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A case report on sulfasalazine induced acute pancreatitis

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Abstract

An 18 years young male patient came to the emergency department with chief complaints of epigastric pain and 3-4 episodes of vomiting since 3 days. On the advice of Doctor, Serum amylase test was done and found to be elevated 7 times than the normal value (512U/L) and USS Abdomen reveals Acute Pancreatitis and was advised for hospitalization. After hospitalization, the patient was on nothing by mouth and was treated with Injection. Cefotaxime 1g twice daily, Injection. Pantoprazole 40mg once daily, Injection. Tramadol 50mg given twice daily, IV fluids.

A thorough history taking revealed that patient was suffering with Juvenile Rheumatoid Arthritis since 6 months and was using Sulfasalazine 1000mg once daily, Etoricoxib 90mg once daily and Rabeprazole 20mg before breakfast. There was no history of abdominal trauma, family history of pancreatits, alcohol or tobacco abuse.

On admission Complete blood picture, Random blood sugar, Renal function tests, Liver function tests, Serum electrolytes, Complete urine examination, CT scan of abdomen, Ultra sound scan of abdomen, serum amylase and lipase levels and HDL levels were advised. The CT scan and ultra sound scan of abdomen reveals acute pancreatitis with minimal ascites. No gall stones or any structural abnormalities seen. Serum amylase levels were 499.0 U/L (0-80 U/L), lipase levels were 116.1U/L (0-60 U/L).The serum calcium and Triglyceride levels were normal.

Based on the objective and subjective evidences the final diagnosis was made to be Sulfasalazine induced acute pancreatitis. Therefore, a cause-and-effect relationship between Sulfasalazine and episode of pancreatitis was highly suggested.

Keywords

acute pancreatitis; sulfasalazine; juvenile rheumatoid arthritis; drug induced pancreatitis

Introduction

Acute pancreatitis is an inflammatory process of the pancreas with varying involvement of other regional tissues or remote organ systems. It is characterized by abdominal pain, nausea, and elevated pancreatic enzymes (serum lipase and/or amylase) greater than three times the upper limit of normal. About 80% of cases of acute pancreatitis are caused by gallstone disease or excessive alcohol intake.

However, up to 2% of acute pancreatitis cases may be caused by drugs, with a higher incidence in specific populations, like females, the elderly, pediatrics, HIV-positive patients and those with inflammatory bowel disease [2].

There have been many published reports of potential cases of drug-induced pancreatitis (DIP). The medical residents in Boston used the mnemonic FATSHEEP to remember the causes of DIP—Furosemide, Azathioprine/Asparaginase, Thiazides/Tetracycline, Statins/Sulfonamides, Hydrochlorothiazide, Estrogens, Ethanol and Pentamidine [5].

One review considers number of reported cases and whether or not a there is documentation of positive rechallenge. Drugs defined as Class I have 20 or more reported cases and at least one report of positive rechallenge. Class-II drugs have more than ten but less than 20 reported cases, with or without positive rechallenge. Class-III drugs are all drugs that have been implicated in pancreatitis, including those with ten or fewer reported cases or unpublished reports of pancreatitis [2].

Pathophysiology: Several mechanisms of DIP appear to be involved, including immune-mediatedor hypersensitivity reactions (onset after four to eight weeks of use), direct toxic effects, bradykinin-induced inflammatory reactions, and mitochondrial toxicity. There is limited evidence that intrinsic toxicity, which causes damage in a dose dependent manner, causes DIP [5].

More likely idiosyncratic reactions occur in most patients with DIP. These reactions are unpredictable; they are not dose-dependent and the incidence is low. They can be further classified as hypersensitivity reactions and those that occur with the accumulation of toxic metabolites or an intermediary damaging substance. Direct immunological effects are usually observed within the first month of drug exposure, whereas toxic effects are noted after a few months of treatment. Indirect mechanisms of pancreatitis include ischemia, an increase in the viscosity of pancreatic enzymes, and intravascular thrombosis [5].

Case Report

An 18-year-young male child was admitted to Gastroenterology unit with 3 days of severe epigastric pain radiating towards back and 3-4 episodes of vomiting. There was no history of alcohol or tobacco use or abdominal trauma. There was no family history of acute pancreatitis. He had Juvenile Rheumatoid Arthritis since 6 months and was receiving Sulfasalazine 500mg once daily for four months and later dose was increased to 1000mg once daily, Etoricoxib 90mg once daily and Rabeprazole 20mg before breakfast. Serum amylase (499.0 U/L) and lipase (116.1 U/L) levels were elevated. Liver function tests were normal: Total bilirubin- 0.4mg/dl, direct bilirubin- 0.2mg/dl, SGOT- 12.6 U/L (<15.3U/L), SGPT- 31.6U/L (20-110U/L), ALP- 111.0 U/L (40-300U/L), Total protein- 7.4gm% (6.5-8.3gm%), Albumin- 3.9gm% (3.5-5.2gm%), Globulin- 3.5gm% (2.3-3.6gm%), A/G Ratio- 1.1:1.0. Other causes of AP such as hyperlipidemia and hypercalcemia were excluded. The white blood cell (WBC) count was significantly elevated at 14,000cells/mm^3 (4000–11,000cells/mm^3). Abdominal ultrasound (US) examination and computerized tomography (CT) scan revealed a normal liver and biliary tract. CT scan also revealed that mild bulky pancreas, irregular in contour and peripancreatic fast stranding which was evidence of acute pancreatitis. US of abdomen revealed acute pancreatitis with minimal ascites. RBS and Renal function tests were normal: 97mg/dl (up to 160mg/dl) and blood urea- 33mg/dl (10-50mg/dl),

