Acute Pancreatitis Associated with Combined Lisinopril and Atorvastatin Therapy

Mehmet Kanbay a Haldun Sekuk b Ugur Yılmaz b Gürden Gur b Sedat Boyacioglu b

Departments of a Internal Medicine, and b Gastroenterology, Baskent University Faculty of Medicine, Fevzi Cakmak Caddesi, Bahcelievler, Ankara, Turkey

Key Words
Atorvastatin · Lisinopril · Abdominal pain · Acute pancreatitis

Abstract
Few data exist about the incidence of drug-induced pancreatitis in the general population. Drugs are related to the etiology of pancreatitis in about 1.4–2% of cases. Although statins are generally well tolerated, acute pancreatitis has been reported in a few cases treated with atorvastatin, fluvastatin and simvastatin. A 86-year-old man with long-standing history of hypertension and hyperlipidemia, who was treated with lisinopril 10 mg and atorvastatin 20 mg once daily presented with acute pancreatitis. Other causes of the disease were ruled out. After cessation of the drugs, his physical condition improved and the amylase level decreased. To our knowledge, pancreatitis induced by a combination of atorvastatin together with lisinopril has never been reported in the literature.

Introduction
Drugs are related to the etiology of pancreatitis in around 1.4–2% of cases [1]. Many drugs have been reported to be associated with acute pancreatitis. Statins and angiotensin-converting enzyme inhibitors are generally well tolerated. Acute pancreatitis has been reported in a few cases treated with atorvastatin, simvastatin, fluvastatin, lisinopril and enalapril [2–6]. To our knowledge, that atorvastatin together with lisinopril induced pancreatitis has never been reported in the literature. We are reporting a case of atorvastatin together with lisinopril-induced pancreatitis. This was a severe and life-threatening allergic reaction to atorvastatin and lisinopril. Because these drugs may come into more widespread clinical use, we wish to alert clinicians and urge close monitoring for other adverse effects as well.

Case History
A 86-year-old male with a long-standing history of hypertension and hyperlipidemia was admitted to our clinic because of epigastric pain radiating to the back for the previous 4 days. The pain was accompanied by nausea. Initial vital signs were heart rate 108/min, blood pressure 100/60 mm Hg, and body temperature 37.6°C. On physical examination, the abdomen was distended and tenderness
A Case of Atorvastatin together with Lisinopril Induced Pancreatitis

was present in the epigastrium. Otherwise, his physical examination was unremarkable, and bowel sounds were normal. The patient had been receiving lisinopril 10 mg/day for 5 years and atorvastatin 20 mg/day for the last 9 months. He was not taking any other drugs. He denied alcohol use and smoking. He had not undergone any other drug therapy and had never suffered from pancreatic disorders before. He had had no previous abdominal surgery.

Admission laboratory studies revealed increased serum levels of amylase: 876 U/l (25–115), lipase: 978 U/l (40–110), C-reactive protein: 86 mg/l (0–6). Serum values of liver-renal-thyroid functions and complete blood cell count level were normal (table 1). Abdominal ultrasonography showed pancreatic edema, whereas the rest of the pancreas was normal. The biliary tree was not dilated and no gallstones were seen (fig. 1). This condition was diagnosed as acute pancreatitis. Occult biliary disease (microlithiasis) or damage to the ampullary region and congenital variation of the pancreatic duct system was excluded by endoscopic retrograde cholangiopancreatography. Possible common causes of acute pancreatitis such as alcohol intake, hypercalcemia, hypertriglyceridemia (1 week before acute pancreatitis, his serum lipid levels were as follows: total cholesterol 196 mg/dl, low-density lipoprotein cholesterol: 126 mg/dl, high-density lipoprotein cholesterol: 38 mg/dl, and triglycerides: 168 mg/dl), neoplasia, infections, family history and abdominal trauma were also excluded. All drugs were stopped and the patient received symptomatic medical treatment. The patient’s clinical status quickly and spontaneously improved within the 48 h following cessation of the drugs. Serum amylase level returned to normal on day 3 after lisinopril and atorvastatin cessation. The patient was discharged from hospital 6 days after admission. After discontinuing lisinopril and ramipril, he was well at follow-up treatment with amlodipine 10 mg/day and a diet for hyperlipidemia. The patient is being followed up and has not suffered a new pancreatic attack for 14 months.

