

LISINOPRIL-INDUCED ACUTE PANCREATITIS

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Abstract

Drugs are an uncommon but well-recognised cause of acute pancreatitis and new agents of drug-induced pancreatitis continue to be reported. We describe only the 10th reported case of lisinopril-induced pancreatitis in a young female patient.

Introduction

Most cases of acute pancreatitis in the United Kingdom are secondary to either gallstone disease or excessive alcohol intake. Amongst the rarer causes listed in Table 1 drugs are implicated in 1.4-2% of cases (2) and azathioprine, frusemide, tetracycline, sulphonamides, oestrogens and pentamidine have all been identified as causative agents. Angiotensin converting enzyme (ACE) inhibitors, such as lisinopril, which are commonly used in the treatment of essential hypertension, have been associated with acute pancreatitis in a few isolated reports(3-8), based on the development of acute pancreatitis after starting the ACE inhibitor, other causative factors being excluded and the patient's condition improved following cessation of the drug. We report a further case of lisinopril-induced acute pancreatitis.

Case Report

A 21 year old woman was admitted to our hospital following an episode of acute epigastric pain. Physical examination revealed a loud pan systolic murmur, marked epigastric tenderness and serum biochemistry showing an isolated, grossly elevated amylase of 2182u/l. All other blood tests were normal including serum cholesterol and calcium levels. At the age of 9 she had been diagnosed with coarctation of the aorta, underwent multiple balloon dilatations and subsequently had a stent inserted. Lisinopril had been started for hypertension 3 years prior to this presentation. She did not drink alcohol and there was no family history of gallstones. A diagnosis of mild acute pancreatitis was made (modified Glasgow score of zero) and she was managed conservatively by restricted oral intake, analgesia and intravenous fluids. An abdominal ultrasound scan performed two weeks previously following a similar attendance at the emergency department with epigastric pain and hyperamylasaemia (>1400u/L) did not demonstrate gallstones. It is unclear why she was not admitted on that occasion. As gallstones remained the most likely aetiology of her pancreatitis, a further ultrasound scan was performed and was again reported as normal. A magnetic resonance cholangiopancreatographic scan (MRCP) was then performed, which excluded pancreatic duct anatomical abnormalities, pancreaticobiliary malignancy and cholithiasis (Fig.1). With normal serum cholesterol, calcium and liver enzymes, attention turned to the possibility of

Table 1. The causes of acute pancreatitis with relative frequency in UK (1)

Gallstones (30-70%)	Idiopathic (10%)
Alcohol (30-70%)	Drugs (1-2%)
Post-ERCP (1-2%)	Blunt trauma
Post-bypass (0.5-5%)	Hypercalcaemia
Hypertriglyceridaemia (>11mmol/L) (2%)	AIDS
Ampullary/pancreatic tumours (3%)	Viruses (mumps, coxsackie, Hepatitis)
Congenital abnormalities (5%)	

her only medication, lisinopril, being the causative agent of her pancreatitis. Her antihypertensive medication was changed to atenolol following discussion with her cardiothoracic team and she continued to recover uneventfully from her acute pancreatitis. She was discharged after 5 days in hospital and has had no further attacks in the 6 months since discharge.

Discussion

After the diagnosis of acute pancreatitis has been made, further investigations are directed towards identifying the cause and if all are negative then consideration must be given to the rarer causes. Drug-induced pancreatitis is uncommon and the pathophysiology differs between medications - ACE inhibitor-induced pancreatitis is thought to be related to tissue accumulation of bradykinin which is usually degraded by ACEs. The resulting vasodilation, inflammation and altered vascular permeability causes a localised angioedema of the gland, resulting in an oedematous pancreas which may be demonstrable on CT with the potential for ductal obstruction (2,3). This is a similar mechanism to that of Hereditary Angioedema (HAE), where patients with low levels of C1 esterase inhibitor suffer self-limiting attacks of subepithelial oedema throughout the gastrointestinal and respiratory tracts. Other hypotheses such as allergic reactions and direct toxicity to pancreatic tissue have also been postulated (5,9). As ACE inhibitors are increasingly being used as first line therapy for a variety of medical disorders including hypertension and congestive heart failure, which are being encountered at

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Figure 1. A MRCP demonstrating normal pancreaticobiliary anatomy



younger ages, they will be taken by a younger subset of patients. Lisinopril has previously been implicated as the causative factor for acute pancreatitis (3-8) on the basis that the patient developed acute pancreatitis within a limited period of time after starting the medication, other causative factors for acute pancreatitis were excluded and the patient's condition improved rapidly following cessation of the drug. However, all reported cases were on multiple medications and older than 40 years. This is the first reported case in a young patient on single therapy of lisinopril which eliminates the possibility of another drug causing the pancreatitis, or age and other co-morbidities being a factor. In all previous reports, acute pancreatitis occurred within 2 years of starting lisinopril whereas in this patient, lisinopril had been used for 3 years.

Conclusion

The definitive diagnosis of lisinopril-induced pancreatitis would include the demonstration of a further attack after re-challenge with the drug, but this is impossible on ethical grounds, but this case provides further evidence for lisinopril-induced pancreatitis. It can occur at any age, following extended periods of usage and should be considered alongside other causes for acute pancreatitis. The prognosis of drug-induced pancreatitis is

generally excellent but it is of crucial importance to recognise the offending drug and discontinue it to avoid unnecessary invasive procedures and ensure an accelerated recovery from a potentially fatal condition. The precise mechanism remains speculative but is likely to be localised angioedema of the gland with ductal obstruction and enzyme activation.

References

1. Burkitt, Quick, Gatt Essential Surgery Churchill Livingstone 1998
2. McArthur KE. Drug-induced pancreatitis. *Aliment Pharmacol Ther* 1996;10:23-38
3. Miller LG, Tan G. Drug-induced pancreatitis (lisinopril). *J Am Board Fam Pract* 1999;12(2):150-3
4. Tosun E, Oksuzoglu B, Topaloglu O. Relationship between acute pancreatitis and ACE inhibitors. *Acta Cardiol* 2004;59(5):571-2
5. Maliekal J, Drake CF. Acute pancreatitis associated with the use of lisinopril. *Ann Pharmacother* 1993;27:1465-6
6. Marinella MA, Billi JE. Lisinopril therapy associated with acute pancreatitis. *West J Med* 1995; 163:77-8
7. Gershon T, Olshaker JS. Acute pancreatitis following lisinopril rechallenge. *Am J Emerg Med* 1998 ;16(5):523-4
8. Kanbay M, Sekuk H, Yilmaz U, Gur G, Boyacioglu S. Acute pancreatitis associated with combined lisinopril and atorvastatin therapy. *Dig Dis* 2005;23(1):92-4
9. Yeung JH, Coleman JW, Park BK. Drug-protein conjugates – IX:immunogenicity of captopril-protein conjugates. *Biochem Pharmacol* 1985;34:4005-4012