Novel Drug Shows Promise For Resistant Hypertension

BY BRUCE JANCIN
Denver Bureau

CHICAGO — The oral type-A–selective endothelin receptor antagonist darusentan achieves impressive blood pressure reduction in patients who remain hypertensive despite full-dose therapy with three or more concurrent antihypertensive agents, Dr. Michael Weber said at the annual scientific sessions of the American Heart Association.

In the first-ever clinical trial of an endothelin receptor antagonist as adjunctive therapy in treatment-resistant hypertension, darusentan also proved "extraordinarily well tolerated" with the exception of an increase in peripheral edema, a side effect intrinsic to the pharmacology of the entire drug class, according to Dr. Weber, professor of medicine and associate dean for research at State University of New York, Brooklyn.

He reported on 115 patients whose blood pressure remained elevated despite baseline use of three full-dose antihypertensive drugs in 65 cases and at least four drugs in 50 others. All were on a diuretic and ACE inhibitor or angiotensin-2 receptor blocker in addition to one or more drugs from other classes.

Participants in the multicenter, double-blind, 10-week, phase II trial were randomized 2:1 to once-daily darusentan or placebo. The darusentan group began on 10 mg/day, titrating up at 2-week intervals to 50, 100, 150, and finally 300 mg per day as tolerated.

The primary study end point was reduction from baseline sitting systolic blood pressure (SBP) with darusentan minus the change with placebo, an outcome measure chosen because elevated SBP is the usual cause of failure to control blood pressure. The placebo-corrected change in SBP from a baseline mean of 149 mm Hg was 7.3 mm Hg with darusentan at 8 weeks and 11.5 mm Hg at 10 weeks. Comparable SBP lowering was obtained in women and men, in patients younger or older than 65 or even 75 years, and in patients with or without diabetes or chronic kidney disease.

Patients with more severe resistant hypertension as shown by baseline use of four or more antihypertensive medications seemed to obtain greater benefit from darusentan, Dr. Weber noted. Their mean placebo-corrected reduction in SBP at 10 weeks was 18.0 mm Hg, compared with 8.7 mm Hg in patients taking exactly three other antihypertensive drugs.

The placebo-corrected reduction in mean 24-hour SBP with darusentan by ambulatory blood pressure monitoring was 9.2 mm Hg. This reduction was coupled with a 7.2–mm Hg placebo-adjusted decrease in mean 24-hour diastolic blood pressure. "I've always felt change in mean 24-hour blood pressure is the most robust way of looking at results," the physician added.

It's not every day that the door swings open on an entirely new potential class of highly effective antihypertensive drugs, and the standing room–only audience reacted enthusiastically to the darusentan results.

Audience member Dr. Elijah Saunders, professor of medicine at the University of Maryland, Baltimore, zeroed in on the racial disparity in outcome. Given the recent evidence that hypertensive blacks have higher endothelin levels than whites, he observed, one would expect an even better response to darusentan in blacks than whites. Yet the placebo-corrected SBP reduction with darusentan was a mere 5.0 mm Hg in black patients, compared with 13.5 mm Hg in whites.

Dr. Weber agreed this result is counterintuitive but cautioned not to make too much of it. The study included fewer than 30 black patients. In addition, some of the other drugs patients were on could affect endothelin levels, further muddying the waters.

What's really required to learn whether darusentan's efficacy varies by race is a study of the endothelin receptor antagonist as monotherapy. That's not immediately in the cards, said Dr. Weber, who is a consultant to Myogen Inc., which sponsored the phase II trial. ■

BP Screen for Stroke Offspring Warranted

TUCSON, ARIZ. — Patients with a parental history of stroke should be screened early for raised blood pressure, Dr. Nigel Hart said at the annual meeting of the North American Primary Care Research Group.

The recommendation was drawn from Dr. Hart's Stroke Offspring Study in which systolic and diastolic blood pressures were significantly higher in patients with a parental history of stroke, compared with matched controls. Stroke offspring also consumed more alcohol than their paired controls but did not differ significantly in body mass index, lipids, diabetes mellitus, diet, smoking status, or exercise.

"These results suggest higher blood pressure in stroke offspring may contribute to their increased risk of stroke," said Dr. Hart of Queen's University, in Belfast, Ireland.

