DRUG INDUCED PANCREATITIS

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Introduction

Pancreatitis is inflammation of the pancreas with acinic cell injury. It is classified into acute and chronic forms. The incidence of acute pancreatitis is about 5-35/100,000 new cases per year worldwide, with a mortality rate of approximately 3%. The number of hospitalizations for acute pancreatitis in the United States is increasing and is now approximated to be 274,119.[1] Among the various etiologic factors, drugs are often overlooked as a causative agent. Drugs are responsible for 0.1 to 2% cases of drug induced acute pancreatitis. However, no prevalence data is available from India. Only some idea about incidence can be obtained from patients admitted in tertiary care centers. At the All India Institute of Medical Sciences (AIIMS), New Delhi, 276 patients with acute pancreatitis (AP) were hospitalized from January 1997 to June 2002, i.e. about 55 patients per year.[2]

Etiology

The various etiologic factors are responsible for acute pancreatitis are given in the table 1, of which alcoholism and cholelithiasis the leading causes.[1]

Table 1: Etiologic Factors Associated with Acute Pancreatitis

Structural	Gallstone disease, sphincter of Oddi dysfunction, pancreas divisum, pancreatic tumors
Toxins	Alcohol (Ethanol) consumption, scorpion bite, organophosphate insecticides
Infectious	Bacterial, viral (including HIV and H1N1 influenza), parasitic
Metabolic	Hypertriglyceridemia, chronic hypercalcaemia
Genetic	Cystic fibrosis, α1-antitrypsin deficiency, hereditary (trypsinogen gene mutation)
Medications	See Table 3
Iatrogenic	Abdominal Surgery, Endoscopic retrograde cholangiopancreatography (ERCP)
Kidney disease	Chronic kidney disease, dialysis related
Trauma	Blunt abdominal trauma
Vascular	Vasculitis, atherosclerosis, cholesterol emboli, coronary artery bypass surgery
Other etiologies	Congenital Crohn's disease, autoimmune, tropical solid organ transplantation, (e.g. Liver, kidney, heart), refeeding syndrome
Idiopathic	Undetermined cause

The information on drug-induced pancreatitis (DIP) is very less. Most data is obtained from case reports, which do not provide reliable information on the incidence.[3] Badalov et al (2007) suggested a classification system for drug-induced pancreatitis which gives an indication of the association of the drug with DIP. In this classification, the drugs causing pancreatitis are divided into five categories: Ia, Ib, II, III and IV (Table 2).

Table 2: Badalov Classification of Drug-induced Pancreatitis

Category	Criteria
Class Ia	• At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs
Class Ib	• At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out
Class II	• At least 4 cases in the literature • Consistent latency (75% of cases)
Class III	• At least 2 cases in the literature • No consistent latency among cases • No rechallenge
Class IV	• Drugs not fitting in the earlier-described classes, single case report published in medical literature, without rechallenge

Mechanism of drug-induced pancreatitis:[3,4]

The mechanism of action of drug induced pancreatitis is speculative. The various case reports, case-control studies, experimental studies and animal studies helped to extract potential mechanism of action of drug induced pancreatitis. Drug-induced acute pancreatitis has also been associated with adverse effects of the drugs like hypertriglyceridemia, hypercalcaemia, which are the risk factors for acute pancreatitis. (Table 3)

Table 3: Commonly used drugs causing Drug-induced pancreatitis and their proposed mechanism of action

Drug/Drug Class causing acute pancreatitis	Proposed mechanism of action	Badalov Class
ACE inhibitors	• Local angioedema of pancreatic duct due to decreased degradation of bradykinin	• Class Ia, III, IV
Statins	• Direct toxic effect to pancreas • Accumulation of toxic metabolite	• Class Ia, Ib, III, IV

