JOP. J Pancreas (Online) 2005; 6(3):264-268.

CASE REPORT

A Case of Acute Pancreatitis Possibly Associated with Combined Salicylate and Simvastatin Treatment

Stavros Antonopoulos[1], Sotiris Mikros[1], Stelios Kokkoris[1], John Protopsaltis[1], Konstantina Filioti[1], Dimitrios Karamanolis[2], Grigorios Giannoulis[1]

[1]Second Department of Internal Medicine and [2]Department of Gastroenterology, 'Tzanio' General Hospital of Piraeus. Athens, Greece

ABSTRACT

Context Drug-induced acute pancreatitis is a rather rare clinical entity. From time to time, several cases have been reported in which statins or salicylates have been associated with the development of acute pancreatitis. There is only one report which implies the involvement of both drugs in pancreatic inflammation.

Case report A 58-year-old Caucasian male with a history of coronary heart disease and hypercholesterolemia, under treatment with acetyl-salicylate for 6 years and simvastatin for 2 months, presented to the Emergency Department of our hospital with epigastric pain and vomiting of 24-hour duration. The clinical and laboratory investigation led to the diagnosis of acute pancreatitis. Conservative and rich-in-fluid treatment resulted in clinical and laboratory amelioration, and the patient was discharged on day 15, after full restoration of his health. In our patient, all possible common causes of acute pancreatitis were excluded.

Conclusion It is a rational assumption to connect this case to the co-administration of simvastatin and acetyl-salicylate. However, the pathophysiological mechanism behind the onset of acute pancreatitis due to a statin, or, even more, due to its combination with salicylate, remains vague.

INTRODUCTION

Several causes for acute pancreatitis have been reported, among which drug intake seems to be responsible for 0.1-2 % [1, 2] of the cases. Drug-induced pancreatitis is a clinical entity which, although appearing from time to time, is generally difficult to establish due to the lack of patient follow up or the absence of specific statistical and experimental data concerning drug involvement in pancreatic inflammation. Numerous (more than 260) pharmaceutical agents have been associated with the pathogenesis of acute pancreatitis [3]. Such agents most commonly include azathioprine, thiazides, furosemide, valproic acid, H_2-receptor antagonists, tetracycline, sulfonamides and a number of others [4, 5]. There is ever growing evidence that statins of all kinds seem to be responsible for many such cases [2, 6, 7, 8, 9]. However, there is only one report on the possible harmful effect of the combination treatment with simvastatin and salicylate [10] on pancreatic tissue.

CASE REPORT

A 58-year-old Caucasian male patient presented to the Emergency Department of our hospital with epigastric pain and vomiting which had started almost 24 hours before. His abdomen was moderately distended, palpation

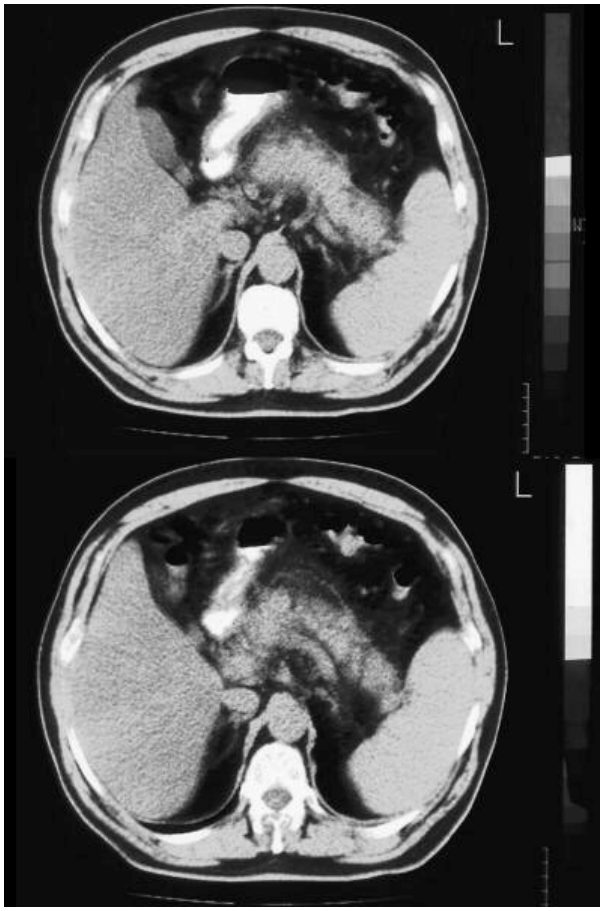

Figure 1. CT scan of the abdomen showed moderate pancreatic edema.

