Delayed Onset of Pulmonary Hypertension Associated With an Appetite Suppressant, Mazindol — A Case Report —

Makoto Hagiwara, MD; Akihito Tsuchida, MD; Masaya Hyakkoku, MD;
Kimio Nishizato, MD; Tateki Asai, MD; Yukinaga Nozawa, MD;
Kazufumi Tsuchihashi, MD; Kazuaki Shimamoto, MD

The use of the appetite suppressant agents aminorex and fenfluramine derivatives has been reported as a risk factor for the development of pulmonary hypertension. A 29-year-old female developed pulmonary hypertension suspected to be due to an amphetamine-like appetite suppressant agent, mazindol ((±)-5-(p-chlorophenyl)-2,5-dihydro-3H-imidazo [2,1-a] isoindol-5-ol). She was admitted to Sapporo Medical University Hospital with dyspnea due to severe pulmonary hypertension. Twelve months prior to admission, she had taken mazindol continuously for a period of 10 weeks. As yet, her pulmonary hypertension has not completely improved. This is the first reported case of mazindol-associated pulmonary hypertension, which developed after a long latent interval, and it suggests that mazindol is also a risk factor for the development of pulmonary hypertension, making long-term follow-up necessary for patients taking this anorectic agent. (*Jpn Circ J* 2000; 64: 218–221)

Key Words: Appetite suppressant; Mazindol; Pulmonary hypertension

It has been reported that the use of the appetite suppressant, aminorex and fenfluramine derivatives is a risk factor for development of pulmonary hypertension.^{1–6} Mazindol ((±)-5-(p-chlorophenyl)-2,5-dihydro-3H-imidazo [2,1-a] isoindol-5-ol), which is an amphetamine-like anorectic agent without a phenyl-ethylamine structure (Fig 1), is also widely prescribed.⁷ We report the first case of mazindole-associated pulmonary hypertension, which occurred after a long latent interval.

Case Report

A 29-year-old woman started taking 0.5 mg/day of mazindol from July 6, 1996 to control obesity. Her height was 160 cm, body weight was 86 kg, and body mass index was 33.6 kg/m². She gradually increased the dose to 1.5 mg/day. She had a history of juvenile bronchial asthma, but no history of pregnancy, smoking, oral contraceptive intake or cocaine intake. There was also no evidence of familial primary pulmonary hypertension or heart disease. After 10 weeks, her body weight had decreased to 81 kg. She experienced slight dyspnea upon effort, but physical examination and laboratory data indicated no abnormalities. Her dyspnea improved when she stopped taking the drug. However, 12 months later, she began to experience dyspnea again, and her exercise capacity was reduced. Cardiomegaly was first detected on chest radiography in August 1998. At the beginning of 1999, dyspnea with

peripheral cyanosis was easily induced by daily activities, a condition that is New York Heart Association (NYHA) III.

She was admitted to the university hospital on March 2, 1999 for evaluation of tachypnea. Blood gas analysis showed severe respiratory insufficiency: PaO₂, 49.3 mmHg; PaCO₂, 27.8 mmHg; pH, 7.459; HCO₃⁻, 19.5 mmol/L; and SaO₂, 84.2% in room air. Her pulse rate was 98/min and systemic blood pressure was 102/70 mmHg. Physical examination revealed a wide splitting of the second heart sound with enhancement of the pulmonic component. Chest radiography revealed marked enlargement of the pulmonary trunk without vascular enhancement (Fig 2). An electrocardiogram showed a tentorial P wave in II, III, aVF, R/S ratio >1 in V₁, right precordial T wave inversion, and a SI QIII TIII pattern, which fulfilled the MacGill-White criteria (Fig 3). Two-dimensional echocardiography showed a dilated main pulmonary artery to 32.2 mm, a hypertrophied right ventricle to 10 mm, and the estimated right ventricular pressure was 76 mmHg (Fig 4). Serological tests for syphilis and various autoimmune antibodies (antinuclear, anti-Ds-DNA, anti-RNP, anti-Sm, anti-cardiolipin (CLB2GPI) and rheumatoid factor) were negative. Inflammatory reactions, such as C-reactive protein and the erythrocyte sedimentation rate (ESR), were within normal ranges. IgG, IgM and IgA were 1190, 48, and 181 mg/dl, respectively. Complement C3 and C4 were 107 and 18 mg/dl, respectively. Activated partial thromboplastin time (APTT) was 33.9 s and prothrombin time (PT) was 72.5%, both within normal ranges. Reactive polycythemia (red blood cell count, 528×10⁴/μl; hemoglobin, 16.8 g/dl; hematocrit, 50.0%) was the only abnormality in the laboratory examinations. ^{99m}Tc-macro aggregated albumin (MAA) lung perfusion scintigraphy revealed no perfusion defects in the lung fields (Fig 5).

Under oxygen administration, oral combined therapy using beraprost (120 μg/day), long-acting nifedipine (40

(Received July 7, 1999; revised manuscript received November 29, 1999; accepted November 30, 1999)

Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

Mailing address: Akihito Tsuchida, MD, Second Department of Internal Medicine, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-ku, Sapporo 060-0061, Japan. E-mail: atutida@sapmed.ac.jp

Fig 1. Chemical structure of amphetamine and various anorectic agents. Only mazindol has an isoindol structure.

Fig 2. Chest radiography on admission.

