# Adverse Effects Using Combined Rate-Slowing Antihypertensive Agents

Joel Handler MD

Case 1: A 65-year-old woman presented to the emergency department with new-onset slurred speech and visual blurriness. She had type 2 diabetes and stage 4 chronic kidney disease. A left forearm antecubutal arteriovenous shunt had been placed 3 months prior to admission and recent estimated glomerular filtration rates (eGFRs) had been 15 to 17 mL/min (normal >89 mL/min). For 20 years, the patient had hypertension, and with progression of her renal disease, blood pressure became more difficult to control. Her antihypertensive regimen had consisted of metoprolol 50 mg twice a day, hydralazine 100 mg twice a day, lisinopril 40 mg daily, furosemide 80 mg twice a day, and amlodipine 10 mg daily. A week prior to admission, with blood pressure 148/68 mm Hg and a heart rate of 62 beats per minute, clonidine 0.1 mg twice a day had been added.

In the emergency department, a heart rate of 35 beats per minute was noted with a blood pressure of 144/70 mm Hg. An electrocardiogram (ECG) showed sinus bradycardia and sinus arrhythmia. Brain magnetic resonance imaging was normal. Metoprolol and clonidine were discontinued and the patient was hospitalized for 2 days with resolution of her bradycardia, slurred speech, and visual complaint.

Case 2: An 88-year-old woman was brought to the hospital by paramedics because of near syncope at home. She had been taking antihypertensive medication for almost 40 years, and for the past several years had been taking a regimen of chlorthalidone 25 mg, lisinopril 40 mg, metoprolol 50 mg twice a day, diltiazem extended release 180 mg daily, hydralazine 50 mg twice a day, and a 0.3 mg clonidine transdermal patch weekly. Blood pressure and heart rate a month prior to admission had been 134/66 mm Hg and 60 beats per minute, respectively. The patient had been feeling gradually more fatigued over the 2 weeks preceding admission. Laboratory results on admission revealed creatinine 1.2 mg/dL (normal 0.7–1.3 mg/dL), eGFR 44 mL/min, hemoglobin 12.1 g/dL (normal 14–17 g/dL), potassium 4.3 mEq/dL (normal 3.5–5.0 mEq/dL), random glucose 132 mg/dL (normal <140 mg/dL), alanine aminotransferase 32 mg/dL (normal <41 U/L), alkaline phosphatase 89 mg/dL (normal 43–121 U/L), total bilirubin 0.4 mg/dL (normal 0.1–1.0 mg/dL), and troponin 0.01 (normal <0.04 ng/mL). Brain computerized axial tomography showed age-related cerebral atrophy. In the emergency department, blood pressure was 148/74 mm Hg and heart rate was 34 beats per minute. An ECG showed junctional escape rhythm with a rate of 32.

The patient was admitted to the hospital and acute myocardial infarction was excluded. Metoprolol, diltiazem, and clonidine were discontinued and she was discharged 3 days later with a blood pressure of 134/62 mm Hg and a heart rate of 56 beats per minute.

## DISCUSSION

### Effects of β-Blockers and Calcium Blockers on the Cardiac Conduction System

β-Blockers should be prescribed with caution for patients with known cardiac conduction disease because adverse effects include severe sinus bradycardia, sinus arrest, and atrioventricular (AV) block. Suppression of $\beta_1$-receptors in the sinoatrial (SA) node causes reduced heart rate, and suppression of $\beta_1$-receptors in the atria, AV node, His-Purkinje system, and ventricles causes reduced automaticity and conduction velocity.[1] The heart rate slowing and hypotensive effects of β-blockers may be discordant. In a study of 10 patients treated with atenolol doses of 25 mg, 50 mg, 75 mg, and 100 mg, blood pressure lowering at the 25-mg and 100-mg doses was the same, but the heart rate response to exercise progressively slowed from 25 mg to 100 mg.[2]

Both verapamil and diltiazem cause sinus bradycardia by decreasing firings from the SA node, as well as slowing AV node conduction.[3] Usually the sinus rate does not change appreciably with nondihydropyridine calcium blockers alone due to peripheral vasodilatation. By blocking reactive sympathetic nerve activation occurring with vasodilatation, however, simultaneous β-blocker treatment can cause synergistic bradycardia. Verapamil slows AV node conduction more than diltiazem and is effective treatment for AV node reentry supraventricular tachyarrhythmias. Clonidine inhibits central nervous system sympathetic outflow and may cause severe bradycardia.

