ACUTE PANCREATITIS AS ADVERSE REACTION TO PERINDOPRIL THERAPY

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Abstract

Many drugs and drug classes have been reported to be associated with acute pancreatitis. Angiotensin-converting enzyme inhibitors are one of the most commonly prescribed classes of medications, as they are used in hypertension, heart failure and proteinuria. Although well tolerated, acute pancreatitis has been reported in a few subjects treated with drugs from this group. We present a rare case of pancreatitis occurring as an adverse reaction to therapeutic doses of perindopril with good outcome.

Case report: We report a case of a 63 year-old-woman presented with clinical signs of acute pancreatitis, 2 months after administration of perindopril 4 mg once daily for treatment of hypertension and reduction of proteinuria. The patient has had a 3-year-history of diabetes treated with metformin 2 x 850 mg daily, which is also classified as a possible drug that causes pancreatitis. Other causes of the disease were ruled out. After cessation of perindopril her clinical status improved and pancreatic enzymes level decreased.

Conclusion: Because perindopril has a widespread clinical use, we wish to alert clinicians and urge close monitoring for pancreatitis as well as other adverse effects. Discontinuation of the drug leads to an improvement in the clinical condition.

Key words: angiotensin-converting enzyme inhibitor, drug-induced pancreatitis, perindopril

Introduction

Drug-induced pancreatitis (DIP) is assumed to be a relative rare entity, and its incidence is reported between 0.1 and 2% of acute pancreatitis (AP) cases [1]. Fortunately, DIP is usually with mild or moderate severity and tends to disappear after drug discontinuation, but rare cases of fulminant drug-induced acute pancreatitis have been reported [2]. Angiotensin-converting enzyme inhibitors (ACE-I) are considered probable causes of pancreatitis. The newer ACE-I are not implicated in so many cases as enalapril [3]. We describe the first case of perindopril-induced pancreatitis encountered in our institution. Although most ACE inhibitors have been reported to cause acute pancreatitis, perindopril- induced pancreatitis has been reported only twice [4, 5]. Early recognition of this reaction is of crucial importance both for rapid discontinuation of the offending drug and for avoidance of unnecessary drug therapy or invasive procedures [6].

Report of a case

A 63-year-old woman with a three year history of non-insulin dependent diabetes was admitted to emergency department because of severe epigastric pain radiating to her back for the previous two days. The pain was accompanied by nausea and vomiting. The patient reported no acholic stools, melena, gas, or fever. She had no previous history of alcohol consumption and gallstones, or recent abdominal trauma and abdominal operations. Two months before admission she had begun taking perindopril, 4 mg a day, for treatment of mild proteinuria and hypertension. She was treated also with metformin, 850 mg twice daily in the last three years.

On physical examination, the patient was afebrile, with a blood pressure of 140/85 mm of mercury, a pulse rate of 90 beats per minute, and respirations of 18 per minute. The abdomen was distended and tenderness was present in the epigastrium without rigidity, or guarding. Laboratory test results revealed increased levels of serum amylase 1080 U/L (reference range 30-110), lipase 869 U/L (10-73), and C-reactive protein 95 mg/L (0-6). The hematocrit was 0.43 (43%) with a leukocyte count of 12.5 x 109 cells per liter. Serum values of liver enzyme, blood urea nitrogen, creatinine and electrolyte

were normal. A serum glucose level was 8.2 mmol/L, and triglyceride level was 1.9 mmol /L. Urine analysis showed only mild proteinuria. The opioid test was negative. An abdominal ultrasound examination revealed normal gallbladder without cholelithiasis, no dilatation of bile and pancreatic ducts. The pancreas was diffusely enlarged and hypoechoic. This condition was diagnosed as acute pancreatitis. Abdominal magnetic resonance imaging (MRI) confirmed the diagnosis and excluded gallstones and anatomical abnormalities of the pancreas. Drug-induced pancreatitis was suspected. Possible common causes of acute pancreatitis such as alcohol intake, hypercalcemia, hypertriglyceridemia, neoplasia and abdominal trauma were also excluded. Perindopril was stopped and the patient received symptomatic medical treatment with bowel rest and intravenous fluids. The patient`s clinical status spontaneously improved within 72 h following cessation of the drug. Serum amylase and lipase level normalized over the following five-six days. A re-challenge test was not performed for ethical reasons and the patient was discharged from hospital 8 days after admission. Perindopril was replaced with angiotensin receptor blocker - losartan. The abdominal pain disappeared and the patient has not suffered another episode of pancreatitis during the subsequent one-year of follow-up. Her diabetes was controlled with metformin, as before, and her blood pressure and proteinuria were normalized using an angiotensin receptor blocker.