Fig 3. Electrocardiogram on admission.

mg/day), mononitrate (40 mg/day), and warfarin (2.5 mg/day) was started. After 2 months, the dyspnea at rest was slightly improved and the blood gas analysis in the supine or sitting position in room air had also improved (PaO₂, 68.5 mmHg; PaCO₂, 39.0 mmHg; pH, 7.422; HCO₃⁻, 23.1 mmol/L; and SaO₂, 91%). Her body weight decreased by 7 kg due to diet therapy during hospitalization. However, there was no change in the right ventricular pressure estimated from echocardiography. While continuing this combined therapy, cardiac catheterization was performed on April 22, 1999, which did not reveal any pulmonary arterial or venous occlusion and/or stenosis, and the pressure parameters were as follows: mean right atrium, 8 mmHg; systolic right ventricle, 90 mmHg; pulmonary

artery, 116/30 mmHg, mean of 59 mmHg; mean pulmonary capillary wedge pressure, 13 mmHg; aortic pressure, 125/70 mmHg; cardiac output, 3.98 L/min; and pulmonary artery resistance, 928 dyne · s · cm⁻⁵. Oxygen was changed to inhalation with 10 L/min for 5 min, but an oxygen test revealed no change in the systolic pulmonary artery pressure. These findings indicated severe pulmonary hypertension. The patient was discharged from hospital on May 22, 1999 and has been continuing intermittent oxygen inhalation therapy in her home.

Fig 4. Two-dimensional echocardiography. (Left panel) Short-axis view at the levels of the aortic valve (AV) and pulmonary artery (PA). (Right panel) Short-axis view at the level of the papillary muscle. LV, left ventricle; RV, right ventricle.

Fig 5. ^{99m}Tc -MAA lung perfusion scintigraphy. (Left) Anterior view; (Middle) right lateral view; (Right) left lateral view.

Discussion

Anorectic agents are now recognized as risk factors for pulmonary hypertension, following reports of aminorex-induced cases in several European countries in the late 1960s and early 1970s²⁻⁴. A recent multicenter trial^{1,5} and a case report⁶ have clearly shown that derivatives of fenfluramine also have the same adverse effects. However, the present case is the first report of mazindol-associated pulmonary hypertension.

Mazindol, an anorectic agent, has a different isoindol structure from that of phenethylamine, but it has the same pharmacological action through serotonin transporter inhibition in the brain as other anorectic agents^{1,7}. In the present case, the clinical history strongly suggests that mazindole induced the pulmonary hypertension after a long latent interval, although the possibility that primary pulmonary hypertension occurred coincidentally can not be completely ruled out. Thus, several anorectic agents may contribute to

the development of pulmonary hypertension in a structurally independent manner.

Pulmonary hypertension was also reported in a patient with severe obesity, in whom it was principally caused by the association of obstructive sleep apnea and obesity-induced hypoventilation⁸. Unfortunately, we did not assess obstructive sleep apnea in the present case. However, the data obtained from blood gas analysis in the supine position did not differ from that obtained in the sitting position. Moreover, her body weight decreased by 7 kg during hospitalization, but the severity of the pulmonary hypertension, as estimated by echocardiography, did not improve. Based on these findings, it is unlikely that the obesity itself induced the pulmonary hypertension.

It has been reported that the effect of the anorectic agents associated with the development of pulmonary hypertension is dose-dependent^{4,5}. In approximately 50% of cases of acute onset of pulmonary hypertension within 6 months of starting to use an anorectic agent, the pulmonary

artery pressure was reversibly normalized after the drug was stopped⁴. However, in the present case, mild symptoms developed during the early period of drug usage and resolved for about 12 months after ceasing the drug. Subsequently, symptoms suggestive of pulmonary hypertension gradually reappeared and could not be completely resolved by any treatment. Such a delayed occurrence of pulmonary hypertension makes it difficult to speculate on the relationship between the symptoms and the drug^{3,7}. Although the mechanism of the development of pulmonary hypertension after such a long latent period remains unclear, a similar delayed development (after a latent period of more than 12 months) has been found in 23% of cases of appetite suppressant-associated pulmonary hypertension⁵. The present case indicates the clinical importance of a programmed follow-up in obese patients who are taking anorectic agents.

In conclusion, mazindol is a risk factor for the development of pulmonary hypertension after a long latent period.

References

1. Gonzalez AM, Smith A, Emery C, Higenbottam T: Pulmonary hypertension, family and environment. *J Hum Hypertens* 1997; **11**: 559–561
2. Cahal DA: Appetite suppressants and pulmonary hypertension. *Lancet* 1969; **1**: 947
3. Follath F, Burkart F, Schweizer W: Drug-induced pulmonary hypertension? *BMJ* 1971; **1**: 265–266
4. Gurtner HJP: Aminorex and pulmonary hypertension: A review. *Cor Vasa* 1985; **27**: 160–171
5. Mark EJ, Patalas ED, Cang HT, Evans RJ, Kessler SC: Fatal pulmonary hypertension associated with short-term use of fenfluramine and phentermine. *N Engl J Med* 1997; **337**: 602–606
6. Abenheim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, et al: Appetite-suppressant drugs and the risk of primary hypertension. *N Engl J Med* 1996; **335**: 609–606
7. USP DI, 11th ed: Appetite suppressants. Drug Information for the Health Care Professional 1991: 511–519
8. Kessler R, Chaouat A, Weitzenblum E, Oswald M, Ehrhart M, Apprill M, et al: Pulmonary hypertension in the obstructive sleep apnoea syndrome: prevalence, causes and therapeutic consequences. *Eur Resp J* 1996; **9**: 787–794