	• Secondary of rhabdomyolysis • Immune mediated inflammatory response	
Anti-HIV Drugs	• HIV infection itself	
	• Direct inflammation of pancreas • Secondary to metabolic disturbances - Protease inhibitors (Insulin resistance, hyperglycemias, hypercholesterolemia, hypertriglyceridemia)	• Lamivudine and Nelfinavir - Class Ib • Didanosine - Class II • Ritonavir - Class IV
Oral contraceptives	• OC induced Hypertriglyceridemia (Risk factor) • OC induced hypercoagulable state leading to pancreatic necrosis	• Class Ib, II
Azathioprine and 6-Mercaptopurine	• Allergic or idiosyncratic	• Class Ib
Antidiabetic drugs (Metformin)	• Drug overdose • Drug accumulation • Acute renal failure triggered by vomiting	• Class III
Mesalamine	• Hypersensitivity reactions	• Class Ia, Ib
Metronidazole	• Free radical production • Immune-mediated inflammatory response • Metabolic effects • Concomitant use with other drugs used in H. pylori infection	• Class Ia
Tetracycline	• Secondary to drug-induced fatty degeneration	• Class Ia
Valproic acid	• Direct toxic effect of free radicals on the pancreatic tissue • Depletion of superoxide dismutase, catalase, glutathione peroxidase • Idiosyncratic reaction	• Class Ia
Diuretics (Loop diuretics, Hydro-chlorothiazide)	• Direct toxic effects to pancreas • Diuretic induced stimulation of pancreatic secretion and ischemia • Hydrochlorothiazide induced hypercalcaemia and hyperlipidemia	• Class II, III, IV

Clinical presentation:[5]

The onset of acute pancreatitis is sudden. The patient presents with epigastric abdominal pain, vomiting and collapse. The pain is steady, boring and severe and often made worse by walking and lying supine

and better by sitting and leaning forward. The pain usually radiates to back, but may radiate to the right or left. The pain is often associated with nausea and vomiting. Marked epigastric or diffuse tenderness on palpation with rebound tenderness and guarding is present in severe cases. The abdomen is often distended and tympanic, with bowel sounds decreased or absent in severe disease. The vital signs may be normal, but hypotension, tachycardia and low grade fever are often observed, especially with widespread pancreatic inflammation and necrosis.[3]

The condition has to be differentiated from other diseases producing acute abdomen such as acute appendicitis, perforated peptic ulcer, acute cholecystitis and infarction of intestine following sudden occlusion of the mesenteric vessels.

Diagnosis:[5,6]

The main objective in the diagnosis of drug-induced pancreatitis is to first diagnose it as acute pancreatitis using defined criteria. The diagnosis should be within 48 hours based on the characteristic abdominal pain and elevation of several markers which includes serum amylase and lipase. Lipase is more sensitive and specific than amylase.[3] Other tests which are useful in diagnosis are serum trypsinogen, pancreatic proteases, C-reactive protein, interleukin-6, and interleukin-8, leucocyte count, urine tests for casts, proteins and glucose, blood glucose levels, blood urea nitrogen and serum bilirubin levels. Lipid profile, serum calcium levels also assist in the diagnosis, since elevated lipid levels and calcium levels considered as risk factors for acute pancreatitis.

While diagnosing drug-induced pancreatitis a detailed medical and medication history should be recorded. The onset of drug-induced pancreatitis after initiation of medications ranges from a few months to several years, with a median of 5 weeks; onset after rechallenge can occur within hours. Drug-induced acute pancreatitis should be suspected in high risk patients, such as those receiving immunomodulating drugs or who have HIV infection, the elderly, or those with diabetes mellitus.[3] Trivedi and Pichumoni (2005)[7] provided an algorithm to diagnose Drug-induced pancreatitis (DIP) (Figure 1).

