CASE REPORTS

Methysergide-induced Heart Disease
A Case of Multivalvular and Myocardial Fibrosis

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SUMMARY  Methysergide (Sansert) is known to cause mitral and aortic valvular fibrosis and dysfunction, but has generally not been known to damage right heart valves or the myocardium, and cardiac fibrosis has not been considered to be a risk if therapy is intermittently interrupted. The woman who is the subject of this case report developed catheterization-proven severe tricuspid and moderate aortic and mitral regurgitation during noncontinuous therapy with methysergide. In addition, right ventricular endomyocardial biopsy revealed extensive endocardial and intramyocardial fibrosis.

METHYSERGIDE, an anti-serotonin agent used for prophylaxis of migraine headaches, produces mitral and aortic valvular fibrosis resulting in valvular dysfunction.1-7 This study reports a unique case both of hemodynamically significant right-sided valvular disease and of intramyocardial fibrosis (diagnosed by transvenous cardiac biopsy) resulting from methysergide administration. Our patient represents the first reported case of cardiac toxicity developing during interrupted (noncontinuous) methysergide therapy.

Case Report

A 52-year-old female took methysergide for migraine headaches for three years on an irregular basis at an average dose of 5 mg/day. Every six months she discontinued the drug completely for three to four weeks. One month before admission she complained of shortness of breath and was found to have ankle edema and a systolic murmur, although she had no history of cardiac disease and denied acute rheumatic fever. Many physical examinations over the previous decade had failed to disclose the presence of a cardiac murmur. A chest X-ray showed cardiomegaly and she was admitted for cardiovascular evaluation. Physical examination revealed a blood pressure of 120/60 mm Hg and a regular pulse rate of 72 beats/min. The jugular veins were distended with prominent “A” and “V” waves. There was a slight right ventricular lift. The heart sounds were normal, and no opening snap, gallop, or click was noted on auscultation. A harsh grade II/VI crescento-decrescendo murmur, which increased in intensity with inspiration, was heard at the lower left sternal border and a grade II/VI early, short diastolic blowing murmur was heard at the mid-left sternal border. No peripheral edema was present. A cardiac series demonstrated moderate cardiomegaly due primarily to right atrial enlargement. An electrocardiogram was normal. An echocardiogram showed normal ventricular, left atrial, and aortic root dimensions. The thickness and motion of the mitral, aortic, and tricuspid valve echoes were normal except for high frequency shuddering of the anterior mitral valve leaflet in diastole. Indices of left ventricular function were normal. A phonocardiogram confirmed the cardiac physical findings, and a jugular venous pulse tracing showed prominent “A” and “V” waves with obliteration of most of the “Y” descent. At cardiac catheterization, right ventricular, left ventricular, and supra-aortic valvular angiograms demonstrated severe tricuspid, moderate aortic, and mild mitral insufficiency. Left and right ventricular contractility was normal. There was a 5 mm Hg transmitral valvular gradient.

At the conclusion of the catheterization, four right ventricular endomyocardial biopsies were obtained by a percutaneous transvenous approach.8 All of the specimens, which were taken from the septal portion of the right ventricular apex, showed fibrotic thickening of the endocardium as well as extension of the fibrotic process into the myocardium to surround and replace myocytes. The myocytes themselves were normal on light and electron microscopy (fig. 1).

Despite these findings, the patient continued to take methysergide, against medical advice, at about one-half her previous dosage until three months after discharge when she discontinued the drug because of increased edema, shortness of breath, and orthopnea. One year after onset of symptoms, the patient developed chest pain and further worsening of her dyspnea which led to repeat cardiac catheterization. The right atrial pressures were 2/1/0 mm Hg, consistent with improvement in the severe tricuspid insufficiency. A wide pulmonary artery pulse pressure (16/3/8 mm Hg) suggested the development of pulmonic valvar insufficiency since the previous catheterization. A left ventriculogram revealed mild mitral regurgitation as before, and normal contractility. A worsening of her aortic valve regurgitation was demonstrated by supravalvular aortography. Selective coronary arteriography showed only a mild mid-left anterior descending lesion.

Discussion

Our patient developed tricuspid, aortic, mitral, and possible pulmonic valve disease, as well as intramyocardial fibrosis, while taking methysergide. Of clinical import is the fact that the patient's cardiac lesions developed despite non-

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Supported in part by NIH Grant HL-5866.

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Received May 2, 1977; revision accepted June 16, 1977.
continuous therapy. It was previously thought that methysergide-induced fibrosis did not occur if therapy was interrupted at least every six months, as recommended by the pharmaceutical manufacturer (personal communication, M.T. Landes, M.D., Sandoz Pharmaceuticals). Furthermore, although her tricuspid lesion regressed, her aortic valvular insufficiency progressed and probable pulmonic insufficiency developed despite discontinuation of the drug.

In patients with methysergide-induced cardiac fibrosis, hemodynamically significant disease had been reported previously to involve only the aortic and mitral valves, although postmortem examination has shown minor, clinically undetected tricuspid involvement in two patients. Spread of a layer of collagen tissue over the chordae tendineae and papillary muscles has been observed at autopsy, but the type of subendocardial and myocardial involvement which we found in our patient has been notably absent in previous autopsy studies. Fibrotic encirclement of the left coronary artery resulting in myocardial infarction was discovered in one patient at surgery, and an additional patient developed angina pectoris while taking methysergide, which resolved upon discontinuation of the drug.

Several speculations regarding the pathophysiology of methysergide-induced fibrosis have appeared in the literature. The migraine diathesis itself does not appear to be a risk factor in development of fibrosis by methysergide users. Bianchine and Friedman pursued the possibility of a drug metabolism deficiency but found N-demethylation of methysergide to be normal in patients who developed retroperitoneal fibrosis. The possibility of an autoimmune process was raised in the case of a patient who developed Coombs-positive hemolytic anemia in association with retroperitoneal and cardiac fibrosis, but no other patients afflicted with methysergide fibrosis have been reported to have evidence of autoimmune disease.

The similarity of the chemical structure of methysergide to that of serotonin, to which it is an antagonist, is striking. As noted by Graham and others, there is also a striking similarity between the cardiac lesion resulting from methysergide and the pathologic lesion identified in the carcinoid syndrome, in which there is an excess of circulating serotonin. In both diseases the fibrous plaque is said to cover, but not invade, the valve leaflet architecture. The major difference between the two is the predominant right-sided cardiac involvement in the carcinoid syndrome compared with the preponderance of left-sided disease due to methysergide. The severe right heart pathology in our patient lends credence to the theory that serotonin and methysergide induce endocardial fibrosis by a similar mechanism.

We recommend that patients receiving methysergide be carefully observed for the development of cardiac complications regardless of the dose schedule, and that patients with pre-existing heart disease be managed with other drugs if possible. Finally, methysergide administration should be added to the brief list of etiologies of tricuspid valvular insufficiency.

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Methysergide-induced heart disease: a case of multivalvular and myocardial fibrosis.
J W Mason, M E Billingham and J P Friedman

Circulation. 1977;56:889-890
doi: 10.1161/01.CIR.56.5.889
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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