide and statin therapy, and more effective inhibition of the renin-angiotensin system by amlodipine/perindopril.

All study end points favored combined use of a calcium channel blocker and an ACE inhibitor.

DR. SEVER

ASCOT raises serious questions about the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure VII guidelines recommending thiazide diuretics and β-blockers as initial treatment.

Discussant Richard Devereux, M.D., professor of medicine at Cornell University in New York, noted that the traditional β-blocker/diuretic combination was certainly not placebo therapy. These drugs are of long-established benefit in treating hypertension. But the calcium channel blocker/ACE inhibitor combination was superior.

Dr. Sever is a consultant to Pfizer Inc. and the Servier Research Group, the study's major sponsors. ■

Nicardipine Seen Safe for Use In Hypertensive Emergencies

BY JANE SALODOF MACNEIL
Contributing Writer

PHOENIX, ARIZ. — Intravenous nicardipine can reduce blood pressure by 15%-20% without impairing blood supply to the brain in hypertensive emergencies, preliminary results from an ongoing case-control study suggest.

Results so far suggest nicardipine therapy might even improve cerebral oxygenation ($PbrO_2$) in ischemic patients, reported study investigator Varun Puri, M.D. "There was no reduction in oxygen delivery to the brain despite significant reduction in [the fraction of inspired oxygen]," he said at a meeting sponsored by the Society of Critical Care Medicine.

Dr. Puri presented data on 17 patients with acute neurologic disorders, 11 of whom were women. The patients' average age was 57 years, and pathologies included seven subarachnoid hemorrhages, four traumatic brain injuries, three intracerebral hemorrhages, two arteriovenous malformations, and one case of anoxia.

The patients had 36 episodes of hypertensive emergency during the study: 11 from acute cardiovascular syndrome, 14 postoperatively, and 11 after trauma. The nicardipine dose, titrated as clinically indicated to lower blood pressure, ranged from 2.5 mg to 15 mg per hour. The duration of treatment ranged from 12 hours to 10 days.

Dr. Puri reported that systolic blood pressure fell from 175 mm Hg pretreatment to 143 mm Hg at 8 hours after treatment, diastolic blood pressure decreased from 84 mm Hg to 69 mm Hg, and mean arterial blood pressure dropped from 114 mm Hg to 95 mm Hg. All the changes were statistically significant.

Brain tissue monitoring over an 8-hour period showed no significant changes in intracranial pressure or partial brain tissue oxygenation ($PbtO_2$). Fraction of inspired oxygen (FiO_2) fell from 0.72 to 0.62, a statistically significant difference.

In six patients presenting with cerebral hypoxia, average $PbtO_2$ was 10.4 mm Hg before treatment with nicardipine, a specific arterial dilator. By 4 hours post treatment, oxygenation had increased to 20.4 mm Hg. At 8 hours, it was 22.2 mm Hg, a statistically significant change.

One severe adverse event was reported: a case of hypotension that responded quickly to a reduction in the nicardipine dose, Dr. Puri said. Five patients eventually required oral antihypertensive agents, and three went on to β-blockers, he said. None had been on β-blockers before the trial, and patients taking two or more agents for hypertension had also been excluded.

The investigators are continuing to enroll patients, said Dr. Puri, of Creighton University Medical Center in Omaha, Neb. Integra LifeSciences Corp., maker of the Licox brain tissue oxygen monitoring system, provided funding for the study. ■

ACE Inhibitor–Related Angioedema Risk Higher in African Americans

BY MITCHEL L. ZOLER
Philadelphia Bureau

ORLANDO, FLA. — About 2% of African Americans treated with an ACE inhibitor develop angioedema within the first 6 months on the drug, according to results from a prospective study of enalapril with more than 12,000 patients.

Although angioedema is a known potential adverse effect of treatment with an ACE inhibitor, prior findings never established the risk patients face in a prospective, controlled study, John B. Kostis, M.D., said while presenting a poster at the annual meeting of the American College of Cardiology. Among whites in the study, about 0.5% developed angioedema during the first 6 months of treatment with enalapril.

Patients who developed angioedema most commonly had it soon after starting enalapril treatment, but the results also showed that the adverse effect could occur at any time, especially in African Americans. A time plot of the appearance of angioedema in African Americans showed an increasing cumulative incidence throughout the 6 months of treatment. For example, about 1% of these patients developed angioedema within the first 40 days on enalapril, and another 0.5% had the effect during the next 30 days. During the final 110 days of the study, another 0.5% were affected. In contrast, virtually all white patients who developed angioedema had their reaction within the first 70 days of treatment.

In the study, African Americans showed a 2.9-fold increased risk of developing angiodema with enalapril, compared with white patients.

This analysis used data collected in a 25,000-patient study that compared the drugs omapatrilat and enalapril in patients with hypertension. Randomization assigned 12,634 patients to treatment with enalapril, of whom about 10% were African American. Patients were allowed to have a history of treatment with an ACE inhibitor, and 35% of enrolled patients had this background. The study excluded patients with a history of angioedema, anaphylaxis, drug-induced or chronic urticaria, or multiple drug sensitivities. Following randomization, dosages of both drugs were titrated during the first 8 weeks so that blood pressures were below 140/90 mm Hg. During the subsequent 16 weeks, adjunctive antihypertensive therapy could be added to help patients reach or maintain the target blood pressure.

Overall, angioedema developed in 86 (0.7%) of the patients treated with enalapril, reported Dr. Kostis, chairman of the department of medicine at the Robert Wood Johnson University Hospital in New Brunswick, N.J.

Most patients' first symptom of angioedema is lip swelling. All patients had been instructed at the start of treatment to immediately stop their medication and contact their physician if this or other symptoms of angioedema occurred. Among the 86 patients with angioedema in the study, 65 (75%) had the mildest form, class I, that required no special treatment aside from stopping enalapril. A class II reaction occurred in 19 (22%) patients, requiring treatment with catecholamines or steroids. Two patients (2%) had a class IIIa reaction that required hospitalization but without airway compromise. No patients had the most severe form of angioedema, class IV, which means that either airway protection is needed or that the patient dies.

A step-wise logistic regression analysis was done using several candidate demographic and clinical variables to calculate the risk contributed by individual factors. The strongest risk factor was a history of rash in response to drugs, which boosted the risk of angioedema 3.8-fold. African Americans had a 2.9-fold increased risk, compared with white patients. The other significant risk factors were a history of seasonal allergies, which raised risk by 79%, and age greater than 65 years, which boosted risk by 60%.

It's unclear why ACE inhibitors cause angioedema. The most commonly proposed hypothesis is that the effect stems from their inhibition of the breakdown of bradykinin, which then accumulates. The swelling seen in angioedema resembles what happens in patients with a C1 inhibitor deficiency, which is known to be caused by excess bradykinin production, said Harold J. Kim, M.D., a cardiologist at Robert Wood Johnson University Hospital and a collaborator on this study. ■