Case Report

Bosentan Improved Syncope in a Hemodialysis Patient With Pulmonary Hypertension and Mild Aortic Stenosis

Asuka YAMANAKA,1 MD, Hiromi TASAKI,1 MD, Yoshiyuki SUZUKI,1 MD, Seiya TANAKA,1 MD, Kazuhito YAMASHITA,1 MD, Masahito TAMURA,1 MD, Haruhiko ABE,1 MD, and Yutaka OTSUJI,1 MD

SUMMARY

Pulmonary arterial hypertension (PAH), caused by collagen diseases, Eisenmenger syndrome or of idiopathic etiology, generally has a poor prognosis. Recently, bosentan, a dual endothelin receptor antagonist, has become available for treating PAH. This report describes a bosentan-effective case of combined PAH, hemodialysis and mild aortic stenosis. A 71-year-old woman on hemodialysis was referred to our hospital because of repetitive syncope. Although neurological examinations revealed no etiological diseases, echocardiography and cardiac catheterization showed PAH and mild aortic valve stenosis. Bosentan abolished syncope with improvement of hemodynamic parameters. This report suggests bosentan was clinically useful in a hemodialysis patient with pulmonary hypertension and mild aortic valve stenosis. (Int Heart J 2006; 47: 911-917)

Key words: Pulmonary hypertension, Syncope, Bosentan, Aortic valve stenosis, Hemodialysis

REPETITIVE syncope is caused by neurological disorders such as seizures, arrhythmic disorders such as block or sick sinus syndrome, and reflex-mediated syncope such as vasovagal reflex, orthostatic hypotension, or organic heart disease. Since it has a wide differential diagnosis, it is sometimes difficult to specify the etiology and treat syncope. Organic diseases with syncopal attacks usually have a poor prognosis, and loss of consciousness often leads to severe injuries. Therefore, diagnosis and treatment of syncope is extremely important for patients.1)

Pulmonary hypertension (PH) exhibits right-sided heart failure, resulting in hypoxia, low cardiac output, and venous congestion. Although PH can be the result of diverse diseases, one of the principal mechanisms is pulmonary arterial hypertension (PAH), including idiopathic PAH (IPAH), Eisenmenger syndrome,
and collagen disease-related PH. PAH has been treated with anticoagulant therapy (warfarin or aspirin) and with prostacyclin (PGI₂) derivatives (beraprost).2) Nitric oxide inhalation3,4) and the phosphodiesterase inhibitor sildenafil5,6) have also been reported in clinical trials. If no desirable effect is obtained with these medications, we have to consider continuous intravenous infusion of the PGI₂ derivative sodium epoprostenol.7,8) Meanwhile, a dual endothelin receptor antagonist, bosentan, has been available in Japan since 2005.9)

We report a case of IPAH in which repetitive syncope was successfully treated by bosentan. Syncope attack in this patient was thought to be related mainly to PH and partially to hemodialysis and mild aortic stenosis.

**CASE REPORT**

A 71-year-old woman was admitted to our hospital with repetitive syncope. She had been treated with hemodialysis for 22 years because of glomerulonephritis-based chronic renal failure. One month prior to admission, she started to feel severe general fatigue while housekeeping or taking a bath. She had also suffered syncope on exertion, such as walking with baggage or going up steps, and injuries to her head and face. She experienced similar episodes on 2 occasions over the next 10 days. All of these syncopal attacks happened during exertion in the morning after hemodialysis, lasted less than 1 minute, and were without seizure, chest discomfort, or neurological deficit.

On physical examination, her 2nd heart sound (pulmonic component) was increased, and she had a holosystolic regurgitant murmur (tricuspid area) and a systolic ejection murmur (aortic valve area). She also had mild hepatomegaly and leg edema. Laboratory examinations (Table I) revealed anemia, azothemia, high brain natriuretic peptide (BNP), and hypoxia due to chronic renal failure and/or heart failure. However, there were no abnormal findings related to thrombus, such as collagen disease, antiphospholipid antibody syndrome, coagulation or fibrinolysis. Moreover, she had no serological signs for human immunodeficiency virus infection or drug-induced allergy.

