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CASE REPORT

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Plasma brain natriuretic peptide as a parameter to assess efficacy of continuous intravenous infusion of prostacyclin (epoprostenol) to treat severe primary pulmonary hypertension: a case report

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Abstract Continuous intravenous infusion of prostacyclin (epoprostenol) as a treatment for primary pulmonary hypertension (PPH) definitely improves the patient's quality of life, but few accurate parameters have been found to evaluate the efficacy of the treatment. We observed a patient with severe PPH whose plasma brain natriuretic peptide (BNP) level changed significantly as her condition and symptoms changed. Plasma BNP may be considered as one of the parameters for assessing the efficacy of prostacyclin treatment.

Key words Pulmonary hypertension · Prostacyclin · Brain natriuretic peptide

Case report

The patient was an 18-year-old woman being treated for primary pulmonary hypertension (PPH). At the age of 14 years she began to complain of frequent fatigue and experienced difficulty climbing one flight of stairs. At age 17 she started having increasingly severe episodes of shortness of breath, and her face and limbs became edematous. Echocardiography showed enlargement of the right atrium and ventricle, and right heart catheterization revealed an elevated pulmonary artery mean pressure of 72 mmHg.

Upon arrival at our hospital she was graded New York Heart Association (NYHA) functional class III. She was given a calcium channel blocker, nitrate, and a PDE III inhibitor, but no improvement was seen in her symptoms. During her hospitalization inflammation of the upper respiratory tract caused her symptoms to worsen, and her status became NYHA functional class IV. She was administered furosemide, 20 mg daily; spironolactone, 25 mg daily; digoxin, 0.125 mg daily; aspirin, 81 mg daily; ticlopidine, 100 mg twice daily; and a continuous infusion of heparin, 10 000 units daily. Right heart catheterization revealed a right atrial pressure of 22 mmHg, right ventricular systolic pressure of 135 mmHg, right ventricular end-diastolic pressure of 31 mmHg, and pulmonary arterial mean pressure of 92 mmHg. However, cardiac output was not measured because it was difficult to perform and retain catheterization of the pulmonary artery. The right ventricular systolic pressure estimated by Doppler echocardiography[1] was also high, at 125 mmHg. The plasma brain natriuretic peptide (BNP) level was 1 069 pg/ml (normal: less than 20 pg/ml). Continuous intravenous infusion of epoprostenol was commenced.

As systemic arterial pressure might decline suddenly with this treatment, her initial dose was set at 4 ng/kg per min. Any sudden increase in the dosage might cause severe symptoms, such as headache and vomiting, so we increased her dosage by only 0.3 to 0.5 ng/kg per min, every 2–4 weeks. The hemodynamics before and during continuous intravenous infusion of epoprostenol are shown in Table 1.

One month after starting the epoprostenol regimen, she was able to walk within her hospital room and her plasma BNP level had declined to 885 pg/ml. At 2 months she was able to walk 100 m without rest on a level surface, and her plasma BNP level had declined further to 397 pg/ml (Fig. 1). However, her pulmonary artery mean pressure measured during right heart catheterization and her right ventricular systolic pressure estimated by Doppler echocardiography were still high, at 74 mmHg and 102 mmHg, respectively. At 3 months she was able to walk 200 m without rest on a level surface and her plasma BNP level had further declined to 191.7 pg/ml. However, shortly thereafter, during an excursion outside the hospital, her feeling of malaise returned and her plasma BNP level returned to 275 pg/ml. Two weeks after this incident, she developed a fever and a cough, and a return of edema in her legs and shortness of breath. Her plasma BNP level had risen to 398 pg/ml (Fig. 1). Six months after commencing the epoprostenol regimen, she was capable of walking 300 m without rest on a level surface, was graded in NYHA functional class III,

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Table 1. Hemodynamics at the baseline and during continuous intravenous infusion of epoprostenol

	Baseline	During epoprostenol treatment		
		At 2 months	At 4 months	At 6 months
Heart rate (beats/min)	90	86	73	70
Systemic arterial pressure (mmHg)	112/80	112/78	116/72	110/72
Right atrial mean pressure (mmHg)	22	12	5	3
Right ventricular systolic pressure (mmHg)	135	115	120	99
Right ventricular end-diastolic pressure (mmHg)	31	18	11	6
Pulmonary arterial mean pressure (mmHg)	92	74	70	61
Cardiac output (l/min)	–[a]	2.95	–[a]	3.88
Pulmonary vascular resistance (units)	–	18.3	–	14.2
Systemic vascular resistance (units)	–	26.1	–	21.1

