Caso Clínico / Clinical Case

ACUTE PANCREATITIS DUE TO SIMVASTATIN

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Resumo

A pancreatite causada por fármacos ocorre numa incidência de 1,4-2% dos casos de pancreatite aguda, e deve ser equacionada sempre que as causas habituais de pancreatite aguda forem excluídas. Na maioria dos casos a gravidade da pancreatite por fármacos é pequena. A pancreatite aguda induzida por estatinas tem sido reportada pouco frequentemente mas, face à existência de referências de casos de pancreatite aguda causadas pela maioria das estatinas em uso, parece razoável admitir que possa estar implicado um efeito de classe das estatinas no mecanismo fisiopatológico. O mecanismo é desconhecido, mas o uso concomitante doutros fármacos parece ser importante em alguns casos. Os autores apresentam um caso de uma doente com pancreatite relacionada com sinvastatina, aconselhando que em geral, todos os doentes com pancreatite aguda causada por estatinas deveriam abdicar definitivamente da utilização destes fármacos. Foi feita uma revisão acerca dos vários tipos de reacções adversas possíveis a fármacos, salientando-se a importância da disciplina da farmacovigilância e da documentação adequada de cada reacção, de molde a tentar-se evitar a tempo lesões causadas por fármacos. A decisão médica de utilização de qualquer fármaco deverá ser baseada na relação entre risco de prescrição de um fármaco e benefícios potenciais nos doentes, considerados individualmente.

Summary

The incidence of drug-induced pancreatitis represents 1.4-2% of all cases of acute pancreatitis, and should be considered whenever the usual causes of acute pancreatitis are excluded. The severity of drug-induced pancreatitis is low in the majority of cases. Statin induced pancreatitis has been reported rarely, but as there have been reports of cases of acute pancreatitis caused by most of the statins in medical use, the possibility of a statin class effect being implicated in the physiopathological mechanism seems reasonable. The mechanism is unknown, but the concomitant use of another drug appears to be important in some cases. The authors present a case of a probable/likely acute pancreatitis due to simvastatin, and recommend that in general, all patients with statin induced acute pancreatitis should discontinue the use of statins permanently. A review of the several types of adverse drug reactions is presented, together with comments on the importance of pharmacovigilance and accurate documentation of these reactions, so that injury can be prevented in time. The medical decision to use a particular drug must consider the risks of prescribing the drug against the potential benefits for each individual patients.

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INTRODUCTION

There are a great number of potential etiologies for acute pancreatitis, one of which is drug-induced pancreatitis. Drug-induced pancreatitis occurs in the general population at a rate of around 1.4-2% of all cases of acute pancreatitis (1). In a case of acute pancreatitis for which no other reasonable aetiology is present, drug aetiology should be considered as the possible cause. Published reports have identified more than 50 drugs that definitely or possibly may be held responsible for inducing acute pancreatitis (2). The most commonly reported causal drugs in adult patients are azathioprine, mesalazine/sulfasalazine, didanosine (ddI), oestrogens, furosemide, hydrochlorothiazide, rifampicin, pentamidine, metronidazole, sulphonamides, tetracyclines and sulindac. In children the most frequently responsible drugs are L-asparaginase, valproic acid and corticosteroids (1,3).

A higher incidence rate has been found in patients with inflammatory bowel disease (4) and AIDS (5).

The severity of drug-induced pancreatitis is generally low, although some reports refer to high incidence of fatal outcome at least from azathioprine (after renal transplantation) (6), ddI (7), frusemide (8) and hydrochlorothiazide (9).

Most studies on drug-induced pancreatitis are case reports that are meant to serve as a warning or signpost for other clinicians. That is the case with statins, which have been recently cited as culprit in isolated cases of acute pancreatitis. We present a case of acute pancreatitis in which simvastatin was considered responsible after exclusion of other known causes of acute pancreatitis.

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CLINICAL REPORT

A 74 year old Caucasian woman was admitted on April 05 with a diagnosis of acute pancreatitis. She denied habitual or occasional alcohol ingestion and had no previous history of biliary lithiasis or abdominal trauma and no family history of pancreatitis. She had been diagnosed with hypercholesterolemia: 294 mg/dL (N 150-225) one year prior to admission, for which simvastatin was prescribed and which the patient had been on ever since. She did not report any other disease and also denied taking any other medication.