Neurological examination, including a head-up tilt test, showed no abnormal findings that could induce syncope. Electrocardiography revealed right axis deviation, right ventricular hypertrophy, right atrial overload, and left ventricular hypertrophy. Holter ECG or ECG monitoring during hemodialysis showed no arrhythmia that might be related to syncope. Chest x-rays showed cardiomegaly (cardiothoracic ratio = 61%), and dilatation of the pulmonary arteries, right atrium and ventricle. Echocardiography demonstrated the presence of a dilated right ventricle, which compressed the left ventricle, and mild left ventricular hypertrophy. Doppler examination measured a tricuspid regurgitation (TR) pres-
sure gradient of 93.7 mmHg and a mean pulmonary artery pressure (PAP) of 57.5 mmHg.\textsuperscript{10,11} It also suggested that the aortic valve was stenosed with 3 calcified leaflets, resulting in a valve area of 1.6 cm\(^2\) and a pressure gradient of 25.4 mmHg. These findings clarified the presence of severe PH and mild aortic valve stenosis.

Enhanced CT revealed dilatation of the pulmonary arteries, but did not detect thrombus or changes in the lung field. Pulmonary perfusion scintigraphy did not detect any perfusion defect. Echo examination of the lower leg did not detect any deep vein thrombosis. A lung capacity examination showed a normal spirometry with 77\% FEV\(_{1.0}\)\% and 80\% volume capacity.

Right heart catheterization revealed elevated PAP, pulmonary vascular resistance, and right ventricular pressure, as well as mildly reduced cardiac output. It also showed mild elevation of the pulmonary artery wedge pressure (PAWP). To
minimize the effect of hemodialysis, catheterization before and 4 weeks after bosentan therapy was performed the morning after hemodialysis (Table II). Left heart catheterization showed mild aortic stenosis, with a pressure gradient across the aortic valve of 20 mmHg, and no significant coronary stenosis.

We concluded that the syncope was a combination of severe PH with mild aortic valve stenosis and a reduction in effective circulatory volume after hemodialysis. The PH was considered to be PAH, especially IPAH, because of the absence of thrombosis or embolic episodes and underlying disease. With the elevation of PAWP, which was reflected by postcapillary PH, it was shown that mild aortic stenosis, left ventricular hypertrophy, and chronic renal failure also contributed to the PH. However, the difference between diastolic PAP and PAWP showed that PH was mainly induced by precapillary PH; that is, PAH (Figure).

The severity of the patient’s condition was considered to be class III according to the WHO functional classification, with mild general fatigue and shortness of breath even at rest, and to be stage 4 according to the Japan Primary PH guideline, based on the presence of a mean PAP of 49 mmHg and right heart failure. The results of examination and the presence of syncopal attack indicated effective therapy for PH. Oxygen inhalation and 180 µg/day beraprost were started immediately on admission. However, the patient still had syncope once after hemodialysis even after starting these therapies. Thus, we decided to add the endothelin receptor antagonist bosentan, 62.5 mg twice daily, immediately after catheterization. Three weeks later, the syncope completely disappeared and dyspnea on exercise improved. Arterial oxygen pressure (Po2) increased from 72 mmHg to 95 mmHg. At the same time, echocardiography revealed reduction of the tricuspid regurgitation pressure gradient from 93.7 mmHg to 42.0 mmHg and of mean PAP from 57.5 mmHg to 30.1 mmHg. Four weeks after starting 62.5 mg twice-daily bosentan, right heart catheterization indicated that all parameters had improved slightly (Table II). Simultaneously, BNP decreased from 652 pg/mL to 213 pg/mL. As an adverse reaction to bosentan, the patient’s iron deficiency ane-

