CASE REPORT

Fenfluramine-Induced Unstable Angina Pectoris

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INTRODUCTION

Fenfluramine is an amphetamine-related anorectic drug marketed in Canada under the trade name Ponderal® by Servier and Pondimin® by Robins.[1,2] It exhibits a hypoglycemic effect independent of the effect on weight in non-insulin dependent diabetics.[3] This paper reports the development of unstable angina in an obese woman with non-insulin dependent diabetes mellitus (NIDDM) shortly after the initiation of fenfluramine therapy.

CASE

On December 31, a 56-year-old, 86 kg woman was admitted to the coronary care unit with the onset of chest pain. She had a 22-year history of NIDDM. Earlier in the month (December 6-15), she had been hospitalized for control of her diabetes. To reduce weight, she was started on fenfluramine (Ponderal®) 60 mg at bedtime. She also received glyburide 2.5 mg daily and her blood glucose levels were reduced to the 7-8 mmol/L range. Six days after her discharge, she began to have sharp, stabbing chest pains with trivial exertion which were relieved with rest. At times, these pains were also associated with dyspnea and palpitation. As a result of a verbal cardiology consult on Dec. 24, the patient was started on diltiazem 60 mg tid and E.C. ASA 325 mg daily. The fenfluramine was discontinued. However, she continued to experience chest discomfort, even at rest, and upon advice from her family physician presented to the emergency department on December 31.

On examination, her blood pressure was 160/80 mmHg, her heart rate was 54 beats/min, and her jugular-venous pressure was 1cm above the sternal angle but there was no hepato-jugular reflex. She had normal S_1, S_2 heart sounds, no S_3, but S_4 heart sounds. The remainder of her examination was unremarkable. All laboratory work was normal. There were no cardiac enzyme changes and the ECG showed no ischemic changes.

The patient had a history of hypothyroidism. She did not have any previous history of cardiac problems with the exception of mitral valve prolapse diagnosed 10 years earlier. However, she did have many cardiac risk factors: diabetes, a positive family history, mildly elevated cholesterol levels, obesity and a positive smoking history (although she had quit five years earlier). She denied any history of hypertension and also denied orthopnea but regularly slept on two pillows. She had no paroxysmal nocturnal dyspnea, cough, nausea, vomiting or abdominal pain.

A diagnosis of fenfluramine-induced unstable angina was made by the attending cardiologist. Heparin and nitroglycerin were added to her regimen and the dosage of diltiazem was increased.

On January 1, in the CCU, she had one episode of chest pain. She was lightheaded and vomited. Her heart rate was 40 beats/min, and blood pressure was not measurable. She responded to nitroglycerin sublingual 0.3 mg. Medical management was optimized and the rest of her hospital stay was unremarkable.

Prior to discharge, she had an exercise stress test which was non-diagnostic and a 2-D echocardiogram which was normal. She was discharged home on diltiazem 90 mg qid, nitroglycerin ointment 1 1/2 inches tid, E.C. ASA 325 mg daily, l-thyroxine 0.1 mg daily, and glyburide 2.5 mg bid. Three months later, as an out-patient, the patient had a stress thallium scan. The exercise treadmill portion was again non-diagnostic but the thallium scan showed a minor inferior wall stress-induced perfusion defect. It was learned through her endocrinologist that, in mid-January, the patient had reinstituted fenfluramine therapy on her own as her diabetes was again out of control and she refused to consider insulin therapy.

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DISCUSSION

Fenfluramine is both pharmacologically and clinically different from the amphetamines but it is a structural amphetamine derivative. The appetite-suppressant activity of fenfluramine involves the central serotoninergic system, while that of amphetamine depends on the integrity of the noradrenergic and dopaminergic systems.[3] Notably, fenfluramine lacks the usual central stimulating effects of amphetamines and, in fact, often causes drowsiness.[1,2]

Amphetamine and its derivatives have been associated with several different cardiovascular adverse reactions: acute hypertension, myocardial infarction,[4,5] cardiomyopathy,[6] sudden death,[7] acute vasospasm[8] and intracerebral hemorrhage.[9,10] Amphetamine acts by releasing noradrenaline from sympathetic nerve endings and, as catecholamines can cause myocardial damage by increasing myocardial oxygen demand or by causing platelet aggregation, this may be a possible mechanism for the cardiovascular adverse effects.[4]

Fenfluramine has been associated with cardiovascular and autonomic adverse effects such as palpitation, hypotension, hypertension, fainting, sweating, chills and blurred vision.[2] Chest pain has been reported[2] in addition to several cases of pulmonary hypertension.[2,11,12] Pulmonary hypertension may be the result of fenfluramine-induced release of serotonin in the pulmonary vasculature.[13] Serotonin causes active constriction of smooth muscle in the walls of both small pulmonary veins and arterioles.[14]

The effect of fenfluramine on endogenous serotonin may also explain the ischemic symptoms in this patient. In the cardiovascular system, serotonin classically causes direct vasoconstriction of most cutaneous, visceral and cerebral blood vessels, while the blood vessels of skeletal muscles are dilated.[15,16] (No information specific to the coronary vessels was found.) Serotonin also has positive inotropic and chronotropic effects of varying intensity on the heart. These result from a direct action on cardiac tissue and an indirect action mediated by the release of norepinephrine.[15] Occasionally, the interplay between autonomic reflexes and the direct action of serotonin in the coronary bed can initiate the coronary chemoreflex (Bezold-Jarisch reflex) leading to profound bradycardia and hypotension.[15,16] In a patient with multiple risk factors and possibly some asymptomatic underlying ischemic disease, it is conceivable that the introduction of fenfluramine therapy could precipitate symptoms of dyspnea, palpitations and chest pain.

