INTERNAL MEDICINE

□ CASE REPORT □

Valsartan-induced Acute Pancreatitis

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Abstract

Gastrointestinal toxicity is uncommon among patients treated with angiotensin II receptor antagonists. A 58-year-old man presented with nausea, vomiting and constant pain in the epigastrium that radiated to the flanks. He received treatment with valsartan (160 mg daily) for hypertension. The clinical, biochemical and radiological findings were compatible with a diagnosis of acute pancreatitis. After the patient achieved a clinical and biochemical recovery, the valsartan therapy was started again. Six weeks later, he returned to the hospital with an attack of pancreatitis. Subsequently, he returned with repeated attacks of pancreatitis twice, and the valsartan was discontinued. Ten months after the treatment, the patient had no complaints. When severe abdominal symptoms occur for no apparent reason during treatment with valsartan, a diagnosis of pancreatitis should be considered.

Key words: valsartan, acute pancreatitis, angiotensin receptor blockers

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Introduction

Angiotensin II receptor blockers are the preferred therapy for hypertension because they are associated with less side effects than angiotensin-converting enzyme inhibitors (1). Gastrointestinal toxicity is uncommon among patients treated with angiotensin II receptor antagonists, and there have been no previously reported cases of pancreatitis among patients using valsartan. We herein report the first case of valsartan-induced pancreatitis.

Case Report

A 58-year-old man presented with a two- to three-day history of nausea, vomiting and constant pain in the epigastrium that radiated to the flanks. He received treatment with valsartan (160 mg daily) for moderate hypertension. His previous history was otherwise unremarkable, and he did not report any acute or chronic pancreatic disease. He also denied alcohol consumption, toxic habits or the use of any other medications, including over-the-counter medications or herbal remedies.

On admission, the patient was fully alert and oriented, afebrile and exhibited normal vital parameters. A physical examination yielded normal findings apart from a severely tender abdomen. The laboratory data showed leucocytosis (16.8×10^3/L) with a normal differential. The blood level of amylase (279 IU/mL; normal range 0-115 IU/L) was elevated; however, those of both lipase (150 IU/mL; normal range 0-190 IU/L) and creatinine (0.7 mg/dL; normal range 0.6-1.3 mg/dL) were within the normal ranges. Haematological variables, the levels of electrolytes, cholesterol and triglycerides and the results of liver function tests were normal. Upper abdominal magnetic resonance and magnetic resonance cholangiopancreatography showed a large number of millimetre-sized gallstones, gallbladder wall oedema, diffuse pancreatic oedema and mild heterogeneous peripancreatic fatty tissue. These findings were compatible with a diagnosis of acute pancreatitis. Endoscopic retrograde cholangiopancreatography (ERCP) revealed a minimally dilated choledoch (Figure A-D). Oddi sphincterotomy was then performed. During treatment, the patient's abdominal pain, nausea and abdominal tenderness persisted. ERCP was therefore performed again, and the choledoch was found to be normal with no gallstones. After the completion of treatment, the

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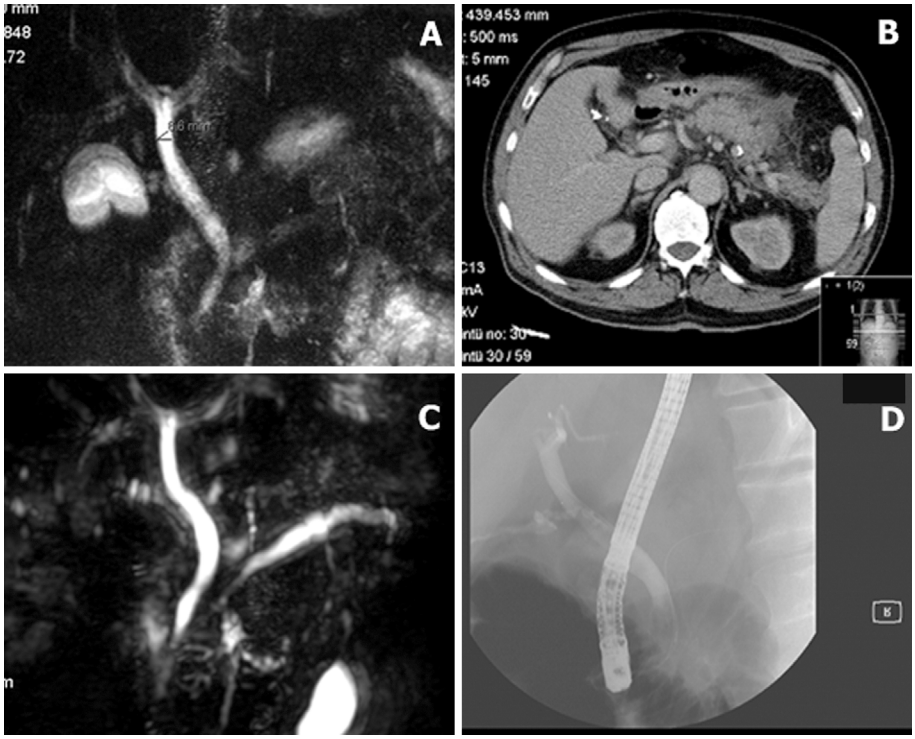