Discussion

In this report, we describe a patient who had no risk factors for pancreatitis and was taking no medications known to cause pancreatitis other than lisinopril and atorvastatin. To our knowledge, acute pancreatitis has not been described as an adverse effect in patients who had to use atorvastatin and lisinopril together. Previously published studies have shown an association between atorvastatin or lisinopril therapy with acute pancreatitis [1–4]; however, no specific study has been performed in animals. Angiotensin-converting enzyme (ACE) inhibitors and statins are first-line agents in cardiovascular disease. The pathogenesis of drug-induced pancreatitis may be due to an allergic response or to a direct toxic effect [1]. ACE inhibitors work against high blood pressure because they inhibit an enzyme which is necessary to produce a substance which increases the blood pressure. But this same action seems to inhibit the breakdown by enzymes of substances in the body which can make blood vessels leaky. Therefore, pancreatic secretion may cause acute pancreatitis. Angioedema is at best an uncomfortable and disfiguring type of temporary swelling; pancreatitis associated with ACE inhibitors is thought to reflect localized angioedema of the gland [1–3] and angioedema due to ACE inhibitors appears to be linked to the decreased degradation of bradykinin because ACE, also known as kininase II, not only activates angiotensin I but also inactivates bradykinin. In addition, it is known that angiotensin II receptors are thought to be important in regulating pancreatic secretion and microcirculation, and this may have an additive effect on the pathogenesis [5]. Statins are generally well tolerated. Statin-induced pan-

---

**Table 1.** The consecutive laboratory analyses of the patient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On admission</th>
<th>2nd day</th>
<th>3rd day</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/l</td>
<td>86</td>
<td>54</td>
<td>14</td>
</tr>
<tr>
<td>Amylase, U/l</td>
<td>876</td>
<td>345</td>
<td>105</td>
</tr>
<tr>
<td>Lipase, U/l</td>
<td>978</td>
<td>312</td>
<td>94</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>15.6</td>
<td>13.4</td>
<td>14.4</td>
</tr>
<tr>
<td>WBC/mm³</td>
<td>8,000</td>
<td>9,600</td>
<td>7,400</td>
</tr>
<tr>
<td>PLT/mm³</td>
<td>303,000</td>
<td>224,000</td>
<td>251,000</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>28</td>
<td>21</td>
<td>36</td>
</tr>
<tr>
<td>AST, U/l</td>
<td>18</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>20</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Cre, mg/dl</td>
<td>1.2</td>
<td></td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Fig. 1.** Sonographic image shows pancreatic head enlargement.
creatitis is very rare and only a few cases have been reported in the literature. Atorvastatin, fluvastatin, simvastatin and lovastatin were the only statins reported to have caused this side effect. As the association between statins and pancreatitis is based mainly on anecdotal case reports, the data do not provide information on absolute or relative risks for this adverse effect. The mechanism of statin-induced acute pancreatitis is unknown [4–7]. Drug-induced pancreatitis has no distinguishing clinical features. The time course of developing the disorder varies within a few weeks to years after the beginning of drug intake. Proving the association with a particular drug may not always be straightforward, even in suspected cases. Thus, patients restarted on their medications should be closely monitored and the drug promptly discontinued if symptoms recur. The prognosis of drug-induced pancreatitis is generally excellent. Early recognition of this reaction is of crucial importance both for rapid discontinuation of the offending drug and for the avoidance of unnecessary drug therapy or invasive procedures. This case suggests that the two drugs may have an additive effect to cause acute pancreatitis. Up to date, there have been no published data about an increased risk of acute pancreatitis with age. Furthermore, there are no data about drug groups that can be used in patients with hyperlipidemia and a history of attacks of pancreatitis. A prospective study to address these issues is warranted.

With increased use of these drugs, additional similar reports may shed light on the incidence, clinical importance and mechanism of this adverse drug effect. In addition to monitoring for efficacy and commonly reported adverse effects, clinicians need to be aware that acute pancreatitis may occur especially in patients who have to use ACE inhibitors and statins together. The physicians must keep in mind drugs in the differential diagnosis of the etiology of the acute pancreatitis.

References