serum creatinine- 0.7mg/dl (0.5-1.5mg/dl) respectively. The patient was kept on nothing by mouth and was treated with Injection. Cefotaxime 1g twice daily, Injection. Pantoprazole 40mg once daily, Injection. Tramadol 50mg given twice daily, IV fluids .DNS 2 pint, NS 1 pint, and RL 2 pint and was advised to stop all past medications. On the 2nd day of admission the pain was decreased and vomiting subsided. On 3rd day patient was advised to take liquid diet and there were no fresh complaints from patients and he was better and continued the same treatment. On 4th day he was advised to take soft diet and abdominal pain subsided completely and was advised to discharge on 5th day of admission with Tablet. Pantoprazole 40mg once daily before breakfast, Capsule. Tramadal 50mg twice daily and Tablet. Maxum once daily. Patient was advised to stop Sulfasalazine which was the cause for acute pancreatitis and recommended physiotherapy and few stretching and breathing exercises which helps to reduce the severity of arthritis.

MRCP/EUS/ERCP was not done in this patient to rule out any pancreas divisum. If pancreas divisum exists the patient may develop the symptoms in the earlier age itself. In this case, pancreatitis was diagnosed after 6 months usage of Sulfasalazine, so the final diagnosis was made to be Sulfasalazine induced acute pancreatitis.

Discussion

Drug induced pancreatitis is a rare occurrence, accounting for an estimated 0.1-2% [7].Regarding their certainty of causing AP, medications can be classified as Definite/Probable/Possible association. A 'definite' association implies a total relationship of drug administration with abdominal pain and hyperamylasemia or a positive response to rechallenge with the causative agent [20].

Drug-induced acute pancreatitis mechanisms are currently based on theories extracted from case reports, case-control studies, animal studies, and other experimental data [8]. Potential mechanisms for drug-induced acute pancreatitis include pancreatic duct constriction, cytotoxic and metabolic effects, accumulation of a toxic metabolite or intermediary, and hypersensitivity reactions [5].

Negative effects of drugs, such as hypertriglyceridemia and chronic hypercalcemia, are also mechanisms for drug-induced acute pancreatitis, as these effects are risk factors for acute pancreatitis. Other possible mechanisms of action are localized angioedema effect in the pancreas and arteriolar thrombosis [20].

Case reports continue to be published that reaffirm medications known to cause drug-induced AP and implicate new medications. There is limited understanding of the mechanisms involved. Many of the hypothesized mechanisms of action are related to the adverse effects of the drug that are risk factors for AP [4].

Based on the number of reported cases and re-exposure confirmation, drugs were classified as Class I, II or III drugs. Class I drugs have been associated with at least 20 reported cases of acute pancreatitis and at least 1case of a positive re-challenge. Class II drugs have been associated with more than 10 reported cases of acute pancreatitis with or without cases with a positive re-challenge. Class III drugs refer to all medications implicated in pancreatitis [7].

In Sulfonamides most of the drugs causing AP are Sulfamethoxazole, Sulfapyridine, and Sulfasalazine [11]. In a critical review, Mallory and Kern suggested that the sulfonamide component of Sulfasalazine was responsible for this adverse effect because of the structural similarity of the

sulfonamides to the Thiazide diuretics, which are a well-recognized cause of drug-induced pancreatitis. Sulfasalazine comprises Sulfapyridine linked by an azo bond to 5-aminosalicylate (5-ASA), which is the active ingredient [17].

Sulfasalazine belongs to Class I drugs according to these guidelines and the mechanism involved in Sulfasalazine induced acute pancreatitis was hypersensitivity which occur four to eight weeks after the drug has been started and is not a dose-related phenomenon. On rechallenge with the drug, AP recurs within hours to days [2,7].

Conclusion

In this case the patient presented with typical epigastric pain and 3-4 episodes of vomiting and elevated serum amylase and serum lipase as well as imaging (CT scan and ultrasonography). CT and ultrasonography revealed no evidence of Cholelithiasis or liver abnormality. In addition, other possible causes of acute pancreatitis were excluded. The final diagnosis was Sulfasalazine induced acute pancreatitis which was an immune mediated or hypersensitivity reaction and discontinuation of drug Sulfasalazine resulted in resolution of symptoms. Recognition and patient awareness of possible side effects of drugs could decrease morbidity and shorten overall hospital stays.

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