CARVEDILOL AGGRAVATES ORTHOSTATIC HYPOTENSION IN A DIABETIC PATIENT WITH CHRONIC RENAL FAILURE

Tsuan-Shih Yu, Chin-Feng Tseng, Lai-King Yeung, Kuo-Cheng Lu, Chuan-Chieh Liu

A 64-year-old male was admitted because of progressive dyspnea, bipedal edema and reduced urine output. His medical history included coronary artery disease with coronary artery bypass graft, hypertension and type 2 diabetes mellitus with chronic renal failure and retinopathy. During admission, he developed severe postural dizziness. Positional blood pressure and heart rate measurements revealed fluctuations in systolic blood pressure greater than 20 mmHg but no significant heart rate change. Two days after stopping carvedilol, systolic blood pressure declined by only 10 mmHg and heart rate increased significantly with positional changes. Orthostatic hypotension due to autonomic neuropathy was suspected. Nerve conduction velocity study showed severe sensorimotor polyneuropathy. Sympathetic skin response and RR interval variability tests indicated autonomic dysfunction.

Combinations of alpha- and beta-blockers should always be administered with caution in diabetics, who are likely to have autonomic nervous system dysfunction and in whom the use of such medications may increase the risk of orthostatic hypotension. (Acta Nephrologica 2006; 20: 120-125)

Key words: orthostatic hypotension, carvedilol, diabetes, renal failure, autonomic neuropathy

INTRODUCTION

The American Autonomic Society and the American Academy of Neurology defines orthostatic hypotension (OH) as a decline in systolic blood pressure of at least 20 mmHg beyond 3 minutes of standing or passive head-up tilt position at 60 degrees. Many factors have been linked to OH, including age, prolonged bed rest, low body mass index, systemic diseases (e.g., diabetic autonomic neuropathy, stroke, multiple sclerosis, amyloidosis, adrenal insufficiency) and medications (e.g., antipsychotic agents, peripheral vasodilators, specifically alpha-blockers and non-dihydropyridine calcium channel antagonists).

If a patient suspected of having OH is hypertensive and requires antihypertensive medications, pre-treatment measurements are necessary to identify the presence of baseline OH. If no baseline OH is detected, antihypertensive medications may be prescribed while regularly monitoring for OH. If pre-treatment OH is found, clinicians should balance the possible risk of worsening postural hypotension due to antihypertensive therapy against the hemodynamic benefits of improved blood pressure control.

We report a patient with diabetic nephropathy and neuropathy, who presented carvedilol aggravated OH.

CASE REPORT

A 64-year-old male was admitted because of progressive dyspnea, bipedal edema and reduced urine output of three weeks duration. He has a history of coronary artery disease with 3-vessel disease for which he had received coronary artery bypass graft surgery one year prior to this admission. He also has had type 2 diabetes mellitus for the past 16 years; diabetic retinopathy, chronic renal failure and hypertension had been noted since 2 years before this admission. At the time of admission, his medical prescription included combined regular and intermediate acting insulin preparations, digoxin 0.125 mg/day, irbesartan 150 mg/day, pravastatin 20 mg/day, clopidogrel 75 mg/day, and...
patient developed tarry stools but upper gastrointestinal motion abnormality. On the third hospital day, the ventricular ejection fraction of 62% and regional wall motion was 22.65 ml/min. Twenty-four hour urine creatinine clearance (CCr) was 22.65 ml/min.

Electrocardiogram revealed sinus rhythm with a heart rate of 90/min, QT interval of 320 msec, and a QTc of 393 msec. Echocardiogram revealed a left ventricular ejection fraction of 62% and regional wall motion abnormality. On the third hospital day, the patient developed tarry stools but upper gastrointestinal panendoscopy revealed only duodenitis and superficial gastritis. He received a transfusion of eight units of packed RBC for severe anemia. Hemoglobin level on the seventh hospital day was 10.2 g/dl. All antihypertensive medications were discontinued upon admission due to hypotension but were resumed on the second hospital day due to recurrence of high blood pressure. Carvedilol (25 mg/day) was given starting on the third hospital day due to persistently high blood pressure. Increased urine output and gradual resolution of bipedal edema were noted following intravenous furosemide administration although mild peripheral edema persisted. The jugular venous pressure level remained approximately 5 cm above the sternal border and there was no evidence of volume depletion.

