

Pancreatitis due to codeine

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ABSTRACT

Pancreatitis is a rare adverse effect of codeine. We report the case of a 42-year-old man who suffered from epigastric pain 1 hour after taking a tablet containing amoxicillin plus clavulanic acid (500/125 mg) and another tablet containing acetaminophen plus codeine (500/30 mg) for a respiratory infection. He was admitted to the emergency room and was treated with metamizol and pantoprazole. A few minutes after receiving intravenous doses of both drugs he developed a maculopapular and itching eruption with facial angioedema. Laboratory tests showed high levels of serum amylase, GOT, GPT and total bilirubin. Serological tests for several viruses showed no evidence of recent infection. Ultrasonography was negative for biliary lithiasis and showed only cholecystectomy performed in 2000. The patient was sent to our department where skin prick and oral challenge tests were performed with negative results. For ethical reasons, oral challenge with codeine was not carried out. We believe that our patient had codeine-induced pancreatitis. The most likely underlying pathophysiological mechanism was probably codeine-induced spasm of the sphincter of Oddi combined with sphincter of Oddi dysfunction related to a previous cholecystectomy. Allergy departments should be aware of possible non-immunological adverse reactions, which can have serious consequences.

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RESUMEN

La pancreatitis es un efecto secundario raramente producido por la codeína. Presentamos el caso de un paciente de 42 años que sufrió dolor epigástrico, una hora después de la ingesta de un comprimido de amoxicilina-clavulánico (500/125 mg) y otro de paracetamol-codeína (500/30 mg) por un cuadro infeccioso de vías altas. Acude al servicio de urgencias donde es tratado con metamizol y pantoprazol por vía intravenosa, presentando unos minutos después de su infusión, una erupción máculo-papulosa muy pruriginosa acompañada de angioedema facial. Las pruebas de laboratorio mostraron niveles elevados de amilasa sérica, GOT, GPT y bilirrubina total. Las pruebas serológicas de distintos virus no mostraron evidencia de infección reciente. El estudio ecográfico fue negativo para litiasis biliar y solamente mostró la existencia de una colecistectomía realizada en el año 2000. Fue derivado a nuestra sección donde se le hicieron pruebas cutáneas y de provocación con resultado negativo con los fármacos implicados, excepto con codeína por razones éticas. Pensamos que la codeína fue la responsable del cuadro de pancreatitis sufrido por el paciente y el probable mecanismo patofisiológico subyacente habría sido el espasmo del esfínter de Oddi inducido por la codeína, combinado con una disfunción relacionada con la colecistectomía previa. Por tanto, los servicios de Alergia deben considerar la posible existencia de reacciones adversas de etiología no inmunológica, que pueden originar patologías graves a los pacientes.

Palabras clave: Pancreatitis aguda. Codeína. Espasmo del esfínter de Oddi. Pancreatitis inducidas por fármacos.

INTRODUCTION

Many drugs have been reported to cause acute pancreatitis (azathioprine, thiazides, sulfonamides, furosemide, estrogens and tetracycline)¹. Pancreatitis is a rare side effect induced by codeine, considering the widespread consumption of this drug, but there have been a handful of published cases of pancreatitis due to treatment with codeine²⁻⁶.

CLINICAL CASE

We report the case of a 42-year-old man who was admitted in emergency room in February of 2004 as he complained of epigastric pain and vomiting without fever. He had taken an amoxicillin plus clavulanic acid (500/125 mg) pill and an acetaminophen plus codeine (500/30 mg) tablet for an upper respiratory tract infection^{2,5,6} an hour ago. Physical examination was normal. He was treated with metamizol and pantoprazol. A few minutes after he received intravenous doses of both drugs, he suffered from a maculo-papular and itching eruption with facial angioedema.

