CASE REPORT

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Hypersensitivity Myocarditis and Hepatitis Associated with Imipramine and Its Metabolite, Desipramine

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ABSTRACT: We present two cases of myocarditis and hepatitis with histologic characteristics of hypersensitivity-mediated drug reactions associated with imipramine and its metabolite, desipramine. In one case, death was directly attributed to myocarditis; in the second case, the patient died of an acute myocardial infarct, but myocarditis may have played a contributory role. One patient was taking imipramine, and therapeutic concentrations of imipramine and desipramine were documented in postmortem blood. The other patient was receiving desipramine documented by in-patient hospital medication records. Both cases had liver lesions associated in the medical literature with adverse drug reaction to imipramine.

Although myocarditis has been previously associated with amitriptyline, these cases appear to be the first reported in association with imipramine/desipramine. The fact that one patient was taking only desipramine suggests that it may be the offending agent.

KEYWORDS: pathology and biology, myocarditis, imipramine, hepatitis, desipramine

Hypersensitivity adverse drug reactions are well known, and myocarditis as a result of drug sensitivity has been described for over twenty drugs [*1*]. We report here two cases of hypersensitivity myocarditis and hepatitis in association with imipramine and its active metabolite, desipramine. Death is attributed to myocarditis in the second case.

Case 1

A 66-year-old man presented to the hospital with a nonlethal incised injury to the neck and fractured ribs as a result of a suicide attempt with attendant fall. He had a long psychiatric history, including several psychiatric hospitalizations and various medications including Stelazine® (trifluoperizine) over 10 years before, a 5-day trial of imipramine in 1974, and lith-

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ium discontinued by the patient some months before admission. Medical history included adult-onset diabetes mellitus treated with glipizide.

After two days of surgical care, he was transferred to the psychiatric unit for evaluation; however, on hospital Day 4 he developed shortness of breath and chest pain. He was transferred to the Medical Intensive Care Unit, where the diagnosis of acute anterior wall myocardial infarct was confirmed. He was managed conservatively, and on hospital Day 30 he was transferred back to the psychiatric unit on Isordil® (isosorbide dinitrate), Inderal® (propranolol), and sublingual nitroglycerine as needed.

Psychiatric evaluation revealed depression, and on Day 20, oral desipramine 25 mg at bedtime was prescribed. The dose of desipramine was then increased incrementally to 50, 75, 100, 125, and 150 mg on hospital Days 22, 26, 31, 35, and 37, respectively. Two days later (Day 39) a blood desipramine concentration was 65 ng/mL (high-performance liquid chromatography [HPLC], Medical Center Hospital of Vermont at Burlington), and the dose was increased to 200 mg (Day 41).

On the morning of the following day, he became tachypneic, diaphoretic, and hypotensive (blood pressure 85/50). He was transferred to the Coronary Care Unit, where a Swan-Ganz catheter was placed via subclavian vein, causing a left pneumothorax effectively managed with chest tube placement. He slowly became bradycardic and more short of breath, developing cardiorespiratory arrest. Resuscitation was unsuccessful and he was pronounced dead on the hospital Day 42.

Autopsy revealed a mildly obese, elderly man with a healed incised wound of the neck and healing rib fractures consistent with the presenting injuries. In addition, a chronic, left subdural hematoma and right fronto-parietal subdural hygroma were considered to be due to the fall associated with the suicide attempt. Neither was considered sufficient to cause significant clinical abnormalities.

There was generalized arteriosclerotic cardiovascular disease, including arteriolar nephrosclerosis (due to adult onset diabetes mellitus) and aortic atherosclerosis. The left anterior descending coronary artery contained atherosclerosis with thrombotic occlusion. There was a large anteroseptal and anterior transmural myocardial infarct consistent with six weeks' duration, associated with a large, adherent, mural thrombus of the left ventricle. In addition, there was an acute transmural infarct of the posterior left ventricular wall of about 12-h duration.

Microscopically, a diffuse myocarditis consisting of a mixed cellular infiltrate, predominantly eosinophils and lymphocytes, and focal fragmentation and necrosis of myofibers was noted in the right ventricle, septum, left atrium, and posterior wall of the left ventricle (Fig. 1*a*). This was not associated with areas of myocardial infarct, although both lesions were present in the posterior left ventricular wall. Portal areas of the liver revealed infiltration with numerous eosinophils and lymphocytes (Fig. 1*c*).

