

# Early Fetal Echo Detects Most Cardiac Lesions

BY ROBERT FINN  
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RENO, NEV. — Fetal echocardiography before 16 weeks of gestation is feasible and can detect a substantial proportion of cardiac lesions, investigators reported in a poster presentation at the annual meeting of the Society for Maternal-Fetal Medicine.

The technique does have limitations regarding accurate visualization of the great artery relationship and the crux of the

heart. It may therefore be best to reserve early echocardiography for cases at the greatest risk for cardiac defects. Second-trimester echocardiograms remain the gold standard, concluded Fionnuala McAuliffe, M.D., of University College Dublin (Ireland) and colleagues.

The study involved 160 fetal echocardiograms performed before the 16th week, with an average gestation time of 13.5 weeks. Investigators used the transabdominal approach for 100 cases, and the

transvaginal approach in 60 cases in which the transabdominal approach yielded poor visualization.

Of the 160 patients, 100 were referred because of nuchal translucency greater than the 95th percentile, 51 because of a family history of congenital cardiac defects, and 9 because of the presence of extracardiac lesions.

Adequate cardiac examinations were possible in 152 cases, and pregnancy outcome was available in 137 cases. Of those,

there were 20 cardiac defects. Fourteen (70%) showed an abnormality on the early echocardiogram, and six (30%) were passed as normal.

The early echocardiogram identified two cases of ectopia cordis, two cases of atrioventricular septal defect, two of hypoplastic left heart syndrome, two of ventricular septal defect, two of left atrial isomerism, two of hypoplastic right ventricle, and one case each of double outlet right ventricle and cardiac diverticulum.

However, the early echocardiogram failed to detect three cases of ventricular septal defect, two cases of dextro-looped transposition of the great arteries, and one case of hypertrophic cardiomyopathy.

A four-chamber view of the heart was obtained in all of the cases. The atrioventricular valves could be visualized 96% of the time, the aorta and pulmonary artery 95% of the time, and the inferior and superior vena cava 76% of the time.

Early fetal echocardiography was less effective in visualizing the aortic and ductal arches (45% of the time), branch pulmonary arteries (37% of the time), and pulmonary veins (19% of the time). ■

## CV Score Predicts Survival in High-Risk Fetuses

RENO, NEV. — A less-than-perfect score on a five-item, 10-point cardiovascular profile predicts a poorer outcome for a fetus with heart failure, according to a poster presented by Aleksandra Roczek, M.D., at the annual meeting of the Society for Maternal-Fetal Medicine.

Fetuses in this high-risk group warrant closer follow-up and management from both the obstetric and prenatal cardiology point of view, concluded Dr. Roczek, of the University of South Florida, Tampa.

Poor scores on three of the five items—cardiomegaly, hydrops, and venous Doppler measurements—were especially predictive of mortality, she noted.

Dr. Roczek and her colleagues conducted a retrospective examination of 92 pregnancies where fetuses were judged to be at risk for heart failure on the basis of echocardiography and Doppler velocimetry. Of those fetuses, 53 (57%) survived and 39 (43%) did not.

The cardiovascular profile score awards two points each for absence of hydrops, normal venous Doppler, heart function, arterial Doppler, and heart size. The score in each domain is decreased by two points for severe signs and by one point for intermediate signs.

Fetuses with abnormal venous Doppler had a mortality rate of 64%. Mortality was 62.5% in fetuses with hydrops, and 60% in fetuses with cardiomegaly.

The other two factors were less predictive of mortality. Fetuses with abnormal heart function had a 33% mortality, and those with abnormal arterial Doppler had a 17% mortality.