After one week of carvedilol administration, he developed progressively severe dizziness with vertigo, particularly with changes in position. On the 9th day of carvedilol treatment, he was noted to have sensory ataxia with involuntary falling episodes. Upon neurological consultation, polyneuropathy due to underlying diabetes with chronic renal failure and/or vertebralbasilar insufficiency were suspected. Nerve conduction velocity study showed severe sensorimotor polyneuropathy. Carotid doppler scanning revealed 50% stenosis of the left common carotid artery and moderate to severe atherosclerosis of both common carotid and internal carotid arteries although total vertebral artery blood flow was adequate. Positional blood pressure and heart rate changes were measured in the supine, sitting and standing positions for 2 consecutive days. Systolic blood pressure declined by more than 20 mmHg with changes in position but heart rate did not change significantly (Table 1). Upon review of his medications, carvedilol was suspected as the most probable cause of OH and was thereby discontinued. Two days after stopping carvedilol, the patient claimed that he felt much better. Electrocardiography was done to record R-R interval in the supine, sitting, and standing positions for at least 3 minutes (Fig. 1). Supine QT was 356 msec and QTc was 430 msec. Sitting QT was 326 msec and QTc was 428 msec. Standing QT was 312 msec and QTc was 414 msec. Simultaneous blood pressure readings showed a 10 mmHg decline in systolic blood pressure; tachycardia was also noted with changes in position (Table 1). No further episodes of postural dizziness or sensory ataxia were noted on follow-up. We suspected that the 10 mmHg fall in systolic blood pressure after stopping carvedilol might be due to underlying diabetic autonomic neuropathy. Thus, sympathetic skin response (SSR) and RR interval variability (RRIV) studies were performed. Results revealed RRIV 4.84% against a normal value > 10% (Fig. 2). Normal SSR was seen on right upper extremities. (Fig. 3) and absent SSR on the left upper and both lower extremities. (Fig. 4) These two studies indicate the presence of autonomic dysfunction in this diabetic patient with chronic renal failure.

DISCUSSION

Diabetes is the leading cause of neuropathy in the Western world, and neuropathy is the most common complication and the greatest source of morbidity and mortality in diabetics. Diabetic neuropathy may manifest as sensorimotor neuropathy, distal symmetrical polyneuropathy or autonomic neuropathy involving the cardiovascular, gastrointestinal and genitourinary systems. Autonomic neuropathy may involve both the sympathetic and parasympathetic innervations of the heart and coronary vessels, with hallmark symptoms of orthostatic hypotension and decreased heart rate variability. The incidence of cardiovascular autonomic neuropathy appears to be around 15% in type 1 and 20% in type 2 diabetes patients. Cardiovascular autonomic neuropathy may contribute to left ventricular dysfunction, silent or asymptomatic myocardial infarction, and exercise intolerance.

Autonomic nervous system dysfunction may also develop in patients with uremia. Impotence, postural dizziness, feeling of gastric fullness or delayed emptying, bowel dysfunction, and reduced sweating are the most common symptoms. Hemodialysis may improve autonomic function in uremic patients.
Table 1. Comparison of postural BP and postural HR before and 2 days after discontinuation of carvedilol

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Abbreviations: BP, blood pressure; HR, heart rate

Fig. 1. Electrocardiography 2 days after discontinuation of carvedilol. (a) in supine position, QTc 430 msec, (b) three minutes after change from supine to sitting position, QTc 428 msec and (c) three minutes after change from sitting to standing position, QTc 414 msec.
Fig. 2. R-R interval variability test

Fig. 3. SSR of right upper extremities

Fig. 4.