### Reports of Adverse Cardiogenic Effects of Combined β-Blockers and Nondihydropyridine Calcium Channel Blockers

Adverse cardiovascular drug reactions due to combined rate-slowing agents occasionally result in hospitalization. In a prospective study of 2574 medical admissions during 2 years, adverse cardiovascular reactions due to combination therapy were responsible for 26 hospitalizations. Twenty-two cases of symptomatic bradycardia resolved within 24 hours of drug discontinuation, including 12 with sinus bradycardia, 4 with junctional escape rhythm, 5 with complete heart

*From Kaiser Permanente, Anaheim, CA*

**Address for correspondence:** Joel Handler, MD, Kaiser Permanente, 411 Lakeview Avenue, Anaheim, CA 92807
**E-mail:** joel.handler@kp.org

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block, and 1 with sinus arrest.[4] In this series, the most common culprit combination was propanolol and verapamil. The more common setting for use of combined β-blockers and calcium channel blockers is coronary artery disease with active angina, although this combination has also found its way into treating more resistant cases of hypertension.

There have been many case series and case reports of hospitalizations due to the adverse effects of combined rate-slowing agents.[5–16] Sometimes the inciting event is general anesthesia or percutaneous transluminal coronary angioplasty.[5,13] In addition to symptomatic bradycardia due to conduction disturbances, heart failure exacerbations principally related to verapamil in combination with β-blocker therapy occur particularly with underlying left ventricular dysfunction. In one review of cardiovascular adversity of the calcium blocker β-blocker combination in patients treated for hypertension, heart failure exacerbations were as common as significant conduction disturbances.[8] Verapamil decreases ejection fraction and stroke volume and may increase left ventricular filling pressure especially with baseline impairment. Drug-related cardiogenic shock without bradycardia resulting from combined verapamil β-blocker therapy has been reported.[11,12] Verapamil may also potentiate the negative inotropic effects of agents used for general anesthesia,[17] and in this situation poses a more dangerous setting for combined agents.[5] The spectrum of adverse cardiovascular events resulting from combined verapamil and β-blocker therapy includes mortality.[5]

## Lack of Dose and Time of Duration Correlation With Adverse Effects From Combined Rate-Slowing Agents

An examination of a series of cases of symptomatic bradycardia resulting from combination therapy of diltiazem and β-blockers concluded that the adverse effects were neither dose-related nor time-related to duration of therapy.[6] In contrast to the experience with the verapamil β-blocker combination, the conduction abnormality was entirely related to impairment of the SA node rather than the AV node. Symptomatic bradyarrhythmias, which included sinus bradycardia, junctional escape rhythm, and sinus pause, did not include complete heart block in this series of 10 patients.[6] Four patients required temporary pacemakers. Diltiazem doses ranged from 90 mg daily to 360 mg daily with propanolol as low as 80 mg daily. The duration of therapy without dosage change before symptomatic presentation ranged from several hours to up to 2 years.[6]

Pathophysiologic explanation of the occasional long duration between onset of combined therapy and symptomatic presentation may be related to aging of the conduction system. In a natural history study of the longer-term prognosis of serious drug-related bradycardia, 38 patients had 18-month follow-up.[18] Ten of the 38 patients (26%) required a permanent pacemaker following drug washout, indicating either that underlying conduction disease was unmasked or that the symptomatic bradycardia was not drug-related. In patients without sinus node disease, β-blocker therapy does not affect sinus node recovery time and sinoatrial conduction time is only slightly increased, but in patients with sick sinus syndrome, β-blockers significantly prolong sinus node recovery time and sinoatrial conduction time is significantly increased.[8] The average age of case series of patients with severe bradycardia, heart failure, and shock with combination therapy patients is almost always elderly: age 73 (4), age 70 (6), age 78 (7), age 65 (10), age 76 (14), and ages 68 and 77 (16). Problems with younger individuals have been reported with intentional overdose.[12]

## Aging Effects of Drug Pharmacokinetics

Alterations in the pharmacokinetic handling of β-blockers and nondihydropyridine calcium blockers with aging may also contribute to adverse cardiovascular events with prolonged combination therapy. Reduction of verapamil clearance by 50% and doubling of the elimination half-life in the elderly has been reported.[19] Another study showed that increased peak plasma concentrations of verapamil associated with age-related changes in clearance and elimination are small and unlikely to be clinically significant.[20] However, even a minimal increase in verapamil may become significant when combined with other rate-slowing agents and also in elderly patients with unrecognized conduction disease or left ventricular dysfunction. There may be increased sensitivity to verapamil in the elderly.[21] These arguments favor the use of dihydropyridine calcium blockers in the elderly.[19]

Studies with diltiazem in the elderly involving absorption and clearance have had somewhat variable results, but first-pass hepatic metabolism is impaired and the drug does have an active metabolite.[22] Therefore, there is rationale for a "start low, go slow" approach.[22] Reduced first-pass metabolism with aging also increases the bioavailability of verapamil and propanolol.[23,24] Age-related decrease in lean body mass and total body water leads to a decrease in the volume of distribution of hydrophilic drugs, but increased fat causes an increase in the volume of distribution of most β-blockers, which are lipophilic drugs.[23] An increased volume of distribution mitigates some of the drug accumulation effects.