Figure. **A: Millimetre-sized gallstones and a minimally dilated choledoch on MRCP, B: Diffuse pancreatic oedema and mild heterogeneous peripancreatic fatty tissue on CT, C: After cholecystectomy, a minimally dilated choledoch on MRCP, D: A minimally dilated choledoch on ERCP.**

levels of amylase and lipase were normal, and the patient was free of abdominal pain. The valsartan therapy was started again, and the patient was discharged. Surgery was suggested for the gallstones, and cholecystectomy was performed one month later. Six weeks later, the patient returned to the hospital with abdominal pain in the epigastrium that radiated to the flank with nausea and vomiting. Laboratory findings showed elevated levels of amylase (830 IU/L) and lipase (1,519 IU/L). He was treated again; however, the cause of the pancreatitis was not determined. After receiving treatment for the pancreatitis, he was discharged and subsequently returned twice with repeated attacks of pancreatitis. Because the same symptoms and laboratory findings were observed, the patient's use of valsartan was thought to be the cause of his pancreatitis. The valsartan was discontinued, and amlodipine therapy was started as treatment for moderate hypertension. Ten months after the initiation of this treatment, the patient had no complaints.

Discussion

According to the definition of drug-related side effects proposed by Naranjo et al. (2), pancreatitis can occur following the administration of valsartan. In addition, the return to normal clinical and laboratory levels after drug cessation explains the lack of other causes of pancreatitis (gallstones, biliary sludge, hyperlipidaemia, alcohol, use of other pharmaceuticals, etc.). Further confirmation is obtained when the symptoms recur and/or an episode of pancreatitis develops after valsartan is readministered. The above-mentioned findings taken together with the results of the present study suggest that valsartan caused the pancreatitis observed in this case.

Five cases of pancreatitis associated with angiotensin receptor blockers have been reported in the literature, including two patients treated with losartan, two patients treated with irbesartan and one patient treated with telmisartan (3-7). Angiotensin-converting enzyme inhibitors affect the kallikrein-kinin system, which may consequently lead to intrapancreatic bradykinin accumulation. The accumulation of intrapancreatic bradykinin is thought to be caused by pancreatitis (8). Angiotensin receptor blockers have no effect on the kallikrein-kinin system, and the mechanisms underlying the development of pancreatitis in patients treated with these agents are unclear (1). However, pancreatic acinar cells contain angiotensin II (especially AT1) receptors, and this system has been reported to play a role in the modulation of the pancreatic microcirculation, the regulation of digestive enzyme secretion and the elevation of the number of receptors during pancreatic inflammation. As the number of these receptors increases, the release of digestive enzymes from the pancreas increases and tissue perfusion decreases, thus inducing tissue damage. Additionally, in experimental animal models, the administration of angiotensin receptor blockers, which block angiotensin II receptors (the AT1 receptor in particular), suppresses the release of exocrine pancreatic enzymes, decreases pancreatic damage and improves the levels of biochemical and histopathological markers of pancreatitis (9, 10). Data obtained from human studies and animal models support the notion that angiotensin II recep-

tor blockers reduce the risk of pancreatitis (11). These results, as well those of Famularo et al. (5), led us to the hypothesis that valsartan can cause pancreatitis via an immune or idiosyncratic mechanism.

Although the exact mechanism is unknown, when severe abdominal symptoms (pain, nausea, vomiting, etc.) occur for no apparent reason during treatment with valsartan, a diagnosis of pancreatitis should be considered. If other causes of pancreatitis are not found, discontinuing valsartan and beginning a different antihypertensive regimen should be considered.

The authors state that they have no Conflict of Interest (COI).

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