Ranolazine Doesn't Need BP Reduction to Work

BY BETSY BATES
Los Angeles Bureau

SNOWMASS, COLO. — A year-old drug believed to inhibit ischemia through a novel mechanism may prove useful for angina patients whose symptoms are not relieved by revascularization or other agents, Dr. C. Richard Conti said at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

Ranolazine, approved in early 2006, is thought to block the late sodium current that results from a decreased oxygen supply to the heart, thereby reducing the sodium-dependent calcium overload that acts as a key player in the development of ischemia, explained Dr. Conti at the meeting, which was cosponsored by the American Academy of Cardiology.

It is the first major advance in antianginal therapy since calcium channel blockers, he noted.

Ranolazine's unusual mechanism translates into important clinical information, because its antianginal and anti-ischemic effects do not depend on reductions in heart rate or blood pressure.

"All of the other drugs do," said Dr. Conti, eminent scholar and professor of cardiology at the University of Florida, Gainesville.

In clinical trials, patients experienced minimal changes in mean heart rate (less than 2 beats/min) and systolic blood pressure (less than 3 mm Hg). In patients with severe renal impairment, ranolazine did increase blood pressure by 10-15 mm Hg, so "you need to be careful" and monitor blood pressure regularly.

Dr. Conti said the "important trial that everyone knows about" was the Combination Assessment of Ranolazine in Stable Angina (CARISA), in which ranolazine significantly improved exercise duration and angina onset at trough and peak dose, as well as reducing angina frequency by 36% and nitroglycerine use by 43%.

The more recent, less well known Efficacy of Ranolazine in Chronic Angina (ERICA) trial was launched at the behest of the FDA and conducted mostly in Eastern European countries.

Among 565 subjects who had a mean of more than 6 angina attacks per week at baseline, angina frequency was reduced to 3.3 attacks per week in those randomly assigned to receive 1,000 mg twice daily of ranolazine, compared with 4.3 in those receiving placebo, a 23% reduction in frequency over placebo. Patients in both groups received 10 mg of amlodipine daily and were permitted to use long-acting and sublingual nitrates as needed.

The ERICA trial also found a 25% reduction in nitroglycerine use among ranolazine users, compared with those receiving placebo.

Dr. Conti pointed out that a dose-related increase in QT intervals has been observed in patients taking ranolazine: "Not way up, but they go up."

In the ERICA trial, the mean change in QT intervals, in milliseconds, was –2.3 in patients taking placebo, 1.9 in patients taking 500 mg twice-daily ranolazine, and 5.4 in those taking 1,000 mg twice-daily ranolazine, with standard deviations of 15.6, 20.6, and 14.7, respectively.

"I suspect that if you go to 1,500 or 2,000 mg twice daily, it'll even go further," he said, adding that he does not believe doses higher than 1,000 mg twice daily should be used.

No incidents of torsades de pointes–type arrhythmias have been reported in patients taking ranolazine, but the grave complication has been associated with other drugs that prolong the QT interval, and the same could occur with ranolazine.

Dr. Conti reserves the agent for patients who have not achieved adequate symptom control with other drugs, and he obtains baseline and follow-up electrocardiograms.

"How often? I think it's a matter of clinical judgment," he said.

Another important point is that ranolazine is metabolized by CYP3A, contraindicating its use with other drugs that are potent or moderately potent inhibitors of that enzyme, including diltiazem, verapamil, ketoconazole and other azole antifungals, macrolide antibiotics, HIV protease inhibitors, and grapefruit products.

For the same reason, doses of simvastatin, digoxin, and drugs that are mainly metabolized by CYP2D6 may need to be reduced if given to patients also taking ranolazine, said Dr. Conti.

Dr. Conti disclosed that he serves on the speakers' bureau for CV Therapeutics, maker of ranolazine, marketed under the name Ranexa. ■