Questionnaires were sent to randomly selected individuals, aged 40-64 years, from 11 general practices representing 6% of the population of Northern Ireland. From the returns, those with a parental history of stroke (cases) were matched on age, gender, and socioeconomic status to those with no parental history of stroke (controls).

Matched pairs answered questions about smoking, alcohol, and medical history, and underwent a clinical evaluation. A total of 458 individuals were screened, and complete data were available on 398 individuals or 199 case-control pairs.

Systolic and diastolic blood pressures were significantly higher in cases than in controls (systolic 146.2 mm Hg vs. 140.6 mm Hg and diastolic 87.7 mm Hg vs. 85.0 mm Hg). There were no significant differences between groups in total cholesterol, homosysteine levels, smoking status, or presence of diabetes, they reported.

The only variable that differed statistically between groups was alcohol intake: Cases drank 3.7 more alcohol units per week than controls (13.8 U vs. 10.1 U). A pint of beer is equal to 2 units, while a glass of wine or hard liquor is equal to 1 unit. The mean paired difference in diastolic (2.4 mm Hg) and systolic (5.5 mm Hg) blood pressures was statistically significant between groups even after adjusting for alcohol consumption using a stepwise logistic analysis, he said.

—Patrice Wendling

Guided Breathing Lowers Blood Pressure in Type 2 Diabetes

BY MIRIAM E. TUCKER
Senior Writer

COPENHAGEN — Self-treatment with a biofeedback device that guides breathing can significantly lower blood pressure among patients with type 2 diabetes, Dr. Moshe H. Schein reported at the annual meeting of the European Association for the Study of Diabetes.

The device, called RESPeRATE, is made by InterCure Ltd., Lod, Israel. It was approved by the U.S. Food and Drug Administration in 2002 for use in stress reduction and as adjunctive treatment for hypertension, together with other pharmacologic and nonpharmacologic interventions. It works by using melodic tones to guide the patient through progressively slower inhalation and exhalation.

Previous data have shown that the device-guided technique results in significant blood pressure reductions among hypertensive patients who use it daily at home (J. Hum. Hypertens. 2001;15:271-8).

In the new study, a total of 60 patients with type 2 diabetes who had blood pressures greater than 130/80 mm Hg were randomized to use of the device for 15 minutes a day along with usual treatment, or to usual treatment alone for 8 weeks. The group was 60% male, with a mean age of 64 years and a mean BMI of 30 kg/m^2.

INTERCURE LTD.

The RESPeRATE device uses melodic tones to progressively slow the patient's breathing.

At baseline, mean blood pressure was 149/82 mm Hg in the treatment group and 146/81 mm Hg in the control group, even though the majority—78% of the treatment group and 89% of the controls—were taking blood pressure medication, said Dr. Schein, director of the Family Medicine Unit, Hadassah University Hospital, Jerusalem.

Systolic blood pressure dropped by 9.5 mm Hg in the group using the device, compared with an increase of 2.1 mm Hg among the controls, a significant difference between the two groups. The change in pulse pressure also was significantly different at 2 months; it dropped by 5.9 mm Hg from a mean of 67 mm Hg at baseline in the guided-breathing group, and increased by 3.6 mm Hg from a mean of 66 mm Hg in the controls.

Diastolic blood pressure dropped slightly in both groups, by 3.5 mm Hg in the guided-breathing patients and by 1.5 mm Hg among the controls. That difference was not significant.

There was a dose-response relationship between use of the device and systolic blood pressure reduction: The longer the patient spent in the slow breathing exercise, the greater the drop. (Although patients had been instructed to perform the device-guided breathing exercise daily, they actually did it for a mean of 5.6 sessions per week. However, the duration of each session lasted 15.9 minutes, slightly longer than the instructed 15 minutes, and patients spent a mean of 40.4 minutes per week in slow breathing.)

Blood pressure control—defined as 130/80 mm Hg or below—was achieved by 8 of 30 (27%) in the device group, compared with just 2 of the 30 (7%) of the controls, Dr. Schein reported. ■

Hypertension Info For Seniors Online

Information about high blood pressure in older adults—including prevention, risk factors, detection, and treatment—is now available on the NIHSeniorHealth Web site.

The site features easy-to-read information based on the latest research, available in formats such as large-print type sizes, open-captioned videos, and a new audio version.

To view the information, visit www.NIHSeniorHealth.gov.