revealed epigastric tenderness, whereas bowel sounds were not heard during auscultation. The rest of the physical examination was normal. His past medical history revealed type 2 diabetes mellitus (treated with insulin) as well as coronary heart disease (he had undergone 4-vessel by-pass surgery 6 years before) and hypercholesterolemia. He had been receiving simvastatin 40 mg *od* for the past 2 months and acetyl-salicylate 100 mg *od* for 6 years. He had not been drinking alcoholic beverages. On admission, his vital signs were as follows: blood pressure 135/80 mmHg, heart rate 82 beats/min, temperature 37.2°C, respiration rate 15 min^{-1}. His laboratory findings were as follows: hematocrit 47.6% (reference range: 37-47%), white blood cells 16,800 μL^{-1} (reference range: 4,000-10,000 μL-1), glucose 180 mg/dL (reference range: 70-105 mg/dL), urea 47 mg/dL (reference range: 15-40 mg/dL), creatinine 0.9 mg/dL (reference range: 0.6-1.1 mg/dL), total bilirubin 1.4 mg/dL (reference range: 0.2-1.0 mg/dL), direct bilirubin 0.8 mg/dL (reference range: 0.1-0.5 mg/dL), aspartate aminotransferase 93 U/L (AST, reference range: 10-40 U/L), alanine aminotransferase 172 U/L (ALT, reference range: 10-35 U/L), Ca^{++} 8.8 mg/dL (reference range: 8.4-10.2 mg/dL), serum amylase 742 U/L (reference range: 0-125 U/L), urine amylase 8,153 U/L (reference range: 0-400 U/L), C-reactive protein 467 mg/L (CRP, reference range: 0-5 mg/L), lactate dehydrogenase 285 U/L (LDH, reference range: 80-240 U/L), total cholesterol 126 mg/dL (reference range: 0-200 mg/dL) and triglycerides 138 mg/dL (reference range: 0-200 mg/dL). Arterial oxygen partial pressure ($p0_2$) was 69 mmHg, whereas the base deficit was more than 4 mEq/L.

The Ranson's score in this patient was equal to three (age greater than 55 years, base deficit greater than 4 mEq/L and white blood cells greater than 16,000 μL^{-1}) and, according to the Atlanta classification system, the acute pancreatitis was clinically mild [11]. Upper digestive tract endoscopy revealed chronic ulcerative lesions and erosive gastroduodenitis, for which he was administered omeprazole i.v. during his hospitalization. Ultrasonography and upper abdominal computed tomography (CT) confirmed the absence of gallstones and revealed only moderate pancreatic edema, compatible with acute pancreatic inflammation (Figure 1). Magnetic retrograde cholangio-pancreatography (MRCP) excluded microlithiasis or gallbladder sludge and showed a normal anatomic morphology of the bile duct, pancreatic duct and ampulla region (Figure 2). Thorough serologic examinations for possible viral infection (coxsackievirus, echovirus, mumps, hepatitis A, B and C, herpes simplex viruses I and II, Epstein-Barr virus and cytomegalovirus) were all negative. Connective tissue disorders with vasculitis were excluded because the autoantibody screening was negative. Conservative and rich-in-fluid treatment resulted in clinical and laboratory amelioration and the patient was discharged on day 15, in apparently good

physical condition. Acetyl-salicylate and simvastatin were replaced by clopidogrel and rosuvastatin, respectively. He was re-examined 2 months later and was found to be in excellent physical condition.

DISCUSSION

The monitoring of adverse drug reactions seems to be acquiring more importance among hospital practitioners, the pharmaceutical industry and responsible authorities worldwide [4]. The information reported concerning drug-induced illness and, especially, drug-induced pancreatitis has increased lately. However, the lack of sophisticated epidemiological studies on the topic renders it difficult to assess the real incidence of adverse drug reactions [1]. Moreover, the degree to which certain drugs associate with certain adverse reactions is often unclear and the definitive causative relationship between the drug and the adverse event is proven in only a small number of cases [5].

