Case Report

Profound Hypotension Following Concomitant Oral Angiotensin Converting Enzyme Inhibitor/Beta-Blocker Administration

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Large scale clinical trials have demonstrated that beta-blockers and angiotensin converting enzyme (ACE) inhibitors independently decrease mortality in post-myocardial infarction (MI) patients.[1-10] However, the use of these agents is limited by contraindications and side efects, including the tendency of both drug classes to induce hypotension. Despite these restrictions, the administration of both a beta-blocker and an ACE inhibitor is appropriate for some MI patients. In these situations, careful monitoring and timing of the administration is necessary to avoid significant hypotension.

CASE

A 67 year-old female presented to the emergency department with complaints of severe chest pain which radiated down her left arm and was associated with diaphoresis. The pain had first occurred 9 hours before admission lasting approximately 90 minutes, then recurred 7 hours later (a half hour before admission) prompting her presentation to the emergency department. A 12-lead electrocardiogram (ECG) revealed ST segment elevations in anterior leads V_1 to V_6. All laboratory investigations, including electrolytes and blood chemistries were within normal limits with the exception of an elevated creatinine kinase (CK) of 605 U/L (normal 0-170 U/L), CK-MB isoenzyme of 82 U/L (normal 0-25 U/L) and apartate aminotransferase (AST) of 84 U/L (normal 0-35 U/L). The patient's heart rate was 70 beats per min (bpm), blood pressure 103/70 mmHg, respiratory rate 20/min and temperature 37.5°C. There were no signs of left ventricular failure, and her chest X-ray was normal showing no evidence of pneumonia or pulmonary congestion. The patient had a 7-year history of non-insulin dependent diabetes mellitus for which she was taking glyburide 5 mg twice daily. Prior to admission she had no known allergies. On the basis of enzyme elevations and ECG, the patient was diagnosed as having an acute MI. A heparin bolus and infusion, tPA, ASA, and a nitroglycerin infusion titrated to relieve chest pain were administered. Two bolus doses of intravenous (IV) morphine 5 mg were required while in the emergency department. Shortly thereafter she was transferred to the intensive/coronary care unit (ICU/CCU).

Upon admission to that unit, the patient was fatigued and had mild chest pain, but was otherwise alert and oriented. She was maintained on a nitroglycerin IV infusion at 40 mcg/minute, IV heparin at 1000 units/hr and was given three 2 mg doses of IV morphine within the first 90 minutes. There was no further chest pain for the duration of her admission. She vomited small volumes (100-150 mL) twice during her first hospital day and was given 25 mg IV dimenhydrinate in each case. Her blood pressure was stable throughout the day ranging from 92/62 mmHg to 115/65 mmHg with a heart rate between 70 to 80 (bpm). She had minimal urine output until mid-afternoon, had a positive fluid balance, and moist mucous membranes. Acebutolol 50 mg po twice daily and enalapril 2.5 mg po twice daily were ordered with the first dose of both medications being given approximately 12 hours after admission to ICU. At that time, her blood pressure was 112/62 mmHg.

One hour later the patient's blood pressure dropped to 80/50 mm Hg, but normalized without intervention within the next 2 hours. However, 4 hours after receiving enalapril and acebutolol her blood pressure again began to fall. The nitroglycerin infusion was stopped and she was administered 6 fluid boluses totalling 1750 mL over the next 4 hours. Despite this, the systolic blood pressure remained between 70 mmHg and 80 mmHg over this period. A Swan Ganz catheter was inserted which revealed a cardiac index of 2.9 L/min/m^2 (normal >2.5 L/min/m^2), pulmonary artery wedge pressure (PCWP) of 19 mmHg (normal 8-12 mmHg), a systemic

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vascular resistance index of 1762 dyne/sec/cm^{-5}/m^2 (normal 2000-2400 dyne/sec/cm^{-5}/m^2). A dopamine infusion was commenced and titrated up to 10 mcg/kg/min with an increase in blood pressure to 100/60 mmHg. Dopamine was required at this dose for the remainder of the admission to maintain a blood pressure of at least 100/60 mmHg and acebutolol and enalapril were discontinued. An echocardiogram later revealed an ejection fraction of 40%. The next morning the patient was transferred to another facility for angioplasty.