Case 2

A 54-year-old woman was found dead in bed. Medical history includes alcoholism, depression, and severe gastritis, with marked bile reflux about 1 year before death. Recently she had complained of abdominal pain, vomiting, and marked weight loss, but medical workup, in progress at the time of death, had not revealed the cause. Medications included hydrochlorothiazide 25 mg/day for over 1 year, Librax® (chlordiazepoxide HCL 5 mg, clidinium bromide 2.5 mg) 1 tablet 3 times a day as needed for about 2½ months, and Carafate® (sucralfate) for about 2½ months. She had taken tricyclic antidepressants intermittently for years, but had not taken any for at least 6 months until 21 days before death, when imipramine 25 mg per os (p.o.) at bedtime was prescribed. Seven days later the dose was increased to 50 mg.

Autopsy revealed a cachetic adult woman with acute and chronic gastritis, acute reflux

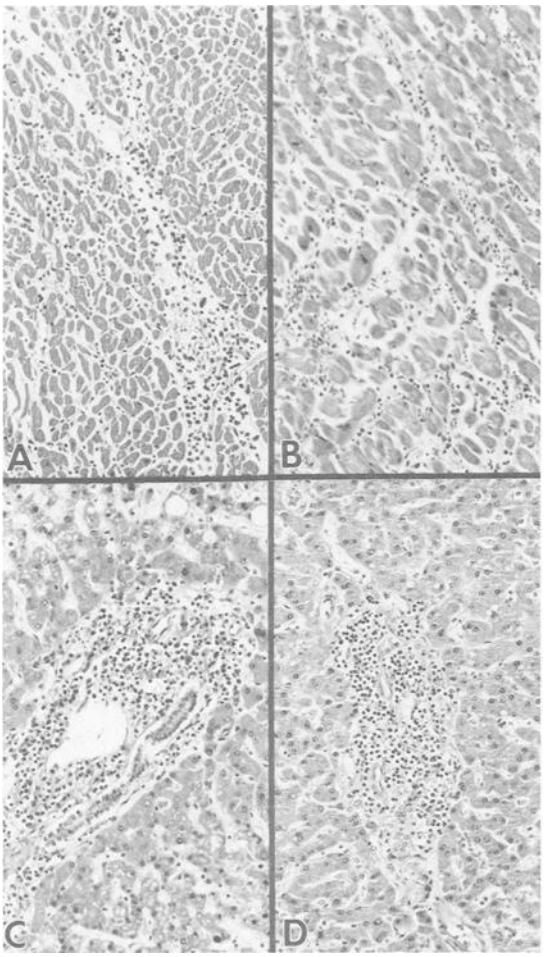

FIG. 1—*Hypersensitivity type myocarditis and hepatitis (H & E. ×20):* (a) *Case 1, myocardium;* (b) *Case 2, myocardium;* (c) *Case 1, liver; and* (d) *Case 2, liver.*

esophagitis, and mild acute and chronic enteritis. Fibrin thrombi of small vessels of gastrointestinal organs, kidney, and brain; ketonuria; and body fat depletion suggested poor nutrition and some degree of dehydration terminally. There were a splenic infarct estimated to be one to two weeks old, chronic bronchitis and emphysema, and mild atherosclerosis.

Microscopical examination revealed diffuse myocarditis characterized by patchy infiltrates of lymphocytes and eosinophils (Fig. 1*b*). Focal degeneration and necrosis of myocytes undergoing phagocytosis by polymorphonuclear leukocytes and histiocytes were seen. Fibrosis was not noted. Sections of liver revealed mixed cellular infiltrates, predominantly lymphocytes and eosinophils, within portal areas (Fig. 1*d*).

Toxicologic examination of postmortem urine specimens revealed desipramine, acetone, salicylates, and nordiazepam. Blood concentrations of imipramine were 106 ng/mL and of desipramine, 261 ng/mL (HPLC, Smith-Kline Laboratories, Waltham, Massachusetts). No other drugs were detected.

Discussion

Figure 2 illustrates the medication histories of our 2 cases. Both patients had been started on tricyclic antidepressants 3 weeks before death (Case 1: desipramine, 22 days before death; Case 2: imipramine 21 days before death). In both cases, the dosage had been increased incrementally: from 25 to 200 mg desipramine in Case 1, and from 25 to 50 mg imipramine in Case 2. Both patients had previous exposure to tricyclic antidepressants. The first patient had been prescribed a short therapeutic trial of imipramine 12 years earlier, and the second patient had been taken tricyclic antidepressants intermittently for years, although it is not known whether imipramine or desipramine specifically were prescribed. Therapeutic concentrations of the drug were documented in both cases: desipramine, 3 days before death in the first case; imipramine and desipramine, postmortem in the second case. Microscopically, similar lesions were observed in the hearts and livers of both patients.

