Fukushima J. Med. Sci.,
Vol. 56, No. 2, 2010

[Case Report]

EFFECTS OF ORAL SUPPLEMENTATION OF L-ARGININE IN THE TREATMENT OF PULMONARY HYPERTENSION SECONDARY TO PULMONARY EMBOLISM : A CASE REPORT

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(Received March 5, 2010, accepted July 23, 2010)

Abstract : We tried L-arginine for the treatment of pulmonary hypertension secondary to pulmonary embolism. The plasma brain natriuretic peptide (BNP) level inversely correlated with the plasma concentration of L-arginine. After oral supplementation of L-arginine, patient's symptoms (shortness of breath and general malaise), state of congestive heart failure, and exercise capacity all improved. L-arginine may be effective in the treatment of pulmonary hypertension secondary to pulmonary embolism.

Key words : L-arginine, pulmonary hypertension, brain natriuretic peptide

INTRODUCTION

Pulmonary hypertension secondary to pulmonary embolism is a life-threatening disease. L-arginine is a physiological precursor of nitric oxide (NO)[1-4)], an important mediator of vasodilatation and inhibition of platelet aggregation. L-arginine has been reported to be effective for patients with primary pulmonary hypertension (PPH)[5-7)]. In PPH, plasma brain natriuretic peptide (BNP) level increases in proportion to the degree of right ventricular dysfunction[8,9)].

The purpose of this investigation is to determine if L-arginine administration is effective for patients with pulmonary hypertension secondary to pulmonary embolism.

CASE REPORT

The patient was a 52-year-old woman with chief complaints of shortness of breath and general malaise, which had begun seven months ago.

On admission, chest X-ray film revealed an increased cardiothoracic ratio (CTR : 57.7%). Doppler echocardiography showed enlargement of the right atrium and ventricle, accompanied by pulmonary arterial pressure elevation (the pressure gradient (PG) estimated from tricuspid regurgitation was 68.7 mmHg). Arterial blood gas analysis revealed PO_2 of 59.3 mmHg, and PCO_2 of 31.2 mmHg (room air). Cardiac catheterization revealed pulmonary arterial hypertension (mean pulmonary arterial pressure ; 47 mmHg, left ventricular end diastolic pressure ; 8 mmHg, cardiac output ; 3.93 L/min). Ischemic heart disease, valvular disease, and cardiomyopathy were excluded by echocardiography and a cardiac catheterization. She had a history of deep vein thrombosis, and showed normal values of D-dimer and FDP on admission. Therefore she was diagnosed as having chronic pulmonary hypertension secondary to pulmonary embolism. The laboratory data on admission are shown in table

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1. The patient gave the written informed consent to follow up her laboratory and clinical data.

She was administered with warfarin, candesartan cilexetil (Angiotensin II Type I receptor antagonist), calcium channel blocker, nitrate, continuous infusion of heparin, and 3 L/min of nasal O_2 (Table 2). However, her symptoms and vital signs did not improve. Five days after admission, oral administration of L-arginine was initiated at 3 g/day and was progressively titrated by 3 g/day every five days.

When the dose of L-arginine was titrated to 12 g/day, the patient's symptoms and laboratory findings significantly improved, PO_2 level improved to 91.3 mmHg and plasma BNP level decreased from 77 pg/mL to 40.5 pg/mL (Fig. 1). Furthermore, when L-arginine was titrated to 15 g/day, her 6-min walk distance on a level surface increased from 50 m to 320 m without a rest. PG decreased to 56.5 mmHg. The hemodynamics before and during oral administration of L-arginine are shown in Table 3. Heart rate and systemic arterial pressure did not show any significant changes after administration of L-arginine.

When the daily L-arginine dose was increased to 15 g/day, the patient's adherence to L-arginine temporarily decreased. This may explain why the

Table 1. Laboratory data on admission

1. Peripheral blood		3. Blood Chemistry			
WBC	8,100 /μL	T-Bil	1.1 mg/dl	Na	141 mEq/L
RBC	649 $\times 10^4$/μL	AST	27 IU/L	K	4.1 mEq/L
Hb	19.5 g/dL	ALT	31 IU/L	Cl	106 mEq/L
PLT	58.8 $\times 10^4$/μL	LDH	265 IU/L	Ca	9.1 mg/dL
		ALP	197 IU/L	Pi	3.7 mg/dL
		BUN	14 mg/dL	Fe	191 μg/dL
2. Serum protein		Crea	0.8 mg/dL	TC	218 mg/dL
TP	7.6 g/dL	UA	8.3 mg/dL	TG	101 mg/dL
ALB	4.5 g/dL			HDL-C	42 mg/dL
		D-dimer	0.5 μg/mL	FBS	88 mg/dL
		FDP	2.5 μg/mL		

There are findings of erythrocytosis secondary to chronic hypoxia.
There are no findings of hepatic or renal dysfunction.