Various models and algorithmic processes for pharmacovigilance have been proposed, and report detection and evaluation through the huge amount of data now available on different databases. A recent publication reports on the over-estimation of drug-induced pancreatitis cases using data mining algorithms due to various confounding factors and reporting biases [4]. Arguments will certainly appear in abundance in the near future as to the most accurate and comprehensive strategy for adverse drug reaction monitoring evaluated by means of statistical analysis.

Drug-induced pancreatitis is among the clinical entities where a vast amount of information is reported in medical literature. In a large Danish retrospective study, based on spontaneous reports on drug-induced pancreatitis from 1968 to 1999, a definite relationship was stated for mesalazine, azathioprine and simvastatin on the basis of rechallenge [1]. An additional 30 drugs were considered to be causative factors in acute pancreatitis; they include 5-acetyl-salycilic acid agents, angiotensin-converting enzyme inhibitors, estrogen preparations, didanosine, valproate, codeine, antiviral agents used in acquired immunodeficiency syndrome therapy, various lipid-reducing agents, interferon, paracetamol, griseofulvin, ticlopine, allopurinol, lithium and the measles/mumps/rubella vaccine [1]. However, uncertainty still exists, even in well-established cases, with re-introduction of the drug and recurrence of symptoms [4, 12].

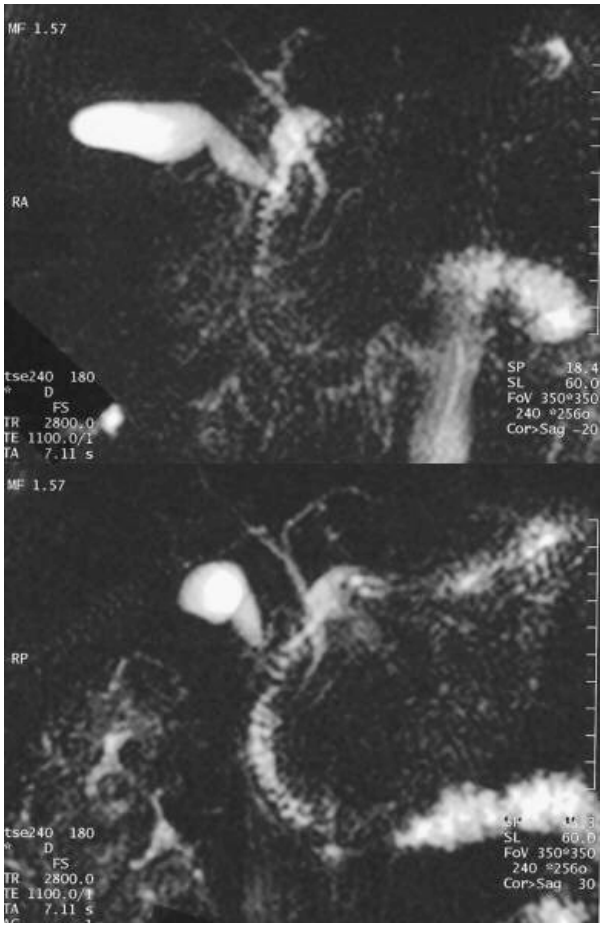

Figure 2. MRCP excluded microlithiasis or gallbladder sludge and showed a normal bile duct, pancreatic duct and ampulla region anatomic morphology.

Reports of statin-induced acute pancreatitis indicate fluvastatin, atorvastatin, lovastatin, simvastatin and pravastatin as possible causative agents [2, 5, 6, 7, 8, 9]. There is also evidence of a possible etiological connection between salicylate and pancreatitis [10]. Our patient had been receiving acetyl-salicylate for 6 years, after 4-vessel by-pass surgery for diagnosed coronary heart disease. Later on, and while no recurrence of the disease took

place, the patient started simvastatin for cholesterol control at 40 mg *od*. In our case, the patient had been receiving the drug for 2 months. Nevertheless, the short period of time during which the patient had been receiving simvastatin cannot definitely link the drug to the onset of the acute pancreatic inflammation. According to Anagnostopoulos *et al.* who report 4 cases of simvastatin-induced pancreatitis, the length of statin treatment until the onset of pancreatitis varies considerably [2]. In two cases, the patient had been receiving the drug for over 6 months, in one case for 3 months and in another for just 12 hours [2]. Furthermore, the severity of acute pancreatitis due to simvastatin therapy may increase after rechallenge [7].