—Robert Finn

### Brief Summary of Prescribing Information as of September 2004

#### ALTACE® Capsules (ramipril)

##### USE IN PREGNANCY

**When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTACE® should be discontinued as soon as possible. See WARNINGS: Fetal/neonatal morbidity and mortality.**

##### CONTRAINDICATIONS

ALTACE is contraindicated in patients who are hypersensitive to this product or any other angiotensin converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

##### WARNINGS

**Anaphylactoid and Possibly Related Reactions: Head and Neck Angioedema** Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (See also **CONTRAINDICATIONS**.) Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 ml to 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 adsorption. **Hypotension** ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril 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 ALTACE. 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 or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE 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 ramipril or diuretic is increased. If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume. **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. **Neutropenia/Agranulocytosis** As with other ACE inhibitors, rarely, a mild- to moderate decrease in the red blood cell count and hemoglobin content, white blood cell or platelet count may develop. In isolated cases, agranulocytosis, pancytopenia, and bone marrow depression may occur. Hematological reactions to ACE inhibitors are more likely to occur in patients with collagen-vascular disease (e.g., systemic lupus erythematosus, scleroderma) and renal impairment. 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, ACE inhibitors should be discontinued as soon as possible. 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. These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible. 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 intrauterine environment. If oligohydramnios is observed, ALTACE should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profile (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 dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE which crosses the placenta can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants. No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a body surface area basis, the doses used were up to approximately 400 times (in rats and monkeys) and 2 times (in rabbits) the recommended human dose.

##### PRECAUTIONS

**Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, 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 angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.** (See **DOSE AND ADMINISTRATION** in the full Prescribing Information.) **Hyperkalemia:** In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE (ramipril). In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. 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, which should be used cautiously, if at all, with ALTACE. (See **Drug Interactions**.) **Cough:** Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive 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. **Impaired Liver Function:** Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function. However, since the renin-angiotensin system may be activated in patients with severe liver cirrhosis and/or ascites, particular caution should be exercised in treating these patients. **Surgery/Anesthesia:** In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion. **Information for Patients. Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible. **Angioedema:** Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of the face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned that light-headedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE should be discontinued until the physician has been consulted. All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of light-headedness and possible syncope. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia. **Drug Interactions. With nonsteroidal anti-inflammatory agents:** Rarely, concomitant treatment with ACE inhibitors and nonsteroidal anti-inflammatory agents have been associated with worsening of renal failure and an increase in serum potassium. **With 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 ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced. (See **DOSE AND ADMINISTRATION** in the full Prescribing Information.) **With potassium supplements and potassium-sparing diuretics:** ALTACE 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. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently. **With lithium:** Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased. **Other:** Neither ALTACE nor its metabolites have been found to interact with food, digoxin, antacid, furosemide, cimetidine, indomethacin, and simvastatin. The combination of ALTACE and propranolol showed no adverse effects on dynamic parameters (blood pressure and heart rate). The co-administration of ALTACE and warfarin did not adversely affect the anticoagulant effects of the latter drug. Additionally, co-administration of ALTACE with phenprocoumon did not affect minimum phenprocoumon levels or interfere with the subjects' state of anti-coagulation. **Carcinogenesis, Mutagenesis, Impairment of Fertility** No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats for up to 24 months at doses of up to 500 mg/kg/day or to mice for up to 18 months at doses of up to 1000 mg/kg/day. (For either species, these doses are about 200 times the maximum recommended human dose when compared on the basis of body surface area.) No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility. **Pregnancy Categories C (first trimester) and D (second and third trimesters).** See **WARNINGS: Fetal/Neonatal Morbidity and Mortality. Nursing Mothers** Ingestion of single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, women receiving ALTACE should not breast feed. **Geriatric Use** Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported 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. **Pediatric Use** Safety and effectiveness in pediatric patients have not been established. Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