Just one day before admission the patient began to complain of increasingly intense flank pain with band irradiation to the epigastrum along with anorexia, nausea and vomiting. She denied other symptoms. She was in distress, but eupneic and hydrated. Blood pressure was 125/75 mmHg, heart rate 63/min, temperature 37.2º C. Heart and lung sounds were normal on auscultation. Pain was elicited in the epigastrum, but there was no peritoneal reaction. Ascites was not clinically evident and there were no cutaneous signs or legs oedema.

Blood tests revealed: leucocytosis (12.400/mm^3) with neutrophilia (90.9%); hemoglobin 12 g/dL; platelets 210.000/mm^3; calcium 9.0 mg/dL (N 8.4-10.2); AST 37 UI /L (N 17-50) and ALT 18 UI/L (21-72); glycemia 203 mg/dL (75-110) (unknown and not confirmed diabetes); cholesterol 166 mg/dL (N < 200); triglycerides 58 mg/dL (N 40-200) amylase > 1300 UI/L (N 30-110); lipase 1848 UI/L (N 23-300); LDH 425 UI/L (N 313-618); albumin 4.3 g/dL; arterial blood gasometry: pH 7.435, pO_2 83.2 mm Hg; pCO_2 33.6 mm Hg. Viral serology for HAV, HBV; HCV, CMV and Herpes virus were all negative.

X-Ray of the thorax and electrocardiogram were normal.

Abdominal ultrasonound and CT scan revealed: an oedematous pancreas (Figure 1) with peripancreatic fluid accumulation in the area of the body and tail of the pancreas with extension to the left perirenal area, which one week later showed peripheral delimitation by radiographic contrast (Figure 2), densification of the mesentery and of the lateroconal and perirenal fasciae. There were no areas of pancreatic necrosis. There was no pleural fluid and no ascites. Biliary and liver pathology were not demonstrated.

The patient had three Ranson/Imrie criteria of clinical severity (age > 55 years, leucocytes > 16000/mm^3, glycemia > 200 mg/dL) and a 3 point severity score of CT scan abnormalities (one peripancreatic fluid accumulation). It was considered that, based on the aforementioned criteria, the patient could probably expect have a relatively favorable clinical course.

The clinical picture improved after a few days of fasting and intravenous fluids. Meanwhile prophylactic omeprazole and ciprofloxacin were administered. Diabetes was not confirmed. Normalisation of all other blood tests was verified only 3 weeks after admission upon discharge from the hospital, when another CT scan of the abdomen revealed a reduction in the volume of the peripancreatic fluid accumulation (Figure 3). The patient was advised not to restart statins again. We only prescribed a low fat diet and decided not to prescribe any drug to lower cholesterol, because her serum cholesterol level was then normal, and there was not any other obvious cardiovascular risk to justify the use of any drug. Three months after the episode the patient was feeling well, serum levels of cholesterol, amylase and lipase were normal. Abdominal CT scan at that time showed further reduction of the volume of the peripancreatic fluid accumulation (Figure 4).

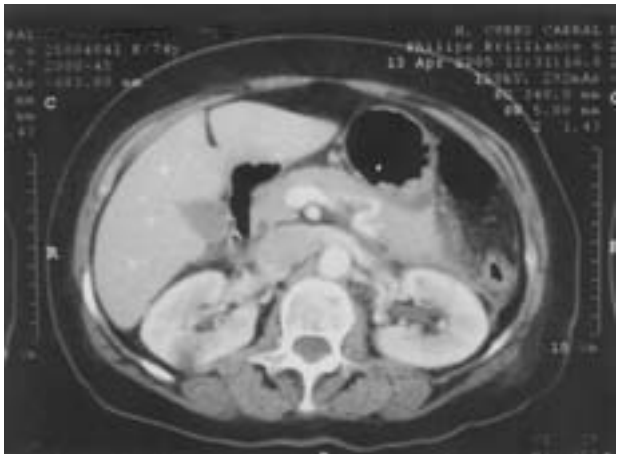

Figure 1 - CT SCAN 05.04.13 - Oedematous pancreas and peripancreatic fluid collection around body and tail of the pancreas and extending to the left perirenal area.

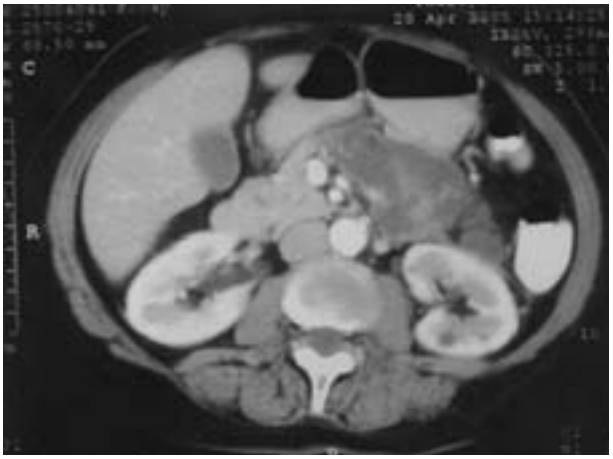

Figure 2 - CT SCAN 05.04.20 - Peripheral delimitation of fluid collection by radiographic contrast.

