JOP. J Pancreas (Online) 2005; 6(6):605-607.

LETTER

Idiosyncratic Pancreatitis Associated with Perindopril

Giuseppe Famularo[1], Giovanni Minisola[1], Giulio Cesare Nicotra[1], Claudio De Simone[2]

[1]Department of Internal Medicine, San Camillo Hospital. Rome, Italy
[2]Department of Experimental Medicine, University of L'Aquila. L'Aquila, Italy

Dear Sir:

The use of angiotensin-converting enzyme (ACE) inhibitors is not associated with an increased risk of acute pancreatitis [1] and, so far, only one case has been linked with the use of perindopril [2]. We report on a second patient with perindopril-induced pancreatitis.

A 72-year-old man presented with a 10-day history of nausea, vomiting, and constant pain in the epigastrium which radiated to the sides. Four weeks before admission, perindopril (4 mg/day) had been added to the usual regimen of glyburide (5 mg/day), metformin (1 g/day) and carvedilol (6.25 mg/day) which the patient had been taking for three years for the treatment of diabetes mellitus and moderate hypertension. His previous history was otherwise unremarkable, except for psoriasis; he did not report any acute or chronic pancreatic disease and denied alcohol use, toxic habits or taking any other medications including over-the-counter medications or herbal remedies. Upon admission, the patient was fully alert and oriented, apyrexial and had normal vital parameters; physical examination yielded normal findings apart from a severely tender abdomen with no bowel sounds. Laboratory data showed increased blood amylase (556 IU/L; reference range: 0-115 IU/L) and lipase (1,396 IU/L; reference range: 0-190 IU/L) levels; electrolytes, hematological variables, cholesterol, triglycerides, liver and renal function tests, and blood gases were normal. The results of serologic tests for the *Mycoplasma* and *Chlamydia* species, viral hepatitis, and a wide range of other viral infections were also negative. Abdominal ultrasonography and computed tomography showed a moderately enlarged and edematous pancreas; furthermore, at imaging techniques no alterations such as stones or sludge of the gallbladder and of the common bile duct were detected. A chest X-ray was also normal.

Perindopril was discontinued and the patient was managed conservatively with bowel rest and intravenous fluids. Five days after admission, blood amylase and lipase values returned to normal and he was free of symptoms. A re-challenge test was not performed for ethical reasons and the patient was discharged on the 8th day. At this time, his blood pressure was below 130/80 mmHg and we decided to not start any antihypertensive therapy. At a follow-up visit one month later, he was doing well with no clinical or laboratory evidence of active pancreatic disease; serologic tests for *Mycoplasma* and *Chlamydia* species and viruses remained negative. Blood pressure was below 145/90 mmHg on repeated measurements while the patient was still not receiving any blood pressure-lowering medications.

Many findings indicate perindopril as the main cause of acute pancreatitis in this patient; however, clinical and laboratory findings point to a mild form of pancreatitis according to the Atlanta criteria [3]. Use of the Naranjo probability scale indicates a probable drug-related event [4] and, before treatment with perindopril was initiated, the

patient had no prior history of acute or chronic pancreatic disorder. As a matter of fact, the four-week temporal relationship between starting therapy with the ACE inhibitor and the presentation with clinical and laboratory findings of pancreatitis is clear and we found no alternative causes, such as biliary stones or sludge, alcohol use, hypertriglyceridemia, hypercalcemia, or an active viral infection, to explain the onset of acute pancreatitis in this case. Furthermore, the patient was not taking recreational drugs, over-the-counter medications, herbal remedies, or any other drugs potentially able to trigger the onset of acute pancreatitis. There is no report of pancreatitis associated with the use of carvedilol and causality attribution in the two cases of pancreatitis so far linked with metformin therapy is flawed by important contradicting factors [5, 6]. The first patient had a metformin over-dose [5] and the second patient had lactic acidosis and acute renal failure, and had been taking several other drugs, including a non-steroidal anti-inflammatory drug and the ACE inhibitor lisinopril at the onset of pancreatitis [6]. The role of glyburide is also unclear. A recent case-control study has found an increased risk of pancreatitis among subjects under 70 years of age treated with glyburide or a combination of glyburide and metformin, but not among those over 70 years of age [7]; the mechanism of pancreatic injury due to glyburide may be linked to the inhibition of ATP-sensitive potassium channels in the pancreatic tissue [8]. However, the patient had been taking glyburide and metformin for several years and he had not had any previous episodes of acute pancreatitis nor did repeated laboratory studies show any increase of pancreatic enzymes at any time during that period. There is no evidence available in supporting the hypothesis that diabetic patients treated with a combination of glyburide and metformin have an increased risk of pancreatitis after exposure to perindopril or other ACE inhibitors. We decided against a re-challenge test with perindopril because of the concern of inducing severe acute pancreatitis.

