Methyldopa-Induced Pancreatitis

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Methyldopa is an effective antihypertensive agent. However, since its introduction more than 15 years ago, several reports have described a variety of adverse effects: fever (1, 2); nausea, emesis, diarrhea, and multiple central nervous system effects (3); myocarditis (4); galactorrhea (5); agranulocytosis (6); positive direct Coomb's reaction (7); hemolytic anemia (8); thrombocytopenia (9); and positive lupus erythematosus cell test, rheumatoid factor, and antinuclear antibody (10, 11). Hepatic reactions ranging from mild transient transaminase elevations to severe massive hepatic necrosis and death (12) have also been reported.

Neither pancreatitis nor hyperamylasemia is as yet recognized as an adverse effect of methyldopa. Recent reviews of the literature concerning the causes of hyperamylasemia and pancreatitis (13, 14) do not cite methyldopa. We report a case of drug-induced pancreatitis in which inadvertent rechallenge and then planned drug rechallenge strongly suggest that methyldopa can cause hyperamylasemia and pancreatitis.

CASE REPORT

A 55-year-old Caucasian female, on medical treatment for essential hypertension with hydrochlorthiazide since 1971 and methyldopa since one month prior to admission, was admitted to the Genesee Hospital in October 1976 for evaluation of an intermittent febrile illness. Her present illness started three weeks prior to admission and was characterized by a 24-hr prodrome of malaise followed by chills, fever to 39.5°C, mild nonradiating epigastric pain, nausea, emesis, diarrhea, and generalized weakness. Because of nausea and emesis, the patient stopped her antihypertensive medications. She resumed them upon feeling improved. The above symptoms waxed and waned until one week prior to admission, at which time she awakened with shaking chills, mild epigastric pain, nausea, and emesis of food particles. The following day she experienced diaphoresis, temperature to 39.5°C, continuing epigastric pain, and nonproductive cough. The patient consulted her local physician who treated her with erythromycin for possible acute bronchitis. Within a few days she began experiencing relief of her symptoms and the fever resolved. She remained home on bedrest. Within 24-hr of resuming her antihypertensive medications, the patient reexperienced shaking chills, fever to 40°C, several episodes of emesis and watery diarrhea, and mild epigastric pain. She was then admitted to the hospital for evaluation.

Her past medical history was remarkable for a radio graphically documented duodenal ulcer which has been asymptomatic following a course of antacids in 1973. There was no history of hepatitis, recent viral infection, allergy, alcohol abuse, or biliary tract disease. The patient's medications at the time of admission included: premarin, 1.25 mg qd; cyclospasmol, 200 mg qid; and erythromycin, 250 mg qid started one week prior to admission. There is no family history of diabetes mellitus, hyperlipidemia, peptic ulcer disease, or other intestinal dysfunction.

The physical examination disclosed an overweight female, flushed facies, with an oral temperature of 38.4°C, pulse 110, respirations 16, and a blood pressure of 115/55 mm Hg. The remainder of the physical examination was unremarkable except for a thyroid collar incisional scar, a systolic bruit over the right carotid artery, a few end-inspiratory rales without rub, a grade I early systolic murmur at the left sternal border without radiation, and an S4 gallop. The abdomen, obese but symmetric, revealed a healed appendectomy scar; bowel sounds were slightly hyperactive without rushes; palpation revealed mild epigastric tenderness with slight guarding; no rebound or flank tenderness could be elicited; no masses or hepatosplenomegaly were appreciated. Pelvic and rectal examinations were normal.

Laboratory values included a WBC of 15,400/mm³ with 81% neutrophils, 8% band forms, 7% lymphocytes, 4% monocytes; the platelet estimate was adequate; the hematocrit 39%. The BUN and electrolytes were within normal limits except for a potassium of 3.4 mEq/liter. The serum calcium, phosphorous, bilirubin, uric acid, creatinine, cho
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Fig 1. Schematic representation of the patient’s hospital course as regards amylase, lipase and temperature, including methyldopa rechallenge on day 9.

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DISCUSSION

Fever is a recognized, although infrequent, side effect following the administration of methyldopa. A review of the literature of reported case histories of methyldopa fever (1, 2) revealed that 8 of 18 patients experienced, in addition to fever, some gastrointestinal symptoms (nausea, emesis, and abdominal pain), although not prominent. However, in none of these studies were serum amylase or serum lipase levels recorded.

To the best of our knowledge this is the first documented case of pancreatitis recorded in a patient receiving methyldopa. The initial inadvertent rechallenge with methyldopa indicates that the time relationship between drug exposure and the development of hyperamylasemia and abdominal pain is strongly suggestive of a causal relationship. We can only speculate that the abdominal symptoms described in some of the patients with methyldopa fever (1, 2) could have been secondary to pancreatitis. The mechanism of pancreatitis in this patient is entirely speculative. However, the short