

Systolic Function No Barrier to Retransplantation

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CARMEL, CALIF. — The 5-year survival rate for heart retransplant patients who have severe heart failure symptoms with preserved systolic function is about 67%, results from a single-center study showed.

“These patients have comparable survival to patients retransplanted due to systolic dysfunction and therefore should

be considered candidates for retransplantation,” Lakshmi Gokanapudy said at the Western regional meeting of the American Federation for Medical Research.

Ms. Gokanapudy, an undergraduate student at the University of California, Los Angeles, and her associates in the department of medicine at the university, evaluated 31 heart transplant patients who underwent retransplantation at the university during 1994-2004. The patients mean age

at time of retransplantation was 51 years, and most (75%) were male.

Of the 31 patients, 24 (77%) had severe heart failure symptoms with preserved systolic function, which was defined as having a left ventricular ejection fraction of at least 40%.

Ms. Gokanapudy reported that each of the 24 patients with preserved systolic function had shortness of breath, fatigue, and decreased exercise tolerance. Echocardiography revealed that eight

(33%) had left ventricular hypertrophy.

Five of the patients (21%) had no rejection episodes, 19 (79%) had an average of 1.4 rejection episodes, and 20 (83%) developed epicardial cardiac allograft vasculopathy.

The 5-year survival rate among the 24 patients with preserved systolic function was 67%, which was similar to the 5-year survival rate among the 7 retransplanted patients in the study who had severe systolic dysfunction (57%).

Lotrel®

(amlodipine besylate and benazepril hydrochloride)
Combination Capsules

2.5 mg/10 mg
5 mg/10 mg
5 mg/20 mg
5 mg/40 mg
10 mg/20 mg
10 mg/40 mg

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

USE IN PREGNANCY

When used in pregnancy, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lotrel should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

INDICATIONS AND USAGE

Lotrel is indicated for the treatment of hypertension.

This fixed combination drug is not indicated for the initial therapy of hypertension (see DOSAGE AND ADMINISTRATION in the full prescribing information).

In using Lotrel, consideration should be given to the fact that an ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that benazepril does not have a similar risk (see WARNINGS, Neutropenia/Agranulocytosis).

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to nonblacks.

CONTRAINDICATIONS

Lotrel is contraindicated in patients who are hypersensitive to benazepril, to any other ACE inhibitor, or to amlodipine.

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Lotrel) may be subject to a variety of adverse reactions, some of them serious. These reactions usually occur after one of the first few doses of the ACE inhibitor, but they sometimes do not appear until after months of therapy.

Head and Neck Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors. In U.S. clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received benazepril. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Lotrel should be discontinued and appropriate therapy instituted immediately. When involvement of the tongue, glottis, or larynx appears likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3-0.5 mL), should be promptly administered (see ADVERSE REACTIONS).

Intestinal Angioedema: Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration, and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Hypotension

Lotrel can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with Lotrel.

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering Lotrel as with any other peripheral vasodilator, particularly in patients with severe aortic stenosis.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria, azotemia, and (rarely) with acute renal failure and death. In such patients, Lotrel therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of the benazepril component is increased or a diuretic is added or its dose increased.

If hypotension occurs, the patient should be placed in a supine position, and if necessary, treated with intravenous infusion of physiologic saline. Lotrel treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients (incidence probably less than once per 10,000 exposures) but more frequently (incidence possibly as great as once per 1000 exposures) in patients with renal impairment, especially those who also have collagen-vascular diseases such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, Lotrel should be discontinued as soon as possible and monitoring of the fetal development should be performed on a regular basis.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

In addition, use of ACE inhibitors during the first trimester of pregnancy has been associated with a potentially increased risk of birth defects. In women planning to become pregnant, ACE inhibitors (including Lotrel) should not be used. Women of child-bearing age should be made aware of the potential risk and ACE inhibitors (including Lotrel) should only be given after careful counseling and consideration of individual risks and benefits.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers, but experience is limited.

Lotrel has not been adequately studied in pregnant women. When rats received benazepril:amlodipine at doses ranging from 5:2.5 to 50:25 mg/kg/day, dystocia was observed with increasing dose-related incidence at all doses tested. On a mg/m² basis, the 2.5 mg/kg/day dose of amlodipine is 3.6 times the amlodipine dose delivered when the maximum recommended dose of Lotrel is given to a 50-kg woman. Similarly, the 5 mg/kg/day dose of benazepril is approximately 2 times the benazepril dose delivered when the maximum recommended dose of Lotrel is given to a 50-kg woman.

No teratogenic effects were seen when benazepril and amlodipine were administered in combination to pregnant rats or rabbits. Rats received dose ratios up to 50:25 mg/kg/day (benazepril:amlodipine) (24 times the maximum recommended human dose on a mg/m² basis, assuming a 50-kg woman). Rabbits received doses of up to 1.5:0.75 (benazepril:amlodipine) mg/kg/day; on a mg/m² basis, this is 0.97 times the size of a maximum recommended dose of Lotrel given to a 50-kg woman.

Similar results were seen in animal studies involving benazepril alone and amlodipine alone.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

General

Impaired Renal Function: Lotrel should be used with caution in patients with severe renal disease.

When the renin-angiotensin-aldosterone system is inhibited by benazepril, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors (including benazepril) may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In a small study of hypertensive patients with unilateral or bilateral renal artery stenosis, treatment with benazepril was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril therapy, concomitant diuretic therapy, or both. When such patients are treated with Lotrel, renal function should be monitored during the first few weeks of therapy.

Some benazepril-treated hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when benazepril has been given concomitantly with a diuretic. Dosage reduction of Lotrel may be required. Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION in the full prescribing information).

Hyperkalemia: In U.S. placebo-controlled trials of Lotrel, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) not present at baseline occurred in approximately 1.5% of hypertensive patients receiving Lotrel. Increases in serum potassium were generally reversible. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes.

Patients With Congestive Heart Failure: Although hemodynamic studies and a controlled trial in patients with NYHA Class II-III heart failure have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.

Patients With Hepatic Failure: In patients with hepatic dysfunction due to cirrhosis, levels of benazepril are essentially unaltered. However, since amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t_{1/2}) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Lotrel to patients with severe hepatic impairment (see also WARNINGS).

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent non-productive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Drug Interactions

Diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Lotrel. The possibility of hypotensive effects with Lotrel can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Lotrel.

Potassium Supplements and Potassium-Sparing Diuretics: Benazepril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. Lotrel and lithium should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended.

Other: Benazepril has been used concomitantly with oral anticoagulants, beta-adrenergic-blocking agents, calcium-blocking agents, cimetidine, diuretics, digoxin, hydralazine, and naproxen without evidence of clinically important adverse interactions.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the coadministration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that coadministration with cimetidine did not alter the pharmacokinetics of amlodipine; and that coadministration with warfarin did not change the warfarin-induced prothrombin response time.