Eosinophilic infiltrates in the portal areas of the liver and in the myocardium have been interpreted as characteristic of hypersensitivity reaction to drugs [*2,3*]. Indeed, a very similar hepatic lesion to that seen in our two cases has been described for hypersensitivity reaction to imipramine [*2*]. Desipramine is the primary active metabolite of imipramine [*4*], and although the histologic pattern was not specifically delineated, hepatitis associated with desipramine alone has been described [*5*]. Likewise, the histologic pattern of eosinophilic myocarditis seen in these two cases is identical to that previously described for hypersensitivity reactions in the myocardium as a result of other drugs [*1,3,6*].

We believe that this is the first report of hypersensitivity myocarditis associated with imipramine or desipramine, although myocarditis has been associated with another tricyclic drug, amitriptyline [*3*]. The only other drug in either of these two patients reported to be associated with hypersensitivity myocarditis was hydrochlorothiazide (Case 2); however, the long duration of therapy without complication makes it an unlikely cause of hypersensitivity reaction (Fig. 2). Furthermore, the only drug these two patients have in common is desipramine (as a metabolite of imipramine in Case 2), and desipramine would account for the

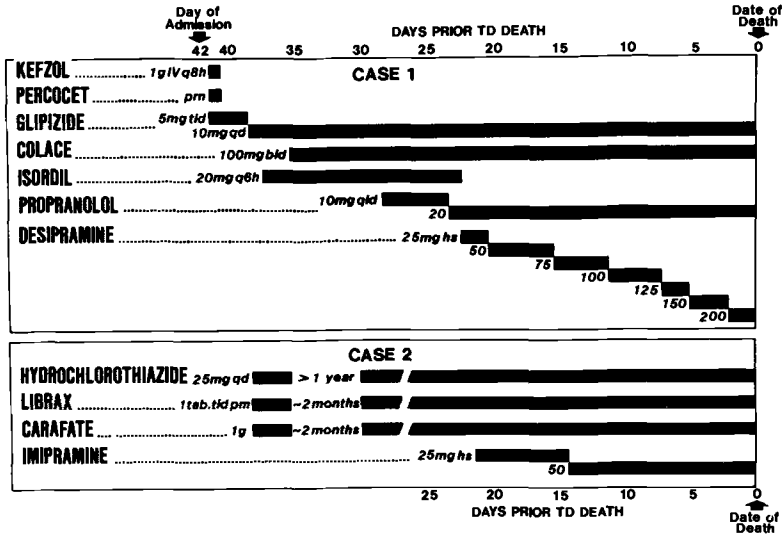

FIG. 2—*Medication history: medications taken by the two patients before death with doses and duration of therapy.*

hepatic lesion observed in both cases. Desipramine has been associated with other eosinophilic reactions in blood [7] and lung [8]. Unfortunately, in neither of our cases were peripheral eosinophil counts available after the administration of the tricyclic drugs.

The cause of death in Case 1 was an acute myocardial infarct; however, death was attributed in the second case to myocarditis. Sudden death as a result of hypersensitivity myocarditis is well known [3]. The long-term prognosis of hypersensitivity myocarditis, however, is not known. Endomyocardial fibrosis associated with eosinophilia resulting in chronic heart failure has been described [9], and a myocardial lesion, remarkably similar to our cases, is reported as part of the pathological spectrum of that disease [10]. Furthermore, at least two cases of endomyocardial fibrosis and eosinophilia as a result of sensitivity to antituberculous drugs have been reported [10].

Other investigators [11] have suggested that myocarditis may represent a spectrum of disease from acute to rapidly progressive to chronic, resulting in some cases in congestive cardiomyopathy. Whether drug-induced hypersensitivity myocarditis progresses to myocardial fibrosis and "nonspecific" cardiomyopathy is unknown.

In summary, we describe two cases of hypersensitivity myocarditis and hepatitis in association with imipramine and desipramine. These cases suggest that hypersensitivity reactions to imipramine may be mediated through its primary metabolite, desipramine. This lesion may cause sudden death. Whether it can progress to chronic cardiomyopathy is a significant, but unanswered, question.

Acknowledgments

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