Discussion

Acute pancreatitis is a heterogeneous disease ranging from a clinically mild to a more severe forms associated with high morbidity and mortality. Gallstone and alcohol use have been considered the most common causes of acute pancreatitis [7]. Other causes include iatrogenic injury (i.e.post ERCP), metabolic and autoimmune disorders, inherited disorders, neoplasia, anatomical abnormalities, infections, ischemia, trauma and drugs. However, up to 2% of acute pancreatitis cases may be caused by drugs, with a higher incidence in specific populations, like females, the elderly, children, HIV-positive patients, and those with inflammatory bowel disease [1]. More than five hundred drugs suspected of causing acute pancreatitis have been reported in the World Health Organization (WHO) database. For most of these drugs, causality remains unproven, and only about thirty of them have been confirmed [8]. There are several classifications of DIP, but the classification of Karch and Lasagna is most preferred. In it, the association of the drug and acute pancreatitis is classified as definitive, probable and possible [9]. Table 1.

DEFINITIVE	Drug reaction that follows a reasonable temporal sequence from administration of the drug, that follows a known response pattern that is confirmed by stopping the drug (de-challenge), that is confirmed by reappearance of the symptoms upon repeated exposure to the drug (re-challenge)
PROBABLE	Drug reaction that follows a reasonable temporal sequence from administration of the drug, that follows a known response pattern, that is confirmed by de-challenge, that could not be explained by the known characteristics of the patients clinical state.
POSSIBLE	Drug reaction that follows a reasonable temporal sequence from administration of the drug, that follows a known response pattern but that could have been produced by the patient`s clinical state or other modes of therapy.

Table1. Classification of evidence according to Karch and Lasagna [9].

ACE-I are one of the most commonly prescribed classes of medications, as they are used in hypertension, heart failure and proteinuria [10]. The first reported case of ACE inhibitor-induced AP was seen with enalapril in 1992 [11]. Since then, enalapril-induced AP has been reported more than 10 times. Other case reports about AP induced by captopril, benazepril, lisinopril, fosinopril, quinapril and ramipril have been also published, but are less common [2, 3]. Our Medline search showed only two case reports of AP induced by Perindopril [4, 5]. In the first case, the association of perindopril with acute pancreatitis was confirmed by a re-challenge test, while in the second one with de-challenge. Pancreatitis usually is not considered a class effect of drugs, so specific drugs are usually noted instead of the entire class [12]. Because most ACE inhibitors are associated with the occurrence of AP, some authors agree that the whole class of ACE-I is associated with the occurrence of DIP [13]. In one European case-control study the use of ACE-I was associated with an increased risk of AP, with an odds ratio of 1.5. The risk increased with higher daily doses and it was highest during the first 6 months of therapy [14]. In our case, the patient did not receive very high doses of perindopril, but the symptoms of acute pancreatitis appeared two months after its introduction.

In this report, we have described a patient with a mild form of pancreatitis according to Atlanta classification, who had no risk factors for pancreatitis and was taking no medication known to cause pancreatitis other than perindopril and metformin. Though metformin has been classified as possible DIP, among the published case reports the mechanisms of inducing pancreatitis include drug overdose, drug accumulation, and acute renal failure triggered by vomiting [15]. Our patient used metformin for three years without any complaints. Thus, we decided not to exclude metformin. The patient`s clinical status improved after cessation of perindopril, and amylase and lipase values normalized within few days. The reasonable temporal sequence from administration of the drug with the patient′s symptoms, the lack of other risk factors, and positive de-challenge support the possibility that perindopril caused patient′s acute pancreatitis. Perindopril was replaced with angiotensin II receptor blocker (losartan) and the patient has not suffered another episode of pancreatitis during the subsequent one-year follow-up. Angiotensin II receptor blockers have been associated with pancreatitis very rarely [16, 17]. Pancreatitis associated with ACE-I is thought to reflect localized angioedema of the gland. ACE-I can induce angioedema in up to 0.7% of treated patients [18]. They are known to affect the kallikrein-kinin system, resulting in intrapancreatic accumulation of bradykinin, thought to be caused by pancreatitis [19]. Molinaro G et al. have concluded that genetic predisposition may exist toward this adverse effect in patients who degrade bradykinin more slowly than average [20]. This may explain the rare incidence of pancreatitis induced by ACE . Angiotensin receptor blockers have no effect on the kallikrein-kinin system and thus the mechanism by which they cause pancreatitis remains unclear. In experimental animal models, the administration of angiotensin receptor blockers decreases pancreatic damage and improves the biochemical and histopathological parameters of pancreatitis [21, 22].

Conclusion

In conclusion, when the diagnosis of acute pancreatitis is established in the absence of other obvious causes, angiotensin-converting enzyme inhibitors, including perindopril, should be considered as etiological cause of acute pancreatitis. The genetically-induced slow decomposition of bradykinin could be an explanation for this rare adverse reaction. Early recognition of this reaction is of great significance both for rapid discontinuation of the offending drug and for avoidance of unnecessary drug therapy or invasive procedures. Cessation of the drug leads to disappearance of symptoms and normalization of biochemical parameters in patients with drug induced pancreatitis. This rare adverse reaction could be prevented if regular monitoring of pancreatic enzymes is carried out along with the initiation of a new drug from the ACE-I group in the therapy.

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