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DRUG-INDUCED DILATED CARDIOMYOPATHY ASSOCIATED WITH ANAGRELIDE

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Anagrelide is an effective drug for essential thrombocythaemia, and its adverse cardiovascular effects are relatively rarely reported. We experienced a 73 year-old man with essential thrombocythaemia developed anagrelide-induced dilated cardiomyopathy. After discontinuation of anagrelide, the patient's left ventricular systolic function was completely recovered.

KEY WORDS: Anagrelide · Cardiomyopathy.

INTRODUCTION

Anagrelide, a phosphodiesterase inhibitor as a potent inhibitor of platelet aggregation, was approved by the FDA as oral treatment for essential thrombocythaemia and thrombocythaemia associated with polycythaemia vera.

Common adverse effects of anagrelide include anemia, headache, dizziness, and diarrhea. Cardiovascular side effects are related to the inhibition of phosphodiesterase such as tachycardia, fluid retention and edema.[1)] However, anagrelide-induced cardiomyopathy is rare. We experienced a 73 years-old man with essential thrombocythaemia developed anagrelide-induced dilated cardiomyopathy.

CASE

A 73 year-old man had been receiving 4 mg to 7 mg of anagrelide per day since April 2005, when he was diagnosed with essential thrombocythemia.

In November 2005, echocardiography showed normal sized chambers and normal heart function (EF=68%). In July 2006, he often complained dyspnea on exertion and palpitation. Echocardiography showed left ventricular enlargement (5.0→5.8 cm), left atrium enlargement (4.2→4.8 cm) and reduced global left ventricle systolic function (68%→40%) as compared with previous echocardiographic data at November 2005. So he was taken remedies atenolol, hydrochlorothiazide, and aldactone. We recommended him to stop taking anagrelide and to take hydroxyurea instead because of cardiac adverse effect of anagrelide, but he refused to stop the medication. He continued to take anagrelide and arrived at the emergency department in September 2006.

He visited the emergency department for dyspnea of NYHA functional class III. He had been receiving 4 mg to 7 mg of anagrelide per day at that time.

On arrival in the emergency department, he had a pulse rate of 122 beats per minutes, blood pressure of 127/88 mmHg and respiration rate of 30 breaths per minutes. His partial pressure of oxygen and carbon dioxide were 86.5 mmHg and 29.9 mmHg at room air. On physical examination, wheezing sounds were heard on both lung fields.

Electrocardiogram in emergency room showed sinus tachycardia and left ventricular hypertrophy. Chest roentgenogram showed mild cardiomegaly (cardiothoracic ratio was 55%) and fibrostreaky nodular density in both upper and middle lung fields.

Complete blood count revealed hemoglobin of 10.2 g/dL and platelet counts of 320×10^9/L. The serum brain natriuretic peptide (BNP) concentration was elevated to 709.13 pg/mL (reference range: 0-100 pg/mL).

Echocardiography showed enlarged four chambers, reduced global left ventricle systolic function (LV ejection fraction=29%) (Fig. 1A), and pseudonormalized filling

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pattern. Myocardial perfusion scan was conducted to rule out ischemic heart disease and revealed no perfusion defect of left ventricle.

We treated heart failure with 20 mg of furosemide intravenously, oxygen, 100 mg of aspirin. We recommended him to stop taking anagrelide and to take hydroxyurea instead. And, we added 6.25 mg of carvedilol and 8 mg of candesartan on 3 days later.

Seven days after discontinuing anagrelide, the patient's symptom improved dramatically and BNP had decreased to 350.45 pg/mL. He was asymptomatic in three months later after discharge. At that time, echocardiography showed decreased left ventricular end diastolic dimension (6.2→5.5 cm), left atrium dimension (4.9→3.9 cm) and improved global left ventricle systolic function (LV ejection fraction: 29%→44%) (Fig. 1B). BNP was normalized to 52.09 pg/mL (Table 1).

