Nitrofurantoin-Induced Pancreatitis

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Nitrofurantoin is a synthetic nitroheterocyclic antimicrobial compound that has been in use since 1935. The leading indication for this drug is to treat and prevent urinary tract infection. The drug is relatively safe. The most common side effect is dose-dependent dyspepsia that necessitates drug withdrawal in 3.8% of patients. Polyneuropathy caused by nitrofurantoin is also dose-dependent. The most important side effects are those that are allergic in nature, and include hepatic toxicity, which appears in 0.3–3/100000 of patients [1]. The incidence of liver damage increases with age and is much more frequent in women, possibly because of its higher use in this patient group. Rarely, hepatotoxicity can be fatal. Another side effect is pneumonitis [2]. Fever and eosinophilia may also appear in patients treated with this drug. Nitrofurantoin-induced pancreatitis was described only twice [3,4]. We present the third case of acute pancreatitis due to nitrofurantoin.

Patient Description

The patient was a 76 year old woman with dementia who lived in a nursing home and was regularly treated with vitamin C 1 g/day. One day before admission she began treatment with nitrofurantoin 100 mg x 4/day for asymptomatic bacteriuria due to *Enterococcus fecalis*. After taking 300 mg of the drug she experienced fever and abdominal pain and was referred to the hospital. On admission she was in a generally good condition and had a temperature of 39°C. The only positive sign in the physical examination was slight epigastric tenderness. Blood results [Table] demonstrated elevated levels of amylase and lipase.

No eosinophilia was seen in the differential leukocyte count, and urine examination was normal. Blood and urinary cultures were negative. Abdominal ultrasonography on the second day of hospitalization demonstrated a normal liver and pancreas. No stones were found in the gallbladder and the bile ducts were normal. On admission, treatment with nitrofurantoin was stopped. The patient improved rapidly and on the second day of hospitalization her fever resolved and the abdominal pain disappeared. She was discharged after 4 days and no bouts of pancreatitis recurred.

Laboratory results during hospitalization

Hospitalization day	1	2	3	4
Leukocyte count	8,000/mm^3	6,500 mm/^{3}		
Amylase (u/L)	1,095	701	524	335
Lipase (u/L)	415	130	36.5	19.9
Bilirubin (mg/dl)	0.9	0.6		
AP (u/L)	90			
AST (u/L)	28			
Triglycerides (mg/dl)	95			
Calcium (mg/dl)	8.6			

Normal values: amylase 180–280 u/L, lipase: 12–32 u/L, bilirubin 0.1–1 mg/dl, alkaline phosphatase (AP) 30–115 u/L, aspartate aminotransferase (AST) 0–40 u/L, triglycerides $\leqslant$ 160 mg/dl, calcium 8.5–10.5 mg/dl.

Comment

Drug-induced pancreatitis can be caused by several drugs, and was estimated to be the cause of 1.4% of cases of pancreatitis [5]. A higher incidence rate was found among patients with diseases associated with pancreatitis, such as inflammatory bowel disease and AIDS [5]. Drugs most commonly causing pancreatitis are angiotensin-converting enzyme inhibitors, valproic acid, H2 blockers, non-steroidal anti-inflammatory drugs, lovastatin, azathioprine and 6-mercaptopurine, gemfibrozil, pentamidine and ddi. Thiazides, estrogens, furosemide, methyldopa and sulfonamides can also cause this disease. Drug-induced pancreatitis usually runs a benign course and the mechanism of this complication is largely unknown.

Pancreatitis induced by nitrofurantoin is very rare and only two cases [3,4] were reported in the past. As in our case, both of them were women. The first patient, reported in 1983, was a 79 year old woman who had fever hyperamylasemia and obstructive jaundice. Dilatation of the bile ducts was demonstrated and no stones or malignant tumor were found. These signs appeared 5 days after she started treatment with nitrofurantoin and disappeared after discontinuation of the drug. The obstructive jaundice was explained by pancreatic swelling due to nitrofurantoin. A single re-challenge dose of nitrofurantoin caused fever, abdominal pain and hyperamylasemia within several hours [3]. The second patient, aged 26, and described in 1994 [4], had been taking nitrofurantoin for 3 days. She suffered epigastric pain and anorexia that appeared after taking the first tablet. Laboratory results showed mild hyperamylasemia and an elevated lipase level. The symptoms resolved a few days after discontinuation of nitrofurantoin. Eight months later when she took nitrofurantoin again, all the symptoms reappeared accompanied by arthralgia and myalgia. Elevated levels

of amylase and lipase were observed on the first day of treatment.

Our patient exhibited some similar features to those of the previous patients. Her symptoms appeared on the first day of treatment and included fever, abdominal pain and elevated levels of amylase and lipase that disappeared soon after discontinuation of the drug. None of the patients had eosinophilia. In all three patients another cause for pancreatitis was ruled out, and no biliary disease, metabolic disorder, alcohol consumption or exposure to other drugs that can cause pancreatitis was found. As in the previously described two cases, we share the impression that the mechanism of pancreatitis was allergic. Although only three cases have been described, it should be noted that in a patient treated with nitrofurantoin for a short duration and who develops fever and abdominal pain, the possibility of drug-induced pancreatitis should be raised and amylase and lipase levels examined. Discontinuation of the drug leads rapidly to complete resolution of the symptoms and correction of the laboratory abnormalities.

References

1. Stricker BH, Blok AP, Class FH, Van Parys GE, Desmet VJ. Hepatic injury associated with the use of nitrofurantoin. A clinicopathological study of 52 reported cases. *Hepatology* 1988;8:599–606.
2. Sovijðrvi ARA, Lemola M, Stenius B, Idanpaan-Heikkila J. Nitrofurantoin induced acute, subacute and chronic pulmonary reactions. A report of 66 cases. *Scand J Respir Dis* 1977;58:41–50.
3. Nelis GF. Nitrofurantoin-induced pancreatitis: report of a case. *Gastroenterology* 1983;84:1032–4.
4. Christophe JL. Pancreatitis induced by nitrofurantoin. *Gut* 1994;35:712–13.
5. Lankisch PG, Drge M, Gottesleben F. Drug induced acute pancreatitis: incidence and severity. *Gut* 1995;37:565–7.

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