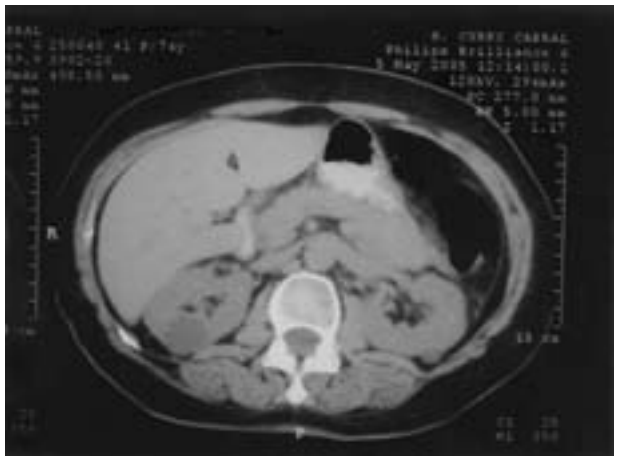

Figure 3 - CT SCAN 05. 05.05 - Lower volume of peripancreatic fluid collection 7 weeks after admission.

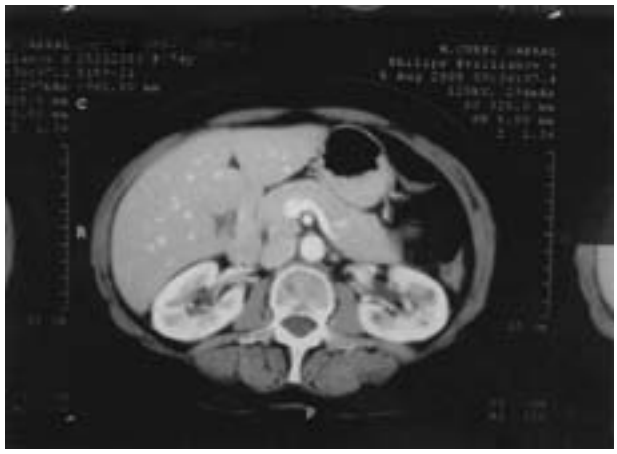

Figure 4 - CT SCAN 05.08.05 - Further reduction of the volume of the peripancreatic collection, 4 months after the first symptoms.

DISCUSSION

Statins are generally well tolerated and statin induced pancreatitis is very rare, with only a few cases having been reported in the literature. The statin induced pancreatitis may be a class effect, as there are published case reports of pancreatitis apparently due to several of the statins currently in use: atorvastatin (10), simvastatin (11), rosuvastatin (12), lovastatin (13), fluvastatin (14) and pravastatin (15). In some patients more than one statin was related to a second episode of drug-related pancreatitis (12). The exact induction mechanism of pancreatitis due to statins is uncertain. Some authors have proposed drug interaction as a trigger mechanism. Wong P. (16) described a patient who had been taking lovastatin for 7 years and who after the administration of erythromycin for a dental procedure, he developed multiple organ toxicity including pancreatitis. Other authors have reported cases of pancreatitis occurring in patients taking statins in combination with salycilates (17), fenofibrate (18), or gemfibrozil (19).

The reported duration of statin treatment until the onset of pancreatitis has varied considerably in the cases reported up until now (15). Some patients had been using the statin for years before the onset of pancreatitis (16,17), but in two cases (10) this adverse drug reaction developed on the first day of therapy. Only in 3 cases (13,14,20) had the statin been reintroduced resulting in recurrence of pancreatitis. The clinical course of statin induced pancreatitis was mild for most of the reported cases. However, in two cases rhabdomyolysis complicated the course of acute pancreatitis and, one of these patients developed renal failure (16). In one case, pancreatitis induced by the combination of lovastatin and gemfibrozil was complicated by pseudocyst formation (19). Only in the case described by McDonald (18), was the co-administration of simvastatin and fenofibrate associated with severe pancreatitis having a fatal outcome.

