

BNP Not a Useful Marker in Transplant Patients

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CARMEL, CALIF. — B-type natriuretic peptide levels are not effective in detecting clinically relevant heart failure following heart transplantation, results from a study of 130 patients showed.

The finding is important because while the role of B-type natriuretic peptide (BNP) levels in detecting symptomatic heart failure in nontransplanted patients

has been well established, its role in patients who have undergone heart transplantation is unclear.

“What we do know is that BNP is elevated right after [heart] transplant,” Meghana Yajnik said during a poster presentation at the Western regional meeting of the American Federation for Medical Research.

“However, several recent studies have said that BNP may have potential as a prognostic marker, in which high levels of

BNP for prolonged periods after transplant may portend poorer outcome,” she noted

Ms. Yajnik, who is a second-year undergraduate student at University of California, Los Angeles, and her associates in the department of medicine at the university, evaluated 130 consecutive patients who received heart transplants at the university between July 2001 and November 2003. All of the patients had BNP levels assessed at the time of their right heart

catheterization and their clinical exams.

The researchers defined heart failure as both the presence of symptoms (including dyspnea, edema, or a documented increase in diuretic dose), and a pulmonary capillary wedge pressure of 15 mm Hg or greater. BNP samples taken during the first 3 months post transplant and those taken in patients with renal insufficiency (defined as a creatinine level of greater than 1.9 mg/dL) were excluded from the analysis. The mean follow-up time

was 28 months.

Of the 130 patients, 67 had 124 BNP measurements with a pulmonary capillary wedge pressure of at least 15 mm Hg. Ms. Yajnik reported that the BNP level was at least 150 pg/mL in 42 of the 124 mea-

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surements (39%). In 29 patients who had symptomatic heart failure and a pulmonary capillary wedge pressure of at least 15 mm Hg, the BNP level was at least 150 pg/mL in only 19 of the 42 measurements (45%).

“Therefore,” the researchers wrote in their abstract, “a BNP level of 150 pg/mL or greater was found to have a sensitivity of only 45.2%, a specificity of 64.9%, a positive predictive value of 3.7%, and a negative predictive value of 2.4% for the detection of heart failure in heart transplant recipients. In addition, a BNP value of 150 pg/mL or greater within 8 weeks of a clinically significant episode of rejection was noted in only 5 of 10 cases.”

Ms. Yajnik noted that the discrepancy between the use of B-type natriuretic peptide levels for detecting heart failure in the nontransplant and transplant populations requires further study. “Differences in the physiology between nontransplant patients and transplant patients may account for these disparate BNP levels,” she said.

Lotrel® (amlodipine besylate and benazepril hydrochloride) Combination Capsules

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was found when benazepril was given, via dietary administration, to rats and mice for 104 weeks at doses up to 150 mg/kg/day. On a body-weight basis, this dose is over 100 times the maximum recommended human dose; on a body-surface-area basis, this dose is 18 times (rats) and 9 times (mice) the maximum recommended human dose. No mutagenic activity was detected in the Ames test in bacteria, in an *in vitro* test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. At doses of 50-500 mg/kg/day (38-375 times the maximum recommended human dose on a body-weight basis; 6-61 times the maximum recommended dose on a body-surface-area basis), benazepril had no adverse effect on the reproductive performance of male and female rats.

Rats and mice treated with amlodipine in the diet for 2 years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day, showed no evidence of carcinogenicity. For mice, but not for rats, the highest dose was close to the maximum tolerated dose. On a mg/m² basis, this dose given to mice was approximately equal to the maximum recommended clinical dose. On the same basis, the same dose given to rats was approximately twice the maximum recommended clinical dose. Mutagenicity studies with amlodipine revealed no drug-related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times the maximum recommended human dose of 10 mg on a mg/m² basis, assuming a 50-kg person).

No adverse effects on fertility occurred when the benazepril:amlodipine combination was given orally to rats of either sex at dose ratios up to 15:7.5 mg/kg/day (benazepril:amlodipine), prior to mating and throughout gestation.

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril, so that a newborn child ingesting nothing but breast milk would receive less than 0.1% of the maternal doses of benazepril and benazeprilat.

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while Lotrel is administered.

Geriatric Use

Of the total number of patients who received Lotrel in U.S. clinical studies of Lotrel, over 19% were 65 or older while about 2% were 75 or older. Overall differences in effectiveness or safety were not observed between these patients and younger patients. Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Benazepril and benazeprilat are substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Amlodipine is extensively metabolized in the liver. In the elderly, clearance of amlodipine is decreased with resulting increases in peak plasma levels, elimination half-life and area-under-the-plasma-concentration curve. Thus a lower starting dose may be required in older patients (see DOSAGE AND ADMINISTRATION in the full prescribing information).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Lotrel has been evaluated for safety in over 2,991 patients with hypertension; over 500 of these patients were treated for at least 6 months, and over 400 were treated for more than 1 year.