Min: 79 bpm  Mean: 81 bpm
Max: 82 bpm  SD: 0.9 bpm
Rate Variance: 4.84%

Normal response
incidence of OH in diabetics with chronic renal failure is 37.5%. Our patient had chronic renal failure due to diabetic nephropathy and presented with azotemia which may have aggravated his underlying autonomic neuropathy.

The regulation of blood pressure and heart rate with changes in position involves the cardiovascular, musculoskeletal, renal, endocrinological and autonomic nervous systems. Conditions that predispose an individual to OH include advanced age, decreased baroreflex sensitivity, impaired β-adrenoceptor-mediated response, increased vascular stiffness and decreased number of pacemaker cells in the sinoatrial node. Drugs which may cause OH or worsen positional blood pressure changes include psychoactive medications such as tricyclic antidepressants, antiparkinsonism agents and cardiovascular medications, such as vasodilators. Some antihypertensive medications may interfere with postural haemodynamic stability, thereby aggravating positional blood pressure and predisposing to OH. On the other hand, certain antihypertensive medications may improve baroreflex sensitivity and decrease vascular stiffness, which may ameliorate positional blood pressure changes and lessen the risk of OH.

It is well known that non-selective beta-blockers reduce blood pressure, heart rate and myocardial oxygen demand. However, animal studies have shown that the alpha-1 blockers may induce vasodilatation, increase peripheral vascular blood flow and decreased the limb vascular resistance. Since peripheral vasoconstriction is an important counter-mechanism during postural changes, patients receiving alpha-blockers may be at increased risk of developing OH.

Carvedilol may preserve renal function without eliciting reflex stimulation of the renin-angiotensin-aldosterone system or fluid retention. Carvedilol also does not affect glucose tolerance or carbohydrate metabolism and is therefore suitable for the treatment of hypertensive patients with type 2 diabetes mellitus. In vitro and animal studies have also shown that carvedilol has cardioprotective and neuroprotective properties that may be beneficial in patients with angina pectoris or congestive heart failure. Our patient has coronary artery disease, type 2 diabetes mellitus with chronic renal failure and hypertension and we used carvedilol for the above reasons. However, carvedilol is a nonselective beta-adrenoceptor with alpha-blocking activity and may be associated with a 40% increased risk of OH in elderly patients. In one study, patients on 25 mg of carvedilol daily developed a dose-dependent fall in supine blood pressure and standing blood pressure. In contrast, beta-blockers with intrinsic sympathomimetic activity produced similar reductions in supine blood pressure but less significant reductions in standing blood pressure. Our patient had systolic blood pressure fluctuations greater than 20 mmHg with changes in position but no significant change in the heart rate. After oral administration, the half-life of carvedilol is 2 to 8 hours although it may only be 2 to 5 hours in the elderly (age > 65 years). Two days after stopping carvedilol, our patient felt much better clinically. Follow up systolic blood pressure declined by only 10 mmHg and heart rate increased significantly with positional changes. The 10 mmHg fall in systolic blood pressure after stopping carvedilol is most probably due to underlying autonomic neuropathy. Our patient has a long history of diabetes and nerve conduction velocity examination showed severe sensorimotor polyneuropathy. The SSR test provides useful information regarding sympathetic postganglionic function and an absent SSR supports a diagnosis of diabetic autonomic neuropathy. A lower RRIV may also be seen in diabetics with cardiac autonomic neuropathy and absent SSR. In our patient, absent SSR and low RRIV both indicate the presence of autonomic dysfunction clinically presenting as OH.

In conclusion, physicians must keep in mind that carvedilol may aggravate orthostatic hypotension in the diabetic patient with chronic renal failure, particularly those with underlying autonomic neuropathy. If OH is a problem, the use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers with intrinsic sympathomimetic activity (e.g., pindolol) and calcium blockers such as verapamil may be considered.

REFERENCES

8. Heidreder E, Schafferhans K, Heidland A: Disturbances of