Efficacy and Safety of Bosentan Treatment for Portopulmonary Hypertension Associated With Syncope

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SUMMARY

Pulmonary arterial hypertension (PAH) in patients with portal hypertension is also referred to as portopulmonary hypertension (PPHTN). Here, we report a case of PPHTN caused by alcoholic liver cirrhosis in a 43-year-old male who experienced repetitive syncope on exertion. The continuous monitoring of pulmonary arterial pressure and radial arterial pressure revealed that his PAH was aggravated with a drop in systemic arterial pressure during an exercise test. Bosentan, an endothelin A/B receptor antagonist, improved the patient’s hemodynamic parameters and abolished his syncope without adverse effects. This is the first report that bosentan may be effective and safe for PPHTN associated with syncope. (Int Heart J 2011;52:243-245) 

Key words: Portopulmonary hypertension, Syncope, Bosentan, Liver cirrhosis

Portopulmonary hypertension (PPHTN) is defined as pulmonary arterial hypertension (PAH) associated with portal hypertension. The diagnostic criteria for PPHTN are abnormal increases in the mean pulmonary arterial pressure (PAP) (>25 mmHg) and pulmonary vascular resistance (>240 dynes/second/cm²), and a normal pulmonary capillary wedge pressure (<15 mmHg) in patients with liver disease causing clinical portal hypertension. The prognosis of PPHTN is very poor, and the pathogenesis and management of PPHTN are not well understood.

We present a patient with PPHTN associated with syncope who was treated successfully with the oral endothelin A/B receptor antagonist bosentan.

CASE REPORT

A 43-year-old male was admitted to another hospital for deterioration of alcohol-related liver damage in September 2009. He recovered after rest and abstinence from alcohol. However, he developed repetitive faintness and syncope during walking or light exertion after leaving the hospital. During an exercise treadmill test, which was performed according to the Bruce protocol, electrocardiography revealed a shift from sinus tachycardia (120 bpm) to an atrioventricular junctional rhythm (60 bpm) with sinus pauses, followed by syncope at 4 minutes in that protocol (Figure 1A). He was admitted to our hospital for syncope in November 2009.

On physical examination, his second heart sound was increased and a pansystolic murmur attributable to a tricuspid regurgitation was detected. No leg edema or cranial or peripheral neuropathy was observed. Resting electrocardiography showed a normal sinus rhythm with negative T waves in the right precordial leads. Echocardiography revealed a tricuspid regurgitation with a high pressure gradient (55 mmHg), a dilated right ventricle and a leftward bulging of the interventricular septum, especially in systole (Figure 1B and 1C). Cardiac catheterization showed that the coronary arteries and left ventricular wall motion were normal. His pulmonary capillary wedge pressure and systemic vascular resistance were within the normal range (14 mmHg and 1493 dynes/second/cm², respectively). However, his pulmonary arterial pressure (PAP) and pulmonary vascular resistance were high (68/30 [43] mmHg and 713 dynes/second/cm², respectively), while his cardiac index was low (2.1 L/minute/m²). The patient performed an exercise treadmill test according to the Naughton protocol, which is milder than the Bruce protocol, with continuous monitoring of his systemic arterial pressure (SAP) and PAP using a radial arterial cannula and Swan-Ganz catheter (Table). His PAP increased suddenly just after the start of exercise, and reached 96/47 [68] mmHg at peak exercise with a drop in SAP (99/57 [71] mmHg). His arterial oxygen saturation decreased from 95% to 90%, but no exacerbation of breathlessness occurred. The patient did not complete the exercise treadmill test due to dizziness.

The results of abdominal computed tomographic and ultrasonographic analyses were compatible with liver cirrhosis. Furthermore, gastrointestinal endoscopy revealed esophageal varices. The laboratory data (bilirubin 2.9 mg/dL, albumin 3.9 mg/dL, and prothrombin time 42.3%), the presence of mild ascites, and the absence of encephalopathy indicated Child-Pugh class B liver dysfunction. Autoimmune disease and pulmonary thromboembolism were ruled out by negative antibody tests and imaging studies. Thus, a diagnosis of portopulmonary hypertension (PPHTN) accompanied by portal hypertension...
caused by alcoholic cirrhosis was made. After written informed consent was obtained, oral treatment with bosentan was initiated at a dose of 62.5 mg twice daily. After 10 days, the patient’s PAP improved to 51/20 [37] mmHg, and he was able to exercise for 6 minutes following the Bruce protocol without hypotension or syncope. The patient experienced no syncope or adverse effects due to bosentan for 3 months after he was discharged from our hospital. His Child-Pugh class improved from B to A; therefore, the dose of bosentan was increased to 125 mg twice daily. The next month, his 6-minute walk test improved from 400 m to 525 m after the administration of bosentan. Echocardiography revealed that the leftward bulging of the interventricular septum had resolved throughout diastole and systole (Figure 1D and 1E). In addition, cardiac catheterization showed that his PAP and pulmonary vascular resistance had decreased to 45/20 [30] mmHg and 195 dynes/second/cm$^5$, respectively, while his cardiac index had increased to 3.6 L/minute/m$^2$ (Figure 2).