Table 2. Medication before and during oral administration of L-arginine

Warfarin potassium	2 mg/day
Candesartan cilexetil (AT1 antagonist)	8 mg/day
Amlodipine (calcium channel blocker)	5 mg/day
Nicorandil (nitrate)	15 mg/day
Famotidine (H_2 blocker)	20 mg/day
Heparin sodium (continuious i.v.)	5,000 units/day
O_2 (nasal)	3 L/min

Medication was not changed before and after the oral administration of L-arginine.

Table 3. Hemodynamics at the baseline and during oral administration of L-arginine

	Baseline	Days after beginning of oral L-arginine administration (days)				
		3	9	15	21	28
Heart rate (beats/min)	81	72	82	72	67	66
Systemic arterial pressure (mmHg)	104/74	118/78	107/72	90/62	104/68	100/70

plasma concentration of L-arginine temporarily decreased to 96.5 nmol/mL, and the plasma BNP level increased to 54.3 pg/mL. During oral L-arginine administration, plasma L-arginine level directly correlated with PO_2 and inversely correlated with plasma BNP level, even though the plasma atrial natriuretic peptide (ANP) level showed almost no change (Fig. 1). Because of the remarkable improvement in the patient's symptoms and improved adherence to taking L-arginine, she was discharged from the hospital about one month after the initiation of L-arginine treatment.

DISCUSSION

A continuous intravenous infusion of prostacyclin is effective for decreasing the pulmonary arterial pressure[8–11], but it also markedly decreases the quality of life(QOL) of a patient. In addition, prostacyclin is not covered by the Japanese public insurance system in the treatment for pulmonary hypertension secondary to pulmonary embolism. In the present case, the symptoms, exercise capacity, pulmonary arterial pressure, and plasma BNP level remarkably improved after administration of oral L-arginine for one month. Meanwhile, D-dimer and FDP were normal on admission, which may suggest that the patient's improvements were not due to the alterations in the fibrinolytic system.

Nagaya *et al.* have reported beneficial effects of short-term oral administration of L-arginine on hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension in a randomized placebo-controlled study. Seven pulmonary hypertension secondary to pulmonary embolism patients were included in the examination[10].

Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension share features of pulmonary remodeling, and the two disorders might be associated with pulmonary endothelial dysfunction[6].

NO is produced by three nitric oxide synthase (NOS) isoforms—neuronal NOS (nNOS) ; inducible NOS (iNOS) ; and endothelial NOS (eNOS)—all

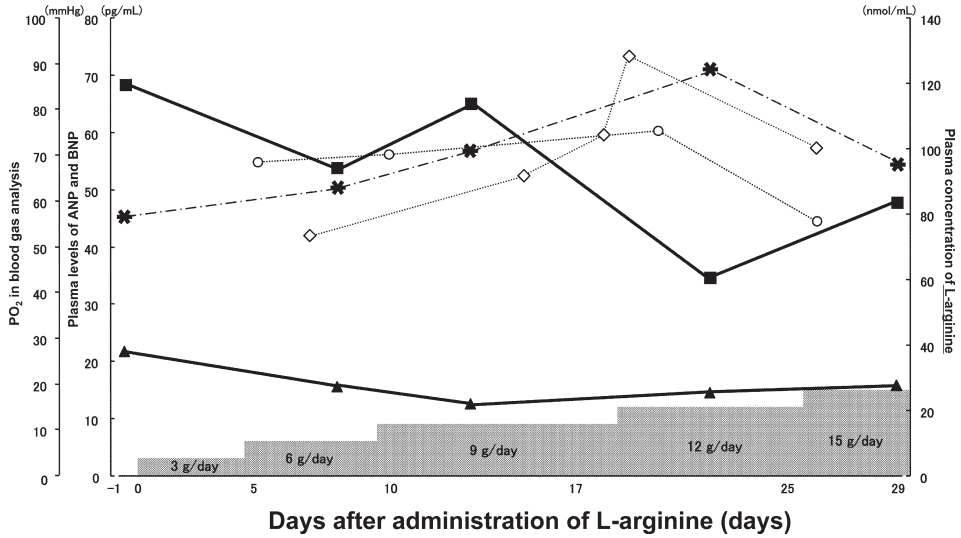

Fig. 1. Changes in plasma levels of ANP and BNP during L-arginine administration

atrial natriuretic peptide (ANP),
brain natriuretic peptide (BNP),
plasma concentration of Arginine,
Arginine Dose,
pressure gradient,
PaO_2

Plasma L-arginine level directly correlated with PO_2 and inversely correlated with plasma BNP level, even though the plasma ANP level showed almost no change.

three of which are present in the lung. Some clinical studies have associated pulmonary arterial hypertension with reduced pulmonary levels of eNOS, which would result in decreased synthesis of NO[4]. As L-arginine is the substrate of NOS in NO formation, administration of L-arginine may increase NO synthesis[1]. The vasodilating effects of NO may decrease pulmonary arterial pressure, decreasing right ventricular afterload. This may explain the inverse correlation between the plasma L-arginine and plasma BNP levels observed in this study. Plasma BNP level may be a useful parameter to assess the efficacy of L-arginine therapy in patients with pulmonary hypertension[12]. Also, oral supplementation of L-arginine may be effective in the treatment of not only PPH but also pulmonary hypertension secondary to pulmonary embolism.

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