DISCUSSION

Based on this patient's age and renal function, the initial doses of both acebutolol and enalapril complied with manufacturer recommendations.[11,12] The patient vomitted twice prior to administration of enalapril and acebutolol, however, hypovolemia was not suspected since the patient had a 2 L positive fluid balance, moist mucous membranes, a normal heart rate, and a stable blood pressure. This was confirmed with insertion of a Swan Ganz catheter after fluid boluses which revealed a PCWP of 19 mmHg. Despite this, the patient required a dopamine infusion to maintain her blood pressure following administration of acebutolol and enalapril. As well, there was no evidence of further ischemia which could have accounted for the decline in blood pressure.

Acebutolol-induced hypotension can occur within 2 hours of administration, which is consistent with the timing of this patient's first drop in blood pressure.[13] The peak onset of enalapril's hypotension occurs within 4 to 8 hours[13] following oral administration, which may explain the second more severe drop in blood pressure. Although this patient's systolic blood pressure was above 100 mmHg when both agents were given, by the time the enalapril reached its peak effect, systolic BP was 85 mm Hg. Evidence from the literature suggests that ACE inhibitors be held when the systolic BP is below 100 mmHg.[4]

Beta-blockers have been shown to decrease mortality in patients with acute myocardial infarction[1-3] and are generally recommended in this population.[14] Although early beta-blocker use (immediate IV beta-blockade, followed by oral therapy initiated on day 1) has been shown to reduce mortality in numerous trials and a widely quoted meta-analysis,[15] two large trials have shown no significant mortality benefit.[1,2] The evidence for reduced mortality from oral beta-blockade initiated 5 to 28 days after MI appears stronger and was associated with a lower odds ratio in a recent meta-analysis.[15] In TIMI-IIB, early beta-blockers were compared to late (initiated on day 6) administration. Early use was associated with a lower incidence of ischemia and reinfarction in the first week, but there was no benefit over late administration in improving ventricular function or reducing mortality.[2]

Our patient had none of the common contraindications to beta-blocker use (e.g., hypotension, bradycardia, secondary and tertiary heart block, asthma, or pulmonary edema[14,16]) and, hence, beta-blocker therapy was initiated. The echocardiogram conducted on the second day post-MI revealed an ejection fraction of 40%, but at the time acebutolol and enalapril were administered there were no clinical signs of heart failure.

Even among patients who qualify for beta-blockade post-MI, hypotension may be a problem. In the MIAMI trial, 4.7% of patients withdrew due to hypotension,[1] while in ISIS-1, 5% of beta-blocker patients required inotropes.[3] However, these trials involved the use of intravenous beta-blocker within the first 24 hours followed by oral therapy. The incidence of hypotension attributed soley to oral beta-blocker use was not reported. When therapy was initiated 5 to 28 days post-MI, hypotension was a common adverse effect[17-19] with 2.8% of patients in the Norwegian Multicenter Study[17] and 1.2% of patients Beta-Blocker Heart Attack Trial (BHAT)[18] withdrawing from the study due to hypotension. None of these trials reported concomitant ACE inhibitor therapy.

The use of ACE inhibitors post-MI has also been shown to decrease mortality and reinfarction, as well as to attenuate progressive left ventricular dysfunction.[4-10] Those benefitting the most include patients with signs and symptoms of failure, ejection fraction less than 40%, and patients with a past or present anterior myocardial infarct.[14-20] While caution is warranted in patients with renal dysfunction, the lowest estimated creatinine clearance of 51 mL/minute in this patient would not preclude ACE inhibitor use nor necessitate dosage adjustment.[12]

With the exception of the SAVE trial,[5] the main reason for withdrawal from the ACE inhibitor trials quoted above was hypotension[4,6-10,20] with the highest incidence being reported at 9.7%.[8] The CONSENSUS II trial was prematurely stopped because of a trend toward increased mortality in the treatment group, possibly due to excessive hypotension from intravenous enalaprilat.[6] However, GISSI-3,[8] ISIS-4,[10] and SMILE[4] results suggest that oral ACE inhibitors can be safely administered within 24 hours post-MI in the majority of patients.