##### ADVERSE REACTIONS

**Hypertension** ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%). Of observed side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE, only asthenia (fatigue) was more common on ALTACE than placebo (2% vs. 1%). In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group, not attributed at that time to ramipril. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of patients requiring discontinuation of treatment. **Heart Failure Post Myocardial Infarction** Adverse reactions (except laboratory abnormalities) considered possibly/probably related to study drug that occurred in more than one percent of patients and more frequently on ramipril are listed below. The incidences representing experiences from the AIRE study (1004 ramipril patients, 882 placebo patients, follow-up time 6 to 46 months) include hypotension (ramipril 11%, placebo 5%), increased cough (ramipril 8%, placebo 4%), dizziness (ramipril 4%, placebo 3%), angina pectoris (ramipril 3%, placebo 2%), nausea (ramipril 2%, placebo 1%), postural hypotension (ramipril 2%, placebo 1%), syncope (ramipril 2%, placebo 1%), vomiting (ramipril 2%, placebo 0.5%), vertigo (ramipril 2%, placebo 0.7%), abnormal kidney function (ramipril 1%, placebo 0.5%) and diarrhea (ramipril 1%, placebo 0.4%). Safety data in the HOPE trial (4645 patients on ramipril and 4652 patients on placebo) were collected as reasons for discontinuation or temporary interruption of treatment. Discontinuation at any time occurred in 34% of patients on ramipril and 32% of patients on placebo. Permanent discontinuation occurred in 29% of patients on ramipril and 28% of patients on placebo. Reasons for stopping included cough (ramipril 7%, placebo 2%), hypotension or dizziness (ramipril 1.9%, placebo 1.5%), and angioedema (ramipril 0.3%, placebo 0.1%). The incidence of cough was similar to that seen in the AIRE trial. The rate of angioedema was the same as in previous clinical trials (see **WARNINGS**). Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain): **Body As a Whole:** Anaphylactoid reactions. (See **WARNINGS**.) **Cardiovascular:** Angina/chest pain, arrhythmias including bradycardia or tachycardia, cardiac arrest, congestive heart failure, symptomatic hypotension (reported in 0.5% of patients in US trials). (See **WARNINGS** and **PRECAUTIONS**.) **Syncope, palpitations, transient ischemia attack, and myocardial infarction or cerebrovascular accident** possibly due to excessive hypotension. **Hematologic:** Pancytopenia, hemolytic anemia and thrombocytopenia. **Renal:** Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See **WARNINGS**.) **Acute renal failure. Angioneurotic edema:** Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See **WARNINGS**.) **Gastrointestinal:** Pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, hepatitis, increased salivation and taste disturbance. **Dermatologic:** Apparent hypersensitivity reactions (manifested by urticaria, pruritus, or rash, with or without fever), photosensitivity, purpura, onycholysis, pemphigus, pemphigoid, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome. **Neurologic and Psychiatric:** Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances. **Miscellaneous:** As with other ACE inhibitors, a symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations. Additionally, as with other ACE inhibitors, eosinophilic pneumonitis has been reported. **Fetal/Neonatal Morbidity and Mortality. Other:** Arthralgia, arthritis, dyspnea, edema, epistaxis (see **PRECAUTIONS**), **Drug Interactions.** Impotence, increased sweating, malaise, myalgia, and weight gain. **Post-Marketing Experience:** In addition to adverse events reported from clinical trials, there have been rare reports of hypoglycemia reported during ALTACE therapy when given to patients concomitantly taking oral hypoglycemic agents or insulin. The causal relationship is unknown. **Clinical Laboratory Test Findings: Creatinine and Blood Urea Nitrogen:** Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values 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 **WARNINGS** and **PRECAUTIONS**.) Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See **WARNINGS** and **PRECAUTIONS**.) **Hemoglobin and Hematocrit:** Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 3%, respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit. **Other (causal relationships unknown):** Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have cases of hyponatremia and scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

##### OVERDOSAGE

Single oral doses in rats and mice of 10-11 g/kg resulted in significant lethality. In dogs, oral doses as high as 1 g/kg induced only mild gastrointestinal distress. Limited data on human overdosage are available. The most likely clinical manifestations would be symptoms attributable to hypotension. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

##### Rx only

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