Discussion

We documented a case of congestive heart failure and reversible dilated cardiomyopathy during the treatment of anagrelide. Pharmacologically, anagrelide inhibits type IV cyclic adenosine monophosphate (cAMP) phosphodiesterase.[2] The mechanism of anagrelide's cardiovascular side effect is unclear, but proposed mechanism of cardiac toxicity is attributed to inhibition of phosphodiesterase, resulting in positive inotropic activity and vasodilation.[2] Phosphodiesterase type III inhibitors such as amrinone and milrinone were associated with increased mortality, particularly in patient with advanced heart failure.[2]

Because of tachyarrhythmia and reversible nature of anagrelide associated cardiomyopathy, anagrelide-induced cardiomyopathy might be related to tachycardia-induced cardiomyopathy.[3] Tachycardia-induced cardiomyopathy is characterized by ventricular dysfunction and dilation and by clinical manifestations of heart failure that are reversible with normalization of heart rate.[4] Collectively, anagrelide can develop dilated cardiomyopathy, which may be related to its inotropic activity and tachycardia.

Anagrelide-induced cardiomyopathy is rarely reported and not yet in Korea. In a retrospective study of 434 patients with essential thrombocythemia or polycythaemia vera in Mayo clinic, 11 patients were identified as an idiopathic cardiomyopathy. In 6 of the 11 patients, anagrelide therapy was temporally associated with idiopathic cardiomyopathy and after withdrawal of anagrelide, the ejection fraction improved in all patients.[3] In a study of 577 patients treated with anagrelide, 132 (24%) had fluid retention or edema and 14 developed flank congestive heart failure.[5] In another study of 942 patients taking anagrelide for thrombocytosis, 15 died of cardiac causes.[6]

Anagrelide-induced cardiomyopathy is a reversible form of dilated cardiomyopathy. Physicians should pay attention to the possibility of anagrelide induced cardiomyopathy in case of a prescription of anagrelide for treating thrombocytosis.

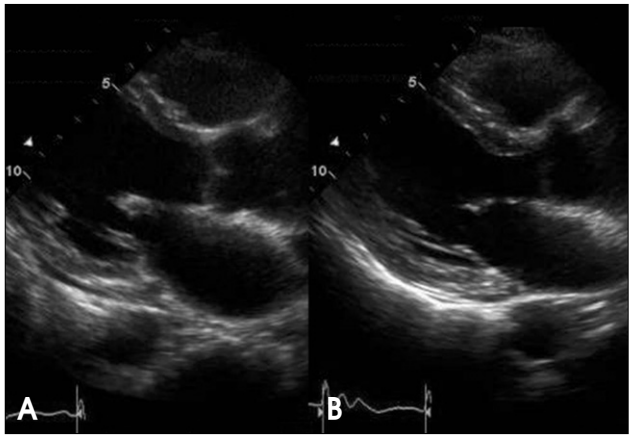

Fig. 1. Parasternal long axis views on ER visit due to dyspnea (A) and 3 month later after discharge (B). Figures shows decreased left ventricular end diastolic dimension (6.2→5.5 cm) and decreased left atrial dimension (4.9→3.9 cm).

Table 1. BNP and echocardiographic parameters before and after anagrelide-induced cardiomyopathy

	BNP (pg/mL)	LVFF (%)	LVEDD (mm)	LAD (mm)	E/A
Baselin		68	5.0	4.2	0.67
After taking anagrelide (2 months before admission)	297.52	40	5.8	4.8	0.64
ER admission	709.13	29	6.2	4.9	1.43
After discontinuation of anagrelide (1 month later)	123.27	35	6.0	4.4	0.5
After discontinuation of anagrelide (3 month later)	52.09	44	5.5	3.9	0.36

BNP: brain natriuretic peptide, EF: ejection fraction, LVEDD: left ventricular end-diastolic dimension, LAD: left atrial dimension

References

1. Engel PJ, Johnson H, Baughman RP, Richards AI. *High-output heart failure associated with anagrelide therapy for essential thrombocytosis. Ann Intern Med 2005;143:311-7.*
2. James CW. *Anagrelide-induced cardiomyopathy. Pharmacotherapy 2000;20:1224-7.*
3. Jurgens DJ, Moreno-Aspitia A, Tefferi A. *Anagrelide-associated cardiomyopathy in polycythemia vera and essential thrombocythemia. Haematologica 2004;89:1394-5.*
4. Umana E, Solares CA, Alpert MA. *Tachycardia-induced cardiomyopathy. Am J Med 2003;114:51-5.*
5. Anagrelide Study Group. *Anagrelide, a therapy for thrombocythemic states: experience in 577 patients. Am J Med 1992;92:69-76.*
6. Petitt RM, Silverstein MN, Petrone ME. *Anagrelide for control of thrombocythemia in polycythemia and other myeloproliferative disorders. Semin Hematol 1997;34:51-4.*