It is acknowledged that the administration of fenfluramine and the subsequent events (i.e., unstable angina pectoris) may be unrelated. The patient had several predisposing cardiac risk factors, but she had no previous history of hypertension or ischemic cardiac disease. The thallium scan showed a small area of inferior wall ischemia. This is indicative that her symptomatology in hospital was cardiac-related and inferior wall ischemia correlates well with her clinical symptoms of chest pain, bradycardia and hypotension. Furthermore, the temporal relationship between the initiation of fenfluramine therapy and the onset of symptoms is highly suggestive.

Another interesting aspect of this case is the use of fenfluramine as an adjunct to sulfonylurea therapy in a patient with inadequately controlled NIDDM. Weight reduction alone often results in improved glucose control in NIDDM patients. However, more specifically, fenfluramine has been shown to exhibit a hypoglycemic effect independent of producing weight loss. Several authors have reported a lowering of blood glucose and an improvement in glucose tolerance in patients with NIDDM following fenfluramine treatment.[3,17,18] This may be due to an increase in insulin sensitivity and enhanced insulin clearance.[5]

Fenfluramine was quite effective in bringing this patient's blood glucose levels under control. Once the medication was resumed, she continued to be maintained on an antiischemic regimen; this could explain why she did not have a recurrence of her unstable angina.

CONCLUSION

This is believed to be the first report of an association between fenfluramine therapy and unstable angina pectoris. Although there are difficulties in establishing cause-effect relations in adverse drug reactions, this case meets the criteria for a "possible" or "conditional" adverse drug reaction report[19] and is categorized as such when using the algorithm developed by Naranjo *et al.*[20] This report demonstrates the need for conscientious drug surveillance even of longtime marketed agents.

REFERENCES

1. Fenfluramine — another appetite suppressant. Med Lett Drugs Ther. 1973; 15:33-4.
2. McEnvoy GK, ed. AHFS drug information. Bethseda, MD: American Society of Hospital Pharmacists, Inc., 1990: 1223-5.
3. Verdy M, Charbonneau L, Verdy I, et al. Fenfluramine in the treatment of non-insulin-dependent diabetics: hypoglycemic versus anorectic effect. *Int J Obes* 1983; 7:289-97.
4. Carson P, Oldroyd K, Phadke K. Myocardial infarction due to amphetamine. *Br Med J* 1987; 294:1525-6.
5. Orzel JA. Acute myocardial infarction complicated by chronic amphetamine use. *Arch Intern Med* 1982; 142:644.
6. O'Neill MB, Arnolda MB, Coles DM, et al. Acute amphetamine cardiomyopathy in a drug addict. *Clin Cardiol* 1983; 6:189-91.
7. Gibbs HR. Diet pills and sudden death (letter). *N Engl J Med* 1988; 318:1127.
8. Kim I, Whitsett TL. Acute vasospasm associated with anorexiant use. *J Okla State Med Assoc* 1988; 81:395-8.
9. Delaney P, Estes M. Intracranial hemorrhage with amphetamine abuse. *Neurology* 1980; 30:1125-8.

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10. Harrington H, Heller HA, Dawson D, et al. Intracerebral hemorrhage and oral amphetamine. *Arch Neurol* 1983; 40:503-7.
11. Douglas JG, Munro JF, Kitchin AH, et al. Pulmonary hypertension and fenfluramine. *Br Med J* 1981; 283:881-3.
12. McMurray J, Bloomfield P, Miller HC. Irreversible pulmonary hypertension after treatment with fenfluramine (letter). *Br Med J* 1986; 293:51-2.
13. Doogan DP. Pulmonary hypertension and fenfluramine (letter). *Br Med J* 1982; 284:1403.
14. Kusajima K, Ozdemir IA, Webb WR, et al. Role of serotonin and serotonin antagonist on pulmonary hemodynamics and microcirculation in hemorrhagic shock. *J Thorac Cardiovasc Surg* 1974; 67:908-14.
15. Gilman AG, Rall TW, Nies AS, et al, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 7th ed. New York: MacMillan Publishing Company, 1985:628-33.
16. Kalant H, Roschlau WHE, Sellers EM, et al, eds. Principles of Medical Pharmacology. 4th ed. University of Toronto, Canada: Department of Pharmacology, Faculty of Medicine, 1985:372.
17. Salmela PI, Sotaniemi EA, Viikari J, et al. Fenfluramine therapy in non-insulin-dependent diabetic patients: effects on body weight, glucose homeostasis, serum lipoproteins, and antipyrine metabolism. *Diabetes Care* 1981; 4:535-40.
18. Pestell RG, Crock PA, Ward GM, et al. Fenfluramine increases insulin action in patients with NIDDM. *Diabetes Care* 1989; 12:252-8.
19. Karch FE, Lasagna L. Adverse drug reactions: a critical review. *JAMA* 1975; 234:1236-41.
20. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981:239-45.