Having excluded all the conventional causes of acute pancreatitis (alcoholic ingestion, gallstones, hypertriglyceridemia, hypercalcemia, connective tissue diseases and infections), it is a rational assumption to connect the onset of acute pancreatitis in our patient with the co-administration of simvastatin and acetyl-salicylate. To our knowledge, there is only one report to date in the international literature, which makes the same assumption and implies the possible harmful effect of the aforementioned combination on pancreatic tissue [10]. The pathophysiological mechanism behind the onset of acute pancreatitis due to a statin, or, even more, due to its combination with salicylate, remains unclear.

It should be mentioned though, that the co-administration of acetyl-salicylate with a statin is a well-known and widely used standard of therapy not only for patients with a previous history of coronary heart disease, but also for healthy individuals with risk factors predisposing to coronary heart disease, such as hypercholesterolemia. Thus, the ever-growing number of patients to be treated with this combination could raise the number of reported cases of acute pancreatitis as a side effect. The documented evidence for drug-associated pancreatitis has recently increased [1, 4]. The clinician should maintain a high level of suspicion for this adverse, sometimes fatal, effect and, if the diagnosis of acute pancreatitis has been established, the suspected drug(s) should be stopped and replaced.

Received February 28th, 2005 - Accepted March 30th, 2005

Keywords Anticholesteremic Agents; Pancreatitis; Salicylates; Simvastatin

Correspondence
Stelios Kokkoris
30 Ermou st
Korydallos 18122
Greece
Phone: +30-694.618.2837; +30-210.496.6459
Fax: +30-210.459.2563
E-mail: skokkoris2003@yahoo.gr

References

1. Andersen V, Sonne J, Andersen M. Spontaneous reports on drug-induced pancreatitis in Denmark from 1968 to 1999. Eur J Clin Pharmacol 2001; 57:517-21. [PMID 11699619]

2. Anagnostopoulos GK, Tsiakos S, Margantinis G, Kostopoulos P, Arvanitidis D. Acute pancreatitis due to pravastatin therapy. JOP. J Pancreas (Online) 2003; 4:129-32. [PMID 12743419]

3. Battillocchi B, Diana M, Dandolo R, Stefanini S, D'Amore L, Negro P. Drug-induced acute pancreatitis: a personal contribution. Chir Ital 2002; 54:605-12. [PMID 12469456]

4. Hauben M, Reich L. Drug-induced pancreatitis: lessons in data mining. Br J Clin Pharmacol 2004; 58:560-2. [PMID 15521907]

5. Makins R, Ballinger A. Gastrointestinal side effects of drugs. Expert Opin Drug Saf 2003; 2:421-9. [PMID 12904098]

6. Tysk C, Al-Eryani AY, Shawabkeh AA. Acute pancreatitis induced by fluvastatin therapy. J Clin Gastroenterol 2002; 35:406-8. [PMID 12394230]

7. Pezzilli R, Ceciliato R, Corinaldesi R, Barakat B. Acute pancreatitis due to simvastatin therapy: increased severity after rechallenge. Dig Liver Dis 2004; 36:639-40. [PMID 15460851]

8. McDonald KB, Garber BG, Perreault MM. Pancreatitis associated with simvastatin plus fenofibrate. Ann Pharmacother 2002; 36:275-9. [PMID 11847949]

9. Belaiche G, Ley G, Slama JL. Acute pancreatitis associated with atorvastatin therapy. Gastroenterol Clin Biol 2000; 24:471-2. [PMID 10844297]

10. Miltiadous G, Anthopoulou A, Elisaf M. Acute pancreatitis possibly associated with combined salicylate and atorvastatin therapy. JOP. J Pancreas (Online) 2003; 4:20-1. [PMID 12555012]

11. 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]

12. Eland IA, van Puijenbroek EP, Sturkenboom MJ, Wilson JH, Stricker BH. Drug-associated pancreatitis: twenty-one years of spontaneous reporting in The Netherlands. Am J Gastrenterol 1999; 94: 2417-22. [PMID 10484002]