Adverse drug reactions cause substantial morbidity and mortality and yet they remain underrated and misunderstood. By definition an adverse drug reaction is a response to a drug which is noxius and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or treatment of disease or for the modification of physiological functions (21). Assessing causal connections between drugs and disease is important for safe practice of medicine. The pharmacovigilance of these aspects requires tools for describing adverse drug reactions, using the following criteria: time relationship between the drug use and the adverse reaction, the pathophysiology of the adverse reaction, response to dechallenge (discontinuation of therapy with the drug or dose reduction), and response to rechallenge (drug readministration). These criteria can be organised to gauge the causal link between a drug and an adverse reaction in terms of 4 discrete levels of certainty (certain, probable/likely, possible, and unlikely) (22,23,24,25). The difference between the certain and the probable/likely grades is that the latter grade does not include a rechallenge procedure.

As the association between the statins and pancreatitis is based on case reports, it is not yet known whether different statins carry different risks (17), or if the reintroduction of another statin or the same type of statin previously associated with another drug, will cause another episode of pancreatitis. Meanwhile it is advisable that clinicians do not reintroduce any statin, unless absolutely necessary (17). We think that it is preferable to recommend a constant low fat diet and, if necessary to use another type of drug to lower cholesterol or tryglicerides.

The lack of rechallenge evidence, consistent statistical data or evidence from experimental studies on a possible mechanism, makes it impossible to come to definitive conclusions about most of the reported cases of statin induced pancreatitis. This is why many of these reports are reported as probable/likely cases of statin induced pancreatitis and not as certain cases of statin induced pancreatitis. The definition of probable/likely cases of drug-induced adverse reactions means a clinical event, including an abnormal laboratory test result, that occurs within a reasonable time frame of the administration of the drug, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition (25).

A consideration of pathophysiological pathways and causal associations can help the physician to identify adverse drug reactions in complex clinical scenarios. The basic unit of an adverse drug reaction is the sequence of pathophysiologically related events originating from one pharmacologic effect of the drug (25). In our case, all the other usual causes of acute pancreatitis were ruled out. There was no history of alcohol use and no family history of pancreatitis. There was no evidence of gallstone disease and serum values of calcium and of cholesterol and triglycerides were normal at the time of the patient's admission to our Unit. Other causes were also excluded by the clinical story and physical examination.

The cause of acute pancreatitis is identified early in 70% to 90% of patients, after an initial evaluation consisting of history, physical examination, focused laboratory testing, and routine radiological investigation (abdominal ultrasonography and CT scan). Patients in whom this initial evaluation does not reveal an underlying aetiology are classified as having "idiopathic" acute pancreatitis. In these patients we can consider undertaking a more extensive evaluation for the diagnosis of certain entities such as occult microlithiasis (bile crystals), sphincter of Oddi dysfunction, pancreas divisum and other congenital abnormalities, pancreatic and ampullary neoplasia, genetic causes and autoimmune pancreatitis (26). No data in our patient pointed to these possibilities. We considered it more probable and safer to follow the diagnostic hypothesis of drug-induced pancreatitis, and this is why we advised the patient not to restart statin therapy. After 3 abdominal CT scans a diagnosis of pancreatic or ampullary carcinoma was highly improbable. Also with the occurrence of only one isolated and fairly mild attack of acute pancreatitis, a conservative approach to diagnosis and therapy appeared to be the logical approach, rather than for example to proceed with an empiric cholecystectomy for a presumed and unproven occult microlithiasis (26).

Despite the low incidence of drug induced pancreatitis, all patients with acute pancreatitis of unknown aetiology should be carefully questioned about drugs that may be responsible for inducing the disease. As the use of statins increases, physicians should consider the diagnosis of drug induced pancreatitis in patients taking these medications who then develop abdominal pain not explained by any other process. If statin induced pancreatitis is suspected, probably the drug should probably be permanently discontinued. In our patient, the aetiology of acute pancreatitis was attributed to simvastatin, which had been prescribed for hyper-cholesterolemia, and which the patient has been taking for one year without any laboratory data monitoring. We considered it unadvisable for the patient to restart statin therapy. Three months after her episode of acute pancreatitis, the patient has recovered well and her cholesterol levels remain normal.

The discipline of pharmacovigilance is very important. Physicians should be required to report accurate data regarding certain and probable/likely adverse drug reactions, including dose information. Not doing this is a major opportunity missed for injury prevention. Adverse drug reactions at established usual doses are eight times more frequent than idiosyncratic reactions. Also important is to mention the severity of the event, the probable causal association between the drug use and the event, for how long the patient had been taking the drug and whether the patient is taking any other drug (25). Accurate documentation assists in future determinations of whether the risks of prescribing of a specific drug or drug class outweight the drug's potential benefits for a particular patient.

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