Life-Threatening Interaction of Mibefradil and β-Blockers With Dihydropyridine Calcium Channel Blockers

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Mibefradil is a T-type and L-type calcium channel blocker (CCB) released in the United States in 1997 for management of hypertension and chronic stable angina. Postmarketing surveillance revealed a potential serious interaction between mibefradil and β-blockers, digoxin, verapamil, and diltiazem, especially in elderly patients. The manufacturer voluntarily withdrew mibefradil on June 8, 1998. We describe 4 cases of cardiogenic shock in patients taking mibefradil and β-blockers who began taking dihydropyridine CCBs. One case resulted in death; the other 3 survived episodes of cardiogenic shock with intensive support of heart rate and blood pressure. Physicians who are preparing to switch patients’ medications from mibefradil to other antihypertensive agents should be aware of these potentially life-threatening drug-drug interactions.

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MIBEFRADIL (Posicor, Roche Laboratories Inc, Nutley, NJ) is a long-acting nontiydrophyridine calcium channel blocker (CCB) that uniquely blocks both the T (transient) calcium channels and the L (long) calcium channels.7 All other CCBs currently approved for use in the United States block the L channel. Less than a year after its release in mid-1997, almost 200,000 Americans were taking mibefradil.8 Roche Laboratories voluntarily withdrew Posicor from the market on June 8, 1998, as numerous cytochrome P-450–mediated drug interactions became apparent. We report 4 cases that suggest that switching to dihydropyridine CCBs the day after taking mibefradil may be hazardous.

Report of Cases

Case 1.—A 79-year-old woman with hypertension was taking daily doses of mibefradil, 100 mg, propranolol, 160 mg, indapamide, and estrogen. Her blood pressure was poorly controlled and her physician discontinued her mibefradil therapy; he prescribed controlled-release nifedipine, 60 mg daily, to start on the following day. One hour after her first dose of nifedipine, she collapsed at home. She presented to the emergency department (ED) with a systolic blood pressure of 60 mm Hg and a diastolic blood pressure of 30 mm Hg. Her heart rate fell into the range of 30 to 40 beats per minute. The patient became unresponsive with a systolic blood pressure of 30 mm Hg and an electrocardiogram demonstrated a junctional bradycardia at 34/min. Despite 2 intravenous doses of atropine, 0.5 mg, her heart rate remained 20 to 25 beats per minute. Her systolic blood pressure remained at 30 mm Hg. She was transferred to the intensive care unit, where a dopamine infusion of 10 µg/kg per minute was titrated to maintain heart rate above 40 and blood pressure above 40/20 mm Hg. A transthoracic echocardiogram revealed normal ventricular function. Her treatment in the intensive care unit included dopamine infusion titrated to a maximal rate of 20 µg/kg per minute and norepinephrine infusion titrated to a maximal rate of 32 µg/min with little improvement in her blood pressure and heart rate. Approximately 10 hours later, when the patient became unresponsive with junctional bradycardia at 40/min to 50/min, she received 1 mg of intravenous glucagon. Minutes later, her rhythm deteriorated to asystole. Resuscitation attempt was unsuccessful. Autopsy revealed a normal heart with no evidence of acute myocardial infarction, aortic dissection, or pulmonary embolism.

Case 2.—A 55-year-old woman with hypertension, non–insulin-dependent diabetes, and osteoarthritis was taking daily doses of nadolol, 80 mg, and mibefradil, 100 mg, in addition to glimepiride, omeprazole, and oxaprozin. Her blood pressure was considered poorly controlled by her physician, with a heart rate of 72/min, so felodipine, 5 mg, and enalapril, 5 mg, were prescribed. She took the first dose at bedtime with her mibefradil. Five hours later, her husband awoke and found her in distress with altered mental status and subternal chest pain. Her systolic blood pressure at home was approximately 60 mm Hg and she was taken to the ED.

In the ED, she appeared pale with a heart rate of 48/min and a blood pressure of 112/77 mm Hg. Her blood glucose level was 13.6 mmol/L (244 mg/dL). A 12-lead electrocardiogram demonstrated a junctional bradycardia at 34/min. Despite 2 intravenous doses of atropine, 0.5 mg, her heart rate remained 42/min with a blood pressure of 96/55 mm Hg. Shortly thereafter, she collapsed in apparent cardiogenic shock. Her heart rate fell into the 30s with a palpable systolic blood pressure of 80 mm Hg. She became obtunded and oliguric. During the remainder of her ED course, her maximal heart rate was 69/min after a total of 2 mg of atropine, 10 mL of 10% calcium gluconate, and an infusion of dopamine at 10 µg/kg per minute. Three mg of intravenous glucagon was administered, after which the patient experienced intense nausea and retching. After metaraminol infusion at 70 µg/min, an additional 20 mL of 10% calcium gluconate, and a total of 4 L of intravenous normal saline were adminis-
tered, her vital signs improved to a blood pressure of 126/60 mm Hg with a heart rate of 90/min. Serial creatine kinase testing was normal. In the intensive care unit, she continued to be treated with dopamine, 10 µg/kg per minute, and metaraminol, 70 µg/min, with gradual improvement in her mental status and urine output. Pressors were tapered over the next 24 hours. She was discharged 4 days later without sequelae.

Case 3.—A 60-year-old woman, whose hypertension remained poorly controlled despite various antihypertensive regimens, was taking mibebradil, 100 mg daily, and extended-release metoprolol, 50 mg daily. Her physician changed her regimen to sustained-release nifedipine, 60 mg daily, with doxazosin, 1 mg daily, and captopril, 25 mg 3 times daily. A few hours after her first doses of the latest regimen, she presented to her physician's office with a systolic blood pressure of 70 mm Hg and heart rate of 50/min. At the ED, her vital signs remained unchanged despite dopamine infusion, 20 µg/kg per minute, 10 mL of 10% calcium gluconate, and intravenous fluids. Approximately 12 hours later, her blood pressure was 70/39 mm Hg with a heart rate of 60/min despite the addition of norepinephrine. Her urine output was 100 mL over 8 hours. After her hypotension and bradycardia gradually resolved over the next 2 days, she was discharged to home without residual effects.

Mibefradil overdose: a potential for adverse effects from dihydropyridine calcium channel blockers. Am J Cardiol. 1997;80:49C–46C.

Felodipine and timolol require a 14-day washout after discontinuation of mibebradil. Angiotensin-converting enzyme inhibitors, angiotensin II antagonists, and diuretics do not require special precautions.

Managing combined myocardial depression and hypotension with CCBs and β-blockers is difficult. High-dose glucagon (5–10 mg intravenously) increases intracellular cyclic adenosine monophosphate and produces positive inotropic, dromotropic, and chronotropic effects. With high doses of glucagon, sterile water and saline are safer diluents than the 0.2% phenol solution provided with the product. Repeated doses of calcium are often necessary to overcome the effects of calcium channel blockers. No single agent is likely to be effective. Vasopressors, intropes (such as amrinone), and temporary pacing may be necessary.

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References