Laboratory tests were as follows: full blood count, serum creatinine and urea and electrolytes were normal. Serum amylase 562 U/l (normal < 120 U/l), GOT 81 U/l (normal < 18 U/l), GPT 32 U/l (normal < 22 U/l), G-GT 142 U/l (normal < 26 U/l), alkaline fosfatase 76 U/l (normal < 170 U/l) and total bilirubine 1,8 mg/dl (normal < 1 mg/dl). Ecographic study made at admission was normal and only showed cholecystectomy that had been performed in 2000 due to severe biliar pancreatitis. Endoscopic study was also normal. Serological tests for B-hepatic, Echo, Parotiditis and Cox-sackie viruses showed no evidence of recent infection⁵. There was no history of alcohol consumption. All the parameters were normalized^{2,5} while he stayed at hospital. A diagnosis of pancreatitis and an adverse reaction by metamizol and pantoprazol were made.

He was sent to our department for drug study. Study with the involved drugs was made and previously written consent was obtained from the patient before conducting provocation tests.

Quantification of specific-IgE antibodies to beta-lactams (benzylpenicilloyl –BPO–, amoxicillin and ampicillin) by RAST was negative. Skin prick and intradermal tests were performed with PPL (penicilloyl-polylysine), MDM (minor determinant mixture), penicillin G, amoxicillin, ampicillin, cefoxitin, amoxicillin plus clavulanic acid and metamizol. All of them were negative.

Oral challenge tests were carried out with amoxicillin plus clavulanic acid, pantoprazol, acetaminophen and metamizol without adverse reaction.

Oral challenge test was not performed with codeine due to ethical and medical reasons. A new exposure to codeine would have been able to provoke serious complications and even a situation beyond medical control. Moreover this drug was not essential for the patient because there were many alternative drugs⁷.

DISCUSSION

Drug-induced pancreatitis is considered to be rare. However the exclusion of other possible etiological factors combined with the coincidence in time with the intake of codeine makes this drug suspect as causative agent. The likely underlying pathophysiological mechanism is codeine-induced spasm of the sphincter of Oddi combined with disfunction of the same sphincter related to a previous cholecystectomy. The former (spasm of the sphincter of Oddi) has been demonstrated by subcutaneous injection with therapeutic doses of morphine and codeine⁵. Constriction occurs within five minutes and lasts for at least two hours. Despite these findings, there are no recorded cases of opiate induced sphincter of Oddi spasm resulting in pancreatitis. On the other hand, a pancreatitis has been reported to occur in association with secondary sphincter of Oddi disfunction, which is related to biliary calculi in more than 90 % of cases⁴. Patients who have had a cholecystectomy often suffer (around 60 %) from fibrosis or smooth muscle hyperplasia, which eventually may lead to stenosis, increasing sphincter of Oddi pressure or spasm. It is possible that codeine ingestion in cholecystectomized patients could also result in a rise in biliary and/or pancreatic sphincter pressure, either by exacerbating an already pre-existing sphincter of Oddi disease or as consequence of reduced storage capacity of the biliary tract in these subjects. Probably in cases of transient distal common bile duct obstruction, the gallbladder, that acts as a reservoir for bile, is able to accommodate the stagnant bile and, thus, will temporarily decompress the biliary tract. Tanaka et al evaluated patients who had intrabiliary pressure measured before and after cholecystectomy, and demonstrated that intrabiliary pressure increased if the sphincter of Oddi pressure was risen using intravenous morphine, only once the gallbladder had been removed. It is possible that both mechanisms (exacerbated spasm in the sphincter of Oddi and reduced bile storage capacity) combined their effects after codeine ingestion to initiate an episode of acute pancreatitis.

This is the case of our patient, as he had been performed cholecystectomy four years ago and we think that codeine ingestion led to acute pancreatitis in him. So, previous cholecystectomy seems to predispose to codeine induced pancreatitis⁴⁻⁶.

We conclude that codeine is a widely used drug, both in over the counter and prescribed preparations, so that acute pancreatitis should be considered as a possible side effect of this compound, especially for patients who have had a cholecystectomy⁵.

Therefore, allergy departments should be aware of other possible sources of adverse reactions different from the traditional immunological ones usually considered in allergy.

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