[a] Not performed

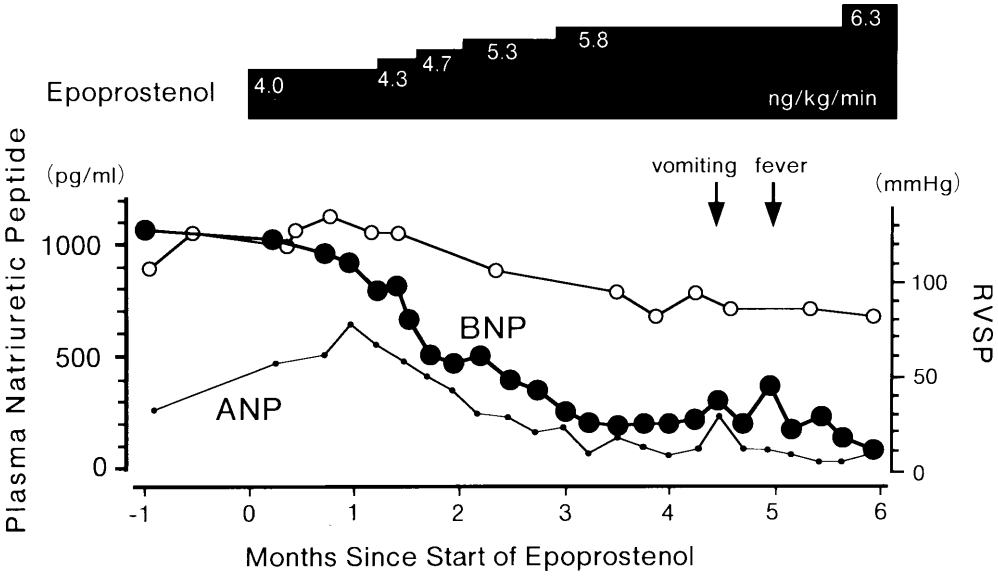

Fig. 1. Changes in plasma levels of atrial natriuretic peptide (*ANP*) and brain natriuretic peptide (*BNP*) during continuous intravenous infusion of epoprostenol. Plasma ANP level (*small solid circles*), plasma BNP level (*large solid circles*), and estimated right ventricular systolic pressure (*RVSP*) using Doppler echocardiography (*open circles*)

and her plasma BNP had declined to 100 pg/ml (Fig. 1). Pulmonary artery mean pressure measured during right heart catheterization was 61 mmHg and right ventricular systolic pressure estimated by Doppler echocardiography was 81 mmHg.

As shown in Fig. 1, the plasma atrial natriuretic peptide (ANP) level had decreased during continuous intravenous infusion of epoprostenol but the change in plasma ANP was small compared with that of plasma BNP. The plasma noradrenaline level had also decreased from 0.22 ng/ml (at baseline) to 0.17 ng/ml (6 months after commencing the epoprostenol regimen) but did not always reflect her condition.

Discussion

PPH is a progressive disease which may lead to death. In recent years, long-term intravenous infusion of epoprostenol, also known as prostacyclin, has been used with success to treat this condition.[2] The drug's antithrombotic effect on platelets and its effect as a powerful systemic as well as pulmonary arterial vasodilator have been described.[3] Intravenous infusion of epoprostenol for the treatment of PPH clearly improves the quality of life of the patient, but its effect on pulmonary artery pressure is slight, and few parameters have been found which reflect its efficacy.

PPH diminishes right heart function by increasing right ventricular afterload.[4] It has also been reported that diminished right ventricular function due to pulmonary hypertension is associated with a lowering of plasma BNP.[5] The following mechanism is thought to cause elevation of the plasma BNP level associated with pulmonary hypertension. (1) During pulmonary hypertension resistance increases within blood vessels in the lungs, resulting in an elevation of right ventricular afterload and diminished right heart function which, in turn, results in elevation of plasma BNP. In this case, we found elevated right ventricular end-diastolic

pressure and decreased cardiac output which had been improved during the continuous intravenous infusion of epoprostenol. This finding supports the possibility of right ventricular dysfunction due to pulmonary hypertension. (2) It has been reported that patients with pulmonary hypertension have high levels of plasma endothelin-1[6] and that a high level of endothelin-1 messenger RNA exists in the endothelial cells of pulmonary arteries of such patients.[7] Since endothelin-1 has been described as a causative element in the production of plasma BNP,[8] the increase of endothelin-1 due to pulmonary hypertension may be a causative factor in the elevation of plasma BNP level.

Plasma ANP and noradrenaline levels had declined during continuous intravenous infusion of epoprostenol, but changes in these hormones were small compared with that of plasma BNP. The plasma BNP level may reflect the patient's condition because plasma BNP is produced in the cardiac ventricular tissue via constitutive pathways[9] and its level immediately responds to ventricular overload resulting in the production of BNP messenger RNA.[10] It has also been reported that during cardiac insufficiency, changes in the plasma BNP level reflect the patient's symptoms more closely than do levels of other hormones.[11,12] Since plasma ANP levels are influenced by several factors including blood pressure, postural change, and sodium intake, plasma BNP may be more suitable than plasma ANP for evaluation of the pathophysiology of pulmonary hypertension.[5] In this case, we also found that the plasma BNP level decreased as the patient's condition improved and rose as it temporarily worsened.

Hemodynamic data and exercise tests are commonly used to assess epoprostenol intravenous treatment for PPH.[13] However, it is too risky to perform these tests many times in NYHA functional class IV patients. Even echocardiography, which requires the patient to remain in a stationary position, may be a burden for these patients.

In patients with severe PPH, measuring the plasma BNP level would be easier to perform and less invasive. Plasma BNP may be considered as one of the parameters for assessing the efficacy of prostacyclin treatment.

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