Case Report

Prior cholecystectomy predisposes to acute pancreatitis in codeine-prescribed patients

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ABSTRACT

In this paper, we report a case of drug-induced pancreatitis just after taking a pain pill including a low-dose combination of acetaminophen and codeine. Codeine-induced pancreatitis has been rarely reported, however, well-established. The proposed mechanism for codeine-induced pancreatitis is by increasing Oddi sphincter pressure. However, the clinically important point is that the codeine-induced pancreatitis is seen almost only in the cholecystectomized patients due to lacking of its reservoir capacity. Codeine is commonly used alone or in combination in pain medicine. Therefore, it is fairly important to question whether a patient underwent cholecystectomy when a physician decides to prescribe codeine-included preparations.

Key Words: Cholecystectomy, codeine, pancreatitis

INTRODUCTION

Acute pancreatitis is an inflammatory process of the pancreas which is characterized clinically by abdominal pain and biochemically elevated pancreatic enzymes in the serum. The pathogenesis of acute pancreatitis is not clearly determined; however, several factors have been identified to induce pancreatitis. Gallstones and alcohol use are the most common etiologic factors. The other most common etiology is drugs. Great number of drugs have been reported to cause acute pancreatitis, and classified as class 1 to 4 based on the number of cases reported, consistent latency period and reaction with challenge. Several drugs that are associated with drug-induced pancreatitis act with various mechanisms.[1-4] In this case we report a case of codeine-induced pancreatitis for two reasons. First, codeine-induced pancreatitis is well-established; however, there have been only few cases reported in the literature. Second, however, the most important reason is to underline the possible association between codeine use and cholecystectomy.

CASE REPORT

A 68-year-old man admitted to our emergency department with complaints of sudden onset of epigastric pain and vomiting. He had a history of coronary by-pass 6 years ago, but he had no history of myocardial infarct. His regular medications were atorvastatin 10 mg/day, acetylsalicylic acid 100 mg/day and ramipril 10 mg/day. Since he had a history of coronary artery disease, he first evaluated for acute coronary syndrome although he had not typical cardiac symptoms. Repeated electrocardiograms and cardiac enzymes were normal. On biochemical work-up amylase [167 U/L (27-131)], lipase [234 U/L (8-78)], liver enzymes [AST 146 U/L (5-34), ALT 250 U/L (0-55), GGT 324 U/L (12-64)], total bilirubin [1.80 mg/dl (0.2-1.0)], and direct bilirubin [1.1 mg/dl (0-0.2)] were found moderately elevated on admission. All other labs were normal. He underwent cholecystectomy 35 years ago and he had no symptoms since then. On a detailed anamnesis he was asked to use any other drugs. He stated that, because he had non-suppurative dry cough and mild muscle ache due to common cold, his family physician prescribed him a pain-killer which includes (300 mg acetaminophen and 30 mg codeine) with a third time daily dose. He stated that almost 60 minutes after taking the drug he experienced a blunt epigastric pain radiating to his back. The severity of the pain increased with time. Abdominal ultrasonography was normal with no dilation of intra-hepatic and extra-hepatic bile ducts and with no sign of bile stones. An abdominal tomography showed mild edema and inflammation of pancreas. Oral feeding was stopped and the patient was supportively managed for pancreatitis. His pain began to decrease after 24 hour
and completely resolved after 48 hours. Amylase and lipase levels returned normal after 48 hours and all other labs normalized within 5 days.

**DISCUSSION**

Codeine is known to cause acute pancreatitis. However, codeine-induced pancreatitis is extremely rare. Only few reports have been published to date. The first report was published by Hastier *et al.* In this report pancreatitis episode developed just after 1.5 hours after taking a pain killer including 1 g acetaminophen and 60 mg codeine. Second case was reported by Renkes *et al.*, with virtually the same presentation and with the same doses. In the year of 2000, Hastier *et al.* reported a 4-patient series of codeine-induced pancreatitis. More recently Torres *et al.* reported a codein-induced pancreatitis 1 hour after taking a combination of 500 mg acetaminophen and 30 mg codeine pill.

According to the drug-induced pancreatitis classification potential drugs falls into four categories (I-IV). Class I and II drugs have more potential to cause acute pancreatitis. Codeine is included in class I. However, the evidence for codeine to fall into class I drug category is only based on the few published reports that we mentioned above.

Several mechanisms of drug-induced pancreatitis have been proposed for different drugs. The proposed mechanism for codeine is Oddi sphincter spasm. Codeine is one of the several drugs that increase Oddi sphincter pressure. This effect was demonstrated by therapeutic doses of morphin and codeine. The effect started in 5 minutes and continued at least for two hours. However, there is no clear evidence of morphine-induced pancreatitis.

The most important point that we want to emphasize is that nearly all the reported cases of codeine-induced pancreatitis were cholecystectomized patients. Similarly, as we mentioned in the case report our patient underwent cholecystectomy 35 years ago. The possible explanation about why codestocystectomy predisposes to acute pancreatitis is the lacking of the reservoir capacity of gallbladder, hence increasing intraductal pressure. The other explanation is the alteration of Oddi sphincter motility because of damaging the nerves that pass between the gallbladder and sphincter of Oddi after cholecystectomy.

Two important clinical interpretations can be inferred from this case and the previous reports. The first one is all physicians should be cautious giving medications that are known to cause Oddi sphincter spasm to a cholecystectomized patient. This point is particularly important in pain medicine since codeine and codeine-included agents are commonly prescribed for pain relieving. Therefore, status of cholecystectomy should be questioned in pain medication. Secondly, we believe that this issue should be questioned when a morphine is decided to be given to a patient. Even if we have not clear evidence that morphine induce acute pancreatitis, effect of morphine on human sphincter of Oddi was clearly shown.

In summary, codeine-induced pancreatitis is not common but is well-established. The clinically important point is that cholecystectomy predispose to acute pancreatitis when a patient is given a drug that increase Oddi sphincter spasm.

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