Both ACE inhibitors and beta-blockers have been demonstrated to decrease mortality when administered within the first 24 hours of infarction.[1-3,8,10,14] However, there are few warnings or recommendations in the literature designed to prevent excessive hypotension when beta-blockers and ACE inhibitors are administered concurrently. The only pertinent comment in the trials quoted above is found in the CONSENSUS II trial where the methodology includes a recommendation that intravenous beta-blockers be completed before administration of enalapril.[6] The Vasotec® product monograph[12] states

only that "beta-adrenergic blocking agents add some further antihypertensive effect to enalapril", while there is no warning about concurrent ACE inhibitor use in any of the acebutolol monographs listed in the Compendium of Pharmaceuticals and Specialties.[11]

In the trials quoted above examining the use of ACE inhibitors post-MI, the percentage of patients entering the trials who received beta-blockers within the first 24 hours of randomization averaged from 2.5% in the SMILE[4] trial to 30% in the GISSI-3 trial.[8] Unfortunately, adverse events were not reported according to concomitant beta-blocker use, however, some trials did report mortality for the subgroups receiving beta-blockers.[4-6] In these trials, there did not appear to be a mortality risk associated with concomitant beta-blocker/ACE inhibitor therapy. Patients receiving both therapies had a lower rate of mortality than those who received a beta-blocker and no ACE inhibitor.[20]

The current literature supports that, in the absence of contraindications IV beta-blockers should be administered as soon as possible after presentation with an acute MI.[14] When IV therapy is given, oral beta-blockers should be initated during the first day of therapy.[14] If IV beta-blockers are not used, initating oral beta-blockers 5 to 28 days post-MI should be considered using the same contraindications mentioned above. Whether or not an IV beta-blocker has been used, oral ACE inhibitor therapy should be initiated in all MI patients without contraindications (hypotension, bilateral renal artery stenosis, renal failure, previous angioedema, or cough associated with ACE inhibitor use).[14,21] It is generally recommended that ACE inhibitor therapy should be administered within 24 hours of the onset of symptoms whenever possible.[14] However, a recent review suggests that, in order to avoid excessive hypotension, ACE inhibition should be delayed until later in day 1 or even day 2 post-MI in patients receiving beta-blockers.[21] Whenever ACE inhibitors are initiated in patients receiving beta-blockers, low doses should be used initially in order to observe for additive hypotensive effects. Captopril may offer an advantage since it has a short duration of effect and, thus, any acute ACE inhibitor-related adverse effects will be short lived. In ISIS-4, captopril was used at a dose of 6.25 mg initially, followed by 12.5 mg 2 hours later, 25 mg 10-12 hr later, to a target of 50 mg bid based on blood pressure response.[10] Once a tolerable maintenance dose is reached, a once daily preparation in an equivalent dose could be administered if desired.[21] Similarly, if oral beta-blockers are initiated for a patient currently receiving ACE inhibitors, low doses of the beta-blocker should be used initially, and the dose should be titrated up carefully with close attention to the blood pressure response.

Chronic therapy should consist of 4 to 6 weeks of ACE inhibitor in all patients without contraindications.[14,21] If the patient has evidence of left ventricular dysfunction or heart failure at that time, therapy should be continued for at least 3 years.[14,20] Chronic beta-blocker therapy should be continued for at least 2 to 3 years in all patients without contraindications.[14,20] Chronic combination therapy with these 2 agents should be carried out using the same strategies as described for the individual classes with gradual dose titration to avoid excessive hypotension.

Both beta-blockers and ACE inhibitors are proven effective therapies in the treatment of acute MI. However, since both therapies can lower blood pressure, administration times should be staggered to avoid the risk of profound hypotension. Unfortunately, there are no clear guidelines specifying which agent should be given first when both drugs are administered orally. Oral ACE inhibitors have been more extensively studied, and results indicate that earlier therapy results in greater mortality benefit.[21] On the other hand, some authors have suggested that the benefit seen with early IV beta-blockers can be extrapolated to oral therapy.[19] A recent review by Canadian cardiologists suggests delaying ACE inhibitor therapy until the maximum blood pressure response to beta-blockers has subsided.[21] In the setting of acute MI, normal hemodynamics should be maintained to avoid compromising patient outcomes.[6]

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