The role of fluoxetine hydrochloride in causing our patient’s clinical, physiologic, radiologic, and pathologic abnormalities is secured by the following: (1) histologic and cytologic findings consistent with hypersensitivity pneumonitis; (2) the temporal correlation of symptom onset with fluoxetine hydrochloride, therapy initiation, symptom relief with drug therapy discontinuation, recrudescence with rechallenge, and eventual progression to a chronic disease requiring corticosteroids; and (3) the exclusion of other etiologies.

The lamellar inclusions we observed in macrophages resemble those seen with amiodarone. The clinical importance of these inclusions in the pathogenesis of the patient’s pulmonary disease is uncertain, but as with amiodarone, these changes may reflect drug use, and not necessarily drug toxicity.

In view of fluoxetine hydrochloride’s increasing use throughout the world, it is important to note the association of a pulmonary disease with this drug. To our knowledge, this is the first report establishing clinicopathologic and roentgenologic documentation of a fluoxetine hydrochloride-associated pulmonary alveolitis. In addition, pulmonary phospholipidosis was found. These two processes may or may not be related. Further studies will be needed to define the relationships between the phospholipidosis-like changes described, drug dosage, and pulmonary symptoms.

References

Acute Myocardial Infarction While Using the Nicotine Patch*

Jan Paul Ottervanger, MD; Jeroen M. Festen, MD; Arje G. de Vries, MD; and Bruno H.C. Stricker, PhD

A 39-year-old man developed an acute myocardial infarction 20 days after starting treatment with nicotine patches. He had not smoked while using the patches. He recovered without complications. Coronary angiography did not reveal coronary stenoses. He had no history of myocardial infarction, hypertension, or diabetes mellitus. Although coincidence cannot be excluded, it is recommended that all patients should be strongly advised not to smoke while using the nicotine patch and to consult a physician if chest pain develops.

(CHEST 1995; 107:1765-66)

Key words: adverse drug reactions; myocardial infarction; nicotine patch; postmarketing surveillance

Smoking increases the risk of cardiovascular events such as acute myocardial infarction, stroke and sudden death, and lung disease. The nicotine transdermal delivery system (“nicotine patch”) is a relatively new supportive method for cessation of smoking, and it has an increasing popularity. It was stated that nicotine patches produce a more steady serum level of nicotine, compared with nicotine gum, avoiding peaks in nicotine level. The side effects of the patches in the trials seemed to be relatively modest, with the most frequent side effect being a minor local skin reaction. It was demonstrated that transdermal nicotine has less effect on platelet activation and catecholamine release than does cigarette smoking, and it was suggested that its use in patients with coronary artery disease is safer than cigarette smoking. However, we report on a patient who developed an acute myocardial infarction after starting use of the nicotine patch.

Case Report

A 39-year-old fireman had been smoking 50 to 100 cigarettes per day for several years, and he had already made several unsuccessful attempts to quit smoking. The medical history revealed no signs of diabetes mellitus, hypertension, thyroid disease, angina pectoris, or preexisting vascular disease, but 2 years before hospital admission, he was referred with chest pain after a thoracic trauma. Cardiac catheterization at that time demonstrated no abnormalities, and he had never had chest pain since. There was no history of Raynaud’s phenomenon, migraine, or Pritzmetal’s variant angina. His father had a myocardial infarction at age 60 years. The patient consumed modest amounts of alcohol and coffee. To help him stop smoking, nicotine patches (Nicotinell; Ciba Geigy; Arnhem, The Netherlands) with a dose of 21 mg (20 cm²) per patch were prescribed. He used no other drugs.

He successfully stopped smoking, but 20 days after starting treatment with the nicotine patches, several hours after administrating the patch, he developed severe substernal chest pain, radiating to the left shoulder with subsequent sweating and nausea without vomiting. He presented to the emergency ward. On admission, he was normotensive (140/80 mm Hg), had normal peripheral pulses, and had no signs of cardiac failure. However, ECG showed an acute transmural inferior myocardial infarction with ST elevation in the leads II, III, aVF and ST depression (partly reciprocal) in the leads I, aVL, V2, and V3 (Fig 1). He was treated with intravenous thrombolysis. Creatine kinase level raised to a maximum of 3,277 U/L (normal, <100 U/L). During the next days, the patient recovered without major complications. He was discharged from the hospital in good clinical condition.

Several weeks after discharge from hospital, an exercise thallium 201 myocardial scintigraphy was performed. The patient reached a maximal work load of 200 W, with a normal rise in heart rate and blood pressure. He did not experience anginal pain at any
moment during or after the test, and there were no ischemic ECG changes. Thallium 201 myocardial scintigraphy showed an irreversible perfusion defect in the inferior-posterior segments of the left ventricular wall.

Total cholesterol level several weeks after hospital discharge was 5.2 mmol/L. Coronary angiography several weeks after scintigraphy demonstrated no coronary stenoses or plaques.

**DISCUSSION**

In view of the temporal relationship between administration of the nicotine patch and acute myocardial infarction in a young patient without previous angina pectoris, and without coronary stenosis, it is possible that the myocardial infarction was caused by the nicotine patch. However, coincidence cannot be excluded. Furthermore, we cannot exclude primary coronary spasm as the cause of the myocardial infarction.

Another cardiac side effect, atrial fibrillation, has previously been associated with both the nicotine patch and chewing nicotine gum.3-5 Furthermore, there have been reports of serious cardiovascular adverse reactions, including acute myocardial infarction and cardiac arrest, associated with continued smoking during use of the patches.6-8 Also, the Australian Centre for Adverse Reactions to Drugs received several reports on cardiovascular adverse effects attributed to nicotine patches.9 Another cardiovascular adverse reaction, stroke, has also been reported.10 However, it is difficult to estimate the causal relationship between use of the nicotine patch and these adverse drug reactions in most cases.

The effects of nicotine on coronary blood flow can lead to ischemia in patients with coronary heart disease.11 This case report now suggests that serious cardiac events also can occur in a patient without a history of heart disease who has stopped smoking during use of the patch. Although serious cardiac events associated with the nicotine patch are probably rare, we advise cautious use of nicotine replacement therapy in patients with known coronary artery disease, in any patient who experiences chest pain during use of this drug, and in patients with a recent history of (increasing) angina pectoris. However, since smoking cessation is a very important treatment of cardiovascular and lung diseases, if the benefits and possible risks (in particular if smoking is continued during use of the patches) are explained to a patient, nicotine replacement therapy may be useful in patients who cannot stop smoking without such therapy.12 It is very important, however, to instruct the patient to consult a physician when he develops persistent chest pain and to insist that he should refrain from smoking during use of the nicotine patch.

Since only epidemiologic studies will clarify whether there is an increased risk of cardiovascular events associated with use of the nicotine patch, we recommend the performance of such postmarketing studies.

**REFERENCES**

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**Independent Ventilation and ECMO for Severe Unilateral Pulmonary Edema After SLT for Primary Pulmonary Hypertension**

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**Figure 1. ECG on hospital admission of a 39-year-old man who experienced chest pain while using the nicotine patch.**

[Image of ECG trace]