CASE REPORTS

Acute Pancreatitis Due to Pyritinol: An Immune-Mediated Phenomenon

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A 23-year-old man experiencing three episodes of acute pancreatitis of undetermined etiology is described. Repeated questioning revealed that all three events had occurred after intake of the drug pyritinol. Controlled rechallenge with a single dose of the drug led to a fourth episode of acute pancreatitis. Skin testing was negative, but lymphocyte stimulation tests and double fluorescence analysis detected pyritinol-activated CD4 and CD8 lymphocytes. Together with the clinical observation that the intervals between drug intake and start of symptoms of acute pancreatitis became shorter with repeated exposure, the data are consistent with an immune-mediated origin of the pancreatitis. Pyritinol has to be added to the list of drugs capable of inducing acute pancreatitis.

There is good evidence that acute pancreatitis can be induced by certain drugs, but very little information exists about the pathogenesis or the dose relationship, and useful animal models are lacking.[1–4] More than 80 different drugs have been reported to cause acute pancreatitis,[5] but most reports are based on anecdotal evidence and are hampered by the facts that the patients have been exposed, at the same time, to different drugs and that the illness for which a drug was administered might cause acute pancreatitis. We describe a young male patient who had multiple episodes of acute pancreatitis while taking the drug pyritinol. Inadvertent reexposure and controlled rechallenge make a causal relationship very likely; the results of immunologic investigations point to hypersensitivity as the most probable pathogenesis.

Case Report

A 23-year-old male engineering student was admitted to the hospital because of acute upper abdominal pain. On clinical examination, abdominal tenderness and reduced bowel sounds were the main findings; laboratory examination showed an increase in serum amylase level to 7796 U/L (upper limit of normal, 115 U/L) and in serum lipase level to 24,300 U/L (<190 U/L). Ultrasonographic examination of the abdomen showed a slight enlargement of the head of the pancreas but no abnormalities in the gallbladder and bile ducts. Serum calcium level was repeatedly normal as were the serum lipids. No abnormalities were found on fiberoptic gastroduodenoscopic examination. The patient was discharged after 12 days with the diagnosis of acute pancreatitis of undetermined etiology.

Seventeen months later, the patient consulted a local physician because of very intensive upper abdominal pain associated with nausea and vomiting. Laboratory investigations revealed an increase in serum amylase level to 222 U/L and in serum lipase to 1106 U/L. He was offered symptomatic treatment with an H_2-receptor antagonist and an analgesic drug. Without any further investigations and treatment, the symptoms disappeared within 1 week.

Ten days later, the patient presented to another physician with similar complaints again. Physical examination revealed signs of slight peritoneal irritation in the right upper abdominal quadrant. Laboratory findings included an increase of serum amylase and lipase levels to 353 U/L and 1629 U/L, respectively. Computerized tomographic findings were consistent with edematous pancreatitis, whereas gallbladder and bile ducts appeared normal. An endoscopic reexamination of the upper gastrointestinal tract was unrevealing.

On repeated questioning, the patient admitted having taken repeatedly the drug pyritinol, a substance approved in many European countries for the supportive or adjuvant treatment of psychoorganic symptoms, for better performance on school examinations. Before the first documented episode of acute pancreatitis, he had been taking the drug during 3 months in a daily dose of 600 mg. Before the second and third episode, the drug was taken during 6 and 4 days, respectively.

Because the patient's history strongly suggested a hitherto undescribed cause-effect relationship between the exposure to the drug pyritinol and the episodes of acute pancreatitis, it was considered legitimate and ethical to propose a reexposure. After receiving extensive information, the patient ingested a single dose of 400 mg of pyritinol; 2–3 hours later, nausea appeared, accompanied by abdominal pain in the right upper quadrant, radiating to the back and to the left side of the abdomen. Two days later, the pain intensity had markedly decreased, whereas a

Abbreviations used in this paper: PPD, purified protein derivative; SI, stimulation index.

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feeling of fullness after meals persisted for a few more days. Laboratory investigations revealed a marked increase of both serum amylase (from 66 to 744 U/L) and serum lipase (from 139 to 2950 U/L) levels 24 hours after drug ingestion. Liver function test results were repeatedly normal during all episodes of acute pancreatitis and during rechallenge. During the follow-up period of 2 years and 6 months, the patient has abstained from retaking the drug and has not complained of any further clinical events suggesting a recurrence of acute pancreatitis.

Immunologic Investigations

Skin testing: scratch and patch-scratch tests. Scratch and patch-scratch tests were performed on the patient's forearm and back, respectively, with pyritinol in concentrations of 0.01, 0.1, and 1 mg/mL. NaCl (0.9%) served as a negative and histamine 1:1000 as a positive control. Scratch tests were interpreted at 20 minutes and patch-scratch tests at 24 and 72 hours; all results were negative.