In a pooled analysis of 5 placebo-controlled trials involving Lotrel doses up to 5/20, the reported side effects were generally mild and transient, and there was no relationship between side effects and age, sex, race, or duration of therapy. Discontinuation of therapy due to side effects was required in approximately 4% of patients treated with Lotrel and in 3% of patients treated with placebo.

The most common reasons for discontinuation of therapy with Lotrel in these studies were cough and edema.*

The side effects considered possibly or probably related to study drug that occurred in these trials in more than 1% of patients treated with Lotrel are shown in the table below.

PERCENT INCIDENCE IN U.S. PLACEBO-CONTROLLED TRIALS

	Benazepril/Amlodipine N=760	Benazepril N=554	Amlodipine N=475	Placebo N=408
Cough	3.3	1.8	0.4	0.2
Headache	2.2	3.8	2.9	5.6
Dizziness	1.3	1.6	2.3	1.5
Edema*	2.1	0.9	5.1	2.2

*Edema refers to all edema, such as dependent edema, angioedema, facial edema.

The incidence of edema was statistically greater in patients treated with amlodipine monotherapy than in patients treated with the combination. Edema and certain other side effects are associated with amlodipine monotherapy in a dose-dependent manner, and appear to affect women more than men. The addition of benazepril resulted in lower incidences as shown in the following table; the protective effect of benazepril was independent of race and (within the range of doses tested) of dose.

PERCENT INCIDENCE BY SEX OF CERTAIN ADVERSE EVENTS

	Benazepril/Amlodipine		Benazepril		Amlodipine		Placebo	
	Male N=329	Female N=431	Male N=269	Female N=285	Male N=277	Female N=198	Male N=217	Female N=191
Edema	0.6	3.2	0.0	1.8	2.2	9.1	1.4	3.1
Flushing	0.3	0.0	0.0	0.7	0.4	2.0	0.5	0.0
Palpitations	0.3	0.5	0.4	1.4	0.4	2.0	0.5	0.5
Somnolence	0.3	0.0	0.4	0.4	0.4	0.5	0.0	0.0

In a trial (n=386) comparing placebo, Lotrel 5/20, and Lotrel 10/20, edema and dizziness were most commonly reported in the Lotrel 10/20 group.

There were no appreciable differences in the safety profile of the 5/40 mg or 10/40 mg doses of Lotrel when studied in two trials (n=329 and n=812) conducted to establish the effectiveness of these doses vs. benazepril monotherapy and amlodipine monotherapy, respectively.

Other side effects considered possibly or probably related to study drug that occurred in U.S. placebo-controlled trials of patients treated with Lotrel or in postmarketing experience were the following:

Angioedema: Includes edema of the lips or face without other manifestations of angioedema (see WARNINGS, Angioedema).

Body as a Whole: Asthenia and fatigue.

CNS: Insomnia, nervousness, anxiety, tremor, and decreased libido.

Dermatologic: Flushing, hot flashes, rash, skin nodule, and dermatitis.

Digestive: Dry mouth, nausea, abdominal pain, constipation, diarrhea, dyspepsia, and esophagitis.

Metabolic and Nutritional: Hypokalemia.

Musculoskeletal: Back pain, musculoskeletal pain, cramps, and muscle cramps.

Respiratory: Pharyngitis.

Urogenital: Sexual problems such as impotence, and polyuria.

Other infrequently reported events were seen in clinical trials (causal relationship unlikely) or in postmarketing experience. These included chest pain, ventricular extrasystole, gout, neuritis, tinnitus, alopecia and upper respiratory tract infection.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Monotherapies of benazepril and amlodipine have been evaluated for safety in clinical trials in over 6,000 and 11,000 patients, respectively. The observed adverse reactions to the monotherapies in these trials were similar to those seen in trials of Lotrel. In postmarketing experience with benazepril, there have been rare reports of Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, and thrombocytopenia. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) severe enough to require hospitalization have been reported in association with use of amlodipine. Other potentially important adverse experiences attributed to other ACE inhibitors and calcium channel blockers include: eosinophilic pneumonitis (ACE inhibitors) and gynecomastia (CCBs).

Clinical Laboratory Test Findings

Serum Electrolytes: See PRECAUTIONS.

Creatinine: Minor reversible increases in serum creatinine were observed in patients with essential hypertension treated with Lotrel. Increases in creatinine are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with Lotrel administration. Elevations of serum bilirubin and uric acid have been reported as have scattered incidents of elevations of liver enzymes.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

[See USP controlled room temperature.]

Protect from moisture. Dispense in tight container (USP).

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