Pancreatitis has occasionally been linked with the use of ACE inhibitors [reviewed in 9] and our MEDLINE search yielded only one other patient with perindopril-associated pancreatitis [2]. A few cases of pancreatitis have also been reported among patients treated with angiotensin II antagonists [reviewed in 10]. Mechanisms of pancreatic damage by ACE inhibitors remain unclear. One important point is that the pancreas contains a local renin-angiotensin system which is involved in the physiological regulation of digestive enzyme secretion and appears to be up-regulated during pancreatic inflammation [11, 12]. Furthermore, ACE inhibitors may alter the kallicrein-kinin system and the accumulation of kallicrein appears to be an important trigger of pancreatic inflammation during treatment with ACE inhibitors [13]. The trigger of pancreatic damage induced by ACE inhibitors is attributed to hypersensitivity or a metabolic idiosyncratic reaction in almost all cases [2]. Our patient had no fever, rash or eosinophilia at any time during the course of his disease, which eliminates the possibility of an allergic or immune-mediated mechanism. In our opinion, a metabolic idiosyncratic reaction seems to be the most likely explanation of perindopril-associated pancreatitis in this case.

Received September 21st, 2005 - Accepted September 23rd, 2005

Keywords Angiotensin-Converting Enzyme Inhibitors; Pancreatitis; Perindopril

Correspondence
Giuseppe Famularo
Department of Internal Medicine
San Camillo Hospital
Circonvallazione Gianicolense
00149 Rome
Italy
Phone: +39-6.5870.4325
Fax: +39-6.5870.4325
E-mail: gfamularo@scamilloforlanini.rm.it

References

1. Cheng RM, Mamdani M, Jackevicius CA, Tu K. Association between ACE inhibitors and acute pancreatitis in the elderly. Ann Pharmacother 2003; 37:994-8. [PMID 12841806]

2. Gallego-Rojo FJ, Gonzalez-Calvin JL, Guilarte J, Casado-Caballero FJ, Bellot V. Perindopril-induced acute pancreatitis. Dig Dis Sci 1997; 42:1789-91. [PMID 9286249]

3. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11 through 13, 1992. Arch Surg 1993; 128:586-90. [PMID 8489394]

4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30:239-45. [PMID 7249508]

5. Ben MH, Thabet H, Zaghdoudi I, Amamou M. Metformin associated acute pancreatitis. Vet Hum Toxicol 2002; 44:47-8. [PMID 11824780]

6. Mallick S. Metformin induced acute pancreatitis precipitated by renal failure. Postgrad Med J 2004; 80:239-40. [PMID 15082849]

7. Blomgren KB, Sundstrom A, Steineck G, Wiholm BE. Obesity and treatment of diabetes with glyburide may both be risk factors for acute pancreatitis. Diabetes Care 2002; 25:298-302. [PMID 11815499]

8. Singer M, Coluzzi F, O'Brien A, Clapp LH. Reversal of life-threatening, drug-related potassium-channel syndrome by glybenclamide. Lancet 2005; 365:1873-5. [PMID 15924984]

9. Anagnostopoulos GK, Kostopoulos P, Tsiakos S, Margantinis G, Arvanitidis D. Fulminant pancreatitis associated with ramipril therapy. Pancreas 2003; 27:278-9. [PMID 14508138]

10. Famularo G, Minisola G, Nicotra GC, De Simone C. Acute pancreatitis associated with irbesartan therapy. Pancreas 2005; 31:294-5. [PMID 16163066]

11. Tsang SW, Cheng CH, Leung PS. The role of the pancreatic renin-angiotensin system in acinar digestive enzyme secretion and in acute pancreatitis. Regul Pept 2004; 119:213-9. [PMID 15120483]

12. Tsang SW, Ip SP, Leung PS. Prophylactic and therapeutic treatments with AT 1 and AT 2 receptor antagonists and their effects on changes in the severity of pancreatitis. Int J Biochem Cell Biol 2004; 36:330-9. [PMID 14643897]

13. Griesbacher T, Lembeck F. Effects of the bradykinin antagonist, HOE 140, in experimental acute pancreatitis. Br J Pharmacol 1992; 2:356-60. [PMID 1384910]