Lymphocyte stimulation tests. The lymphocyte transformation test was performed with mononuclear cells obtained by Ficoll-metrizoate density centrifugation of heparinized blood. Cells (2×10^6) were cultured in RPMI 1640 medium supplemented by 20% AB serum with the respective antigens/drugs; after 6 days, [^{3}H]thymidine was added and [^{3}H]thymidine incorporation determined by scintillation counting. The increase in DNA synthesis was expressed as a stimulation index (SI). The SI corresponds to the value measured with antigen divided by the control value, an SI of >2.0 being indicative of a positive test. At a concentration of 0.5 μg/mL, lymphocyte proliferation was increased with an SI of 3.50. The same concentration of pyritinol was tested in two control cultures without eliciting an enhanced proliferation, thus excluding a mitogenic effect of the drug. Previous toxicity examination had shown a marginal reduction of lymphocyte proliferation after concentrations of >1 μg/mL (17% reduction of phytohemagglutinin stimulation) and a strong reduction or inhibition >10 μg/mL, whereas concentrations of 0.5 and 0.25 μg/mL were shown to be nontoxic (Table 1).

Double fluorescence analysis. To determine the type of reactive cell, cells from the cell culture (with or without pyritinol) were stained with fluorescein isothiocyanate– or phycoerythrin-labeled monoclonal antibody. The activation of CD4-and CD8-positive lymphocytes was measured on days 0, 2, 5, and 8 by their interleukin 2 receptor (CD25) and HLA-DR expression. The respective stimulation was compared with tetanus toxin and purified protein derivative (PPD) (tuberculin)-driven cultures[6] and an unstimulated control culture. At pyritinol concentrations of 0.5 and 1 μg/mL, CD4/CD25 expression was slightly enhanced; for 1 μg/mL, the percentage of CD4/CD25-positive T cells was 4.3% on day 5 and 5.6% on day 8 (compared with 2.5% and 2.8% in the control cultures); HLA-DR expression on CD4 cells was also enhanced on day 5 (12.1% vs. 7.1% in the control). Tetanus-stimulated cultures contained 11.8% and PPD-stimulated cultures 15.7% double-positive HLA-DR/CD4–positive T cells on day 5. CD8 cells were also somewhat activated, however, to a minor degree (2.6% vs. 0.4% on day 5).

Table 1. Lymphocyte Stimulation Test

Antigen	C *(μg/mL)*	20% AB serum SI
Pyritinol	1	1.60
	0.5	3.50
	0.25	1.70
	0.1	1.50

NOTE. All data are from triplicates, the variance of the proliferative values being consistently below 15%.
C, concentration of the antigen; SI, stimulation index, reflecting increase in DNA synthesis rate.

Discussion

After gallstones and excessive alcohol consumption, drugs are the third important cause of acute pancreatitis. They account for less than 10% of cases.[5] Azathioprine, mercaptopurine, and didanosine belong to the drugs with a high incidence of this complication, and the cause-effect relationship is generally accepted to be definite. As with other etiologies of acute pancreatitis, the pathogenesis of drug-induced disorders of the pancreas is far from being elucidated.

We report this observation for three reasons: first, because the reexposition makes a causal relationship between the intake of pyritinol and the occurrence of acute pancreatitis very likely; second, because this side effect of pyritinol has not been described previously; and third, because the immunologic investigations point to a probable T cell–mediated hypersensitivity reaction. The in vitro data suggest the involvement of both T-cell subsets (CD4 and CD8) as described for other hypersensitivity reactions.[6,7]

Pyritinol is a drug widely used in Europe for the treatment of memory disturbances and is, in many countries, available without restrictions. As the disulfide of 5-thiopyridoxine, it contains an active sulfydryl moiety and is closely related to D-penicillamine. Hepatotoxicity caused by pyritinol has been reported; histologically, cholestasis with slight liver cell necrosis and microvesicular steatosis were the prominent features,[8] resembling the pattern found in hepatic reactions to penicillamine, a drug well known to induce systemic immune-mediated toxic phenomena in various organs such as the kidney (membranous glomerulopathy), nervous system (myasthenia gravis), and skin (pemphigus).

It is notoriously very difficult to prove the causal role of a certain drug in creating acute organ damage, especially when the pancreas is concerned. In our case, the repeated occurrence of acute pancreatitis after repeated inadvertent and controlled exposure to the same drug

makes a cause-effect relationship very likely. The patient had no other risk factor predisposing to acute pancreatitis. The clinical observation of the intervals between drug intake and start of symptoms of acute pancreatitis becoming shorter with repeated exposures, together with the detection of pyritinol-activated CD4 and CD8 lymphocytes, are very strong arguments for an immune-mediated origin of the pancreatitis. The observation suggests that pyritinol has to be added to the list of drugs capable of inducing an acute pancreatitis.

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