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery pressure (mean) (mmHg)</td>
<td>89/31 (49)</td>
<td>55/22 (33)</td>
</tr>
<tr>
<td>Right ventricular pressure (mmHg)</td>
<td>90/18</td>
<td>52/5</td>
</tr>
<tr>
<td>Right atrial pressure (mean) (mmHg)</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne/sec/cm-5)</td>
<td>590</td>
<td>221</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure (mmHg)</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.9</td>
<td>4.0</td>
</tr>
</tbody>
</table>
mia became worse. Thus, 3,000 IU epoetin beta and 40 mg chondroitin sulfate iron colloid were started. Although bosentan should be usually increased to 125 mg twice-daily, we decided that 62.5 mg twice-daily should be the maintenance dosage, because the symptoms and data improved and increasing the dosage might trigger other side effects.14)

**DISCUSSION**

PH has a diverse etiology but its prognosis is generally poor, especially in patients with severe disease according to the New York Heart Association (NYHA) classification or PH guideline.7) The present case is considered to be a complicated case, combining PH with hemodialysis and aortic stenosis. Syncope
is a common symptom and is accompanied by preceding transient PAP elevation and a drop in systemic blood pressure. In our case, syncope occurred on exertion on the morning after hemodialysis. This suggested that her syncope might have been related to hemodialysis and aortic stenosis. Indeed, patients on hemodialysis often feel dizziness or fainting immediately after hemodialysis, because of an acute reduction of the effective circulatory volume. In the present case of PH with hemodialysis and aortic stenosis, we explored treatment based on 3 mechanisms of syncope. Firstly, to decrease transient circulatory volume reduction, dry weight was increased. However, this had to be stopped, because leg edema due to right heart failure worsened. Secondly, it was unlikely that the mild aortic stenosis caused the syncope, and we had no fundamental correction for valve stenosis except valve replacement. Finally, we concluded that treatment for PH might be the most effective for her syncope. Administration of bosentan completely abolished her syncopal attacks and improved her hemodynamic parameters, including BNP. It has been reported that bosentan administration results in an improvement in a 6-minute walk after 4 weeks. It is natural to attribute these effects to this endothelin receptor blocker, because no other conditions were changed in the 4 weeks of treatment. Although hemodynamic data were compared after 12 weeks in other studies, we observed a hemodynamic improvement with bosentan even after 4 weeks and further improvement in pressure gradient of TR by echocardiography. A clear early hemodynamic response was not observed in our case. Further pharmacokinetic study of bosentan in hemodialysis patients is needed.

Since the introduction of bosentan in Japan in 2005, this dual endothelin receptor antagonist has become established as a useful drug for improving pulmonary arterial PH and its prognosis. Now, we have an indication in patients with moderate to severe pulmonary arterial PH (NYHA III or IV). The mechanism is thought to involve inhibition of vasoconstriction, cell hyperplasia and hypertrophy, and an increase in the extracellular matrix.

Although our patient was considered to have primary PH, collagen disease-related PH is more common, and the WHO recommends annual echocardiography for patients with collagen disease, who are prone to PH. Collagen disease also causes renal failure and sometimes end-stage renal failure. The bosentan dosing regimen for patients with renal failure does not need any adjustment, because it is metabolized by the liver. Furthermore, patients on hemodialysis have specific problems with medications for PH. Firstly, sometimes it is difficult to stop bleeding at blood access sites with anticoagulants. Secondly, calcium antagonists reduce blood pressure not only in the pulmonary artery but also in the systemic arteries, resulting in worsened syncope. In contrast, bosentan has no effect on the coagulation and fibrinolysis system, and only a weak effect on
systemic blood pressure. Because stable and safe hemodialysis is extremely important for patients on hemodialysis, bosentan is a promising medicine for those with PH.

**ACKNOWLEDGMENT**

The authors would like to express their gratitude to Jun Matsushita, MT (medical technician), Akemi Nakazono, MT, Kyoko Sakamoto, MT, and Sawami Yuhkawa, MT for their excellent help with the echocardiological examinations.

**REFERENCES**