Chronologic aging has been shown to significantly prolong the half-life of atenolol.[25] Because the primary route of atenolol clearance is renal excretion, most of the accumulation is due to reduction in renal clearance. In addition to reduced excretion, renal insufficiency has multiple complex and interactive effects on drug activity with individual variability, particularly involving alterations in drug absorption, protein-binding, absorption, volume of distribution, and the accumulation and metabolism of pharmacologically active metabolites.[26] Although diltiazem is metabolized in

**TABLE.** Select Antihypertensive Drug Disposition in the Elderly

| Drug | Half-Life in Elderly | Primary Route of Elimination |
|---|---|---|
| Diltiazem | Increased | Hepatic |
| Verapamil | Increased | Hepatic |
| Clonidine | No change | Hepatic/renal |
| Propanolol | Increased | Hepatic |
| Metoprolol | No change | Hepatic |
| Atenolol | Increased | Renal |
| Amlodipine | Increased | Hepatic |
| Lisinopril | Increased | Renal |
| Losartan | No change | Hepatic |
| Terazosin | Increased | Hepatic |

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the liver, chronic renal failure concentrations have been found to be 25% higher due to a reduced volume of distribution.[7] Below a glomerular filtration rate of 30 cc/min, accumulation of atenolol with a significant bradycardia risk favors a switch to a β-blocker subject to hepatic metabolism, such as metoprolol. The primary route of clearance for selected antihypertensive agents is listed in the Table.

### Possible Systemic Effects of Ophthalmic Beta Blockers

Glaucoma is a common comorbidity in the elderly, and the systemic effects of β-blocking ophthalmic drops to treat this condition may rarely include bradycardia.[27] Entry to the systemic circulation may occur via drainage into the lacrimal ducts, highly vascular nasal mucosa, as well as ophthalmic and facial veins. Absorbed in this fashion, β-blockers may avoid the usual 90% first-pass hepatic metabolism.[27]

### Acute Therapy of Severe β-Blocker and Calcium Blocker Toxicity

Usually, severe bradycardia, hypotension, and heart failure precipitated by combined nondihydropyridine calcium blockers and β-blockers reverses fairly quickly with drug discontinuation. Sometimes, however, more aggressive therapy is indicated. First-line treatment for β-blocker overdose is glucagon, which activates adenylate cyclase in cardiac tissue. An intial bolus dose of 50 μg/kg to 150 μg/kg is administered over 1 to 2 minutes. Benefit is seen within 5 minutes but is also transient, and should be followed by an infusion of 2 mg/h to 5 mg/h.[28] The initial calcium channel blocker antidote is intravenous calcium, followed by insulin with supplemental dextrose and potassium.[28] Intravenous calcium 1 g to 2 g by slow bolus infusion over 5 to 10 minutes, each gram over 5 minutes, has been found to provide effective reversal for both shock and severe bradycardia due to dihydropyridine calcium channel blockers.[7,11,12]

### Caution With β-Blocker and Clonidine Use in the Elderly

It should be noted that $\beta_1$-receptor cardioselective and nonselective β-blockers in common use for the treatment of hypertension in the elderly, particularly atenolol, do not have a good indication for routine initial antihypertensive therapy because they have been shown to be less effective than comparator agents.[29,30] Sometimes β-blockers need to be added in more resistant cases as alternative fourth-line therapy. Heart rates should be managed >55 beats per minute in these individuals.

Occasionally used as add-on therapy in more resistant cases, clonidine is poorly tolerated in the elderly and has been associated with bradycardia, syncope, hypotension, and severe drowsiness. The combination of clonidine with a β-blocker can be especially deleterious because abrupt discontinuation of clonidine while taking a β-blocker may lead to discontinuation syndrome with rebound hypertension due to catecholamine surge.[31] Catecholamine-induced vasoconstricting α effects with abrupt clonidine withdrawal in the presence of β-blockade blunting of compensatory vasodilatation may generate significant overshoot hypertension. One review found that sudden clonidine cessation did not result in rebound hypertension at a total daily dose <1.2 mg/d,[31] and overshoot hypertension has been reported with discontinuation of transdermal clonidine therapy between 0.2 mg and 0.4 mg.[32]

## CASE SUMMARIES

These two cases represent a sampling of potentially avoidable elderly hospitalizations resulting from the adverse cardiovascular effects of combined rate-slowing agents used to treat more-resistant hypertension. Case 1 was taking 5 antihypertensive drugs and case 2 was taking 6 drugs. The first case occurred a week following the introduction of clonidine to longstanding metoprolol therapy causing severe sinus bradycardia. The second case occurred a couple of years after taking metoprolol, diltiazem, and clonidine transdermal therapy, resulting in a junctional escape rhythm. Concomitant hydralazine in both patients did not overcome these bradycardias. Age-related drug accumulation, along with the possible development of occult degenerative cardiac conduction system disease led to the delayed presentation in case 2. It took 3 days in the hospital following drug discontinuation for severe bradycardia to resolve in the second patient who was 88 years old.

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