For a year, no symptoms including syncope developed and the hepatic adverse effect due to bosentan was absent in the patient.

**DISCUSSION**

Portopulmonary hypertension (PPHTN) is defined as pulmonary arterial hypertension (PAH) associated with liver disease or portal hypertension. The prognosis of PPHTN is poor, with an average life expectancy of 15 months after diagnosis, if untreated. The pathogenesis of PPHTN is not well understood. One putative mechanism involves an imbalance in endogenous vasoconstrictive substances (eg, endothelin-1), originating from the damaged liver or splanchnic circulation via portosystemic shunts. It was reported that the levels of endothelin-1 were elevated in rat models of PAH and in patients with cirrhosis.

Syncope is common in patients with PAH; however, only one case of PPHTN with syncope has been reported, and that patient died before treatment. Our patient experienced repetitive faintness and syncope during light exertions and an exercise treadmill test. It is difficult to imagine that a decrease in

**Table. Cardiopulmonary Hemodynamics During the Exercise Treadmill Test According to the Naughton Protocol**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>4 minutes</th>
<th>8 minutes</th>
<th>Peak Exercise</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (bpm)</td>
<td>70</td>
<td>105</td>
<td>109</td>
<td>118</td>
<td>78</td>
</tr>
<tr>
<td>Cardiac Index (L/minute/m$^2$)</td>
<td>2.3</td>
<td>-</td>
<td>-</td>
<td>5.6</td>
<td>-</td>
</tr>
<tr>
<td>SaO$_2$ (%)</td>
<td>95</td>
<td>-</td>
<td>-</td>
<td>90</td>
<td>94</td>
</tr>
</tbody>
</table>

SAP indicates systemic arterial pressure; PAP, pulmonary arterial pressure; and SaO$_2$, arterial oxygen saturation.

**Figure 1.** (A) Baseline electrocardiography performed during the exercise treadmill test showed sinus tachycardia (120 bpm), which changed to an atrioventricular junctional rhythm (60 bpm) with sinus pauses followed by syncope (arrow). (B and C) Short-axis view of echocardiography in diastole and systole demonstrated a leftward bulging of the interventricular septum before the bosentan treatment (arrowheads). (D and E) The abnormal motion of the interventricular septum disappeared throughout diastole and systole 4 months after the treatment. LV indicates left ventricle and RV, right ventricle.

**Figure 2.** Time course of hemodynamic parameters obtained before and during bosentan treatment. The grey-shaded area and dotted line indicate the systemic arterial pressure (SAP) and its mean pressure, respectively. The lined area and dotted line indicate the pulmonary arterial pressure (PAP) and its mean pressure, respectively. PVR indicates pulmonary vascular resistance and CI, cardiac index.
heart rate to 60 bpm for such a short time during the exercise test could have caused the syncpe. Although his SAP was not monitored continuously at that time, it seems likely that the hypotension contributed to the syncpe. In the subsequent exercise treadmill test, syncpe was not induced; however, an increase in PAP and decrease in SAP were noted. Syncpe would likely have occurred under a more strenuous or prolonged exercise regime.

Exercise is known to aggravate PAH, which causes an elevation in right ventricular pressure and a leftward bulging of the interventricular septum, followed by a collapse of the left ventricular cavity (the so-called “reverse Bernheim phenomenon”). Another hypothesis is that right ventricular dysfunction may cause a decrease in left ventricular preload, with simultaneous hyperkinetic left ventricular wall motion due to sympathetic stimulation during exercise. As a result, mechanoreceptors in the ventricular wall are stimulated, followed by a vagal reflex reaction, including bradycardia and hypotension. Such exercise-induced hemodynamic changes and vagal reflexes may have led to syncpe in the present case. Our findings suggest that an improvement in PAH can interrupt these mechanisms and prevent syncpe.

Bosentan is an oral endothelin A/B receptor antagonist that has been shown in randomized trials to have long-term therapeutic benefits in patients with PAH. Bosentan is expected to be pharmacologically effective in PPHTN because endothelin is considered to be a pathogenic factor for PPHTN. However, bosentan is contraindicated in patients with liver cirrhosis, because of its liver toxicity. In this case, bosentan produced a marked reduction in the patient’s PAP, improved his ability to tolerate exercise, and prevented syncpe. Additionally, the patient’s liver damage was improved, perhaps because the reduction in PAP reversed hepatic congestion. To our knowledge, this is the first report of a patient with PPHTN associated with syncpe that was successfully treated with bosentan. Thus, bosentan may be useful as a treatment in patients with PPHTN associated with syncpe.

REFERENCES