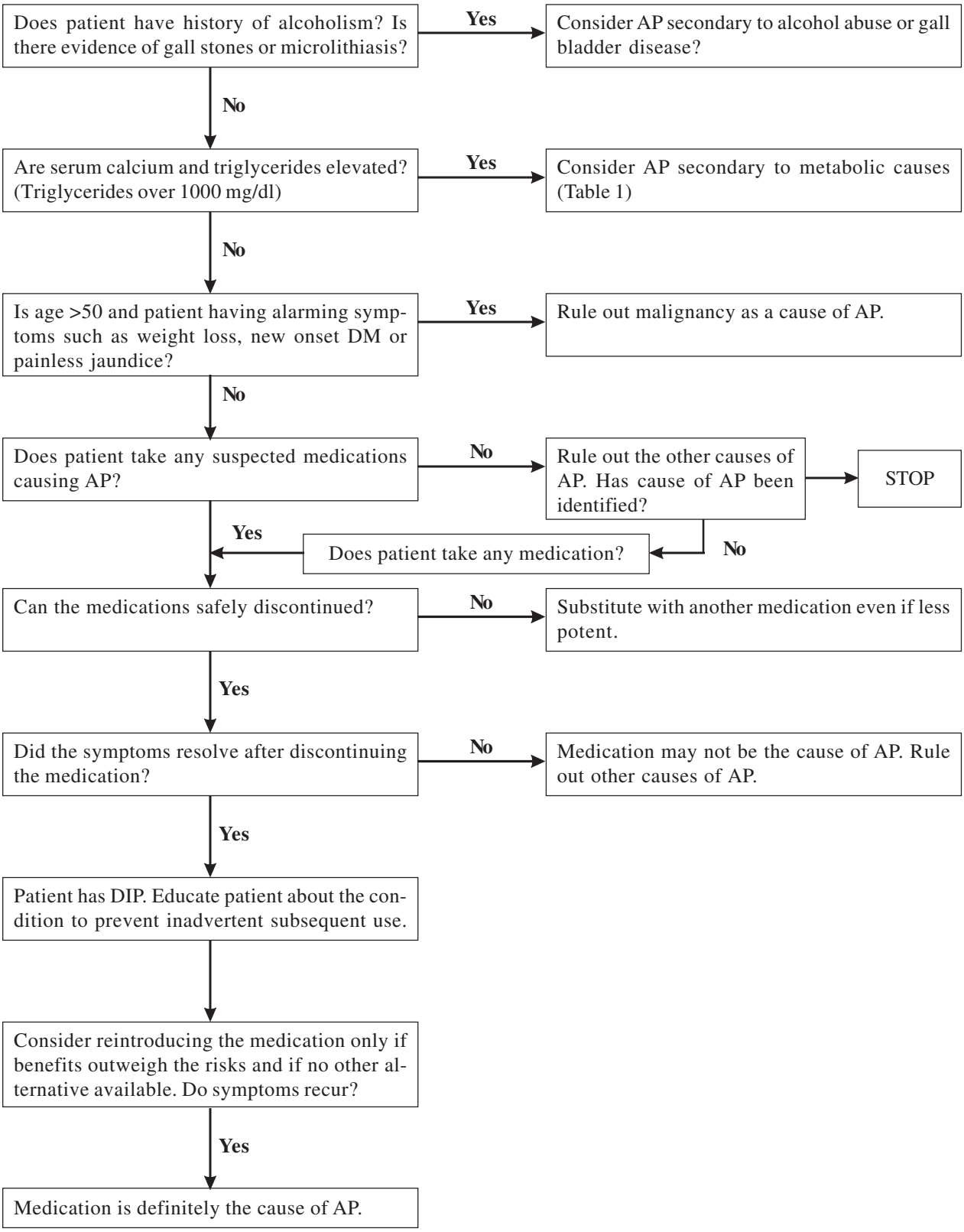

Figure 1 : Algorithm to diagnose DIP

Management:

One of the most important strategies to manage drug-induced pancreatitis is the withdrawal of the offending agent to prevent further pancreatic injury. The offending drug may be substituted for a drug from a different class.

Management of drug-induced acute pancreatitis is similar to that of acute pancreatitis due to other causes. The aims of treatment of acute pancreatitis are:

- To relieve abdominal pain and nausea
- To provide fluid replacement therapy
- To correct electrolyte, glucose and lipid abnormalities
- To minimize systemic complications
- To prevent pancreatic necrosis and infection

Relief of abdominal pain

Parenteral opioid analgesics are used to control abdominal pain associated with acute pancreatitis. Injection Pethidine 100-150 mg i.m. every 3-4 hours may be used to control pain. In patients with liver or kidney disease, the dose needs to be reduced. Oral intake of fluids and foods can be resumed when the patient is largely free from pain and has bowel sounds however in 20% of patients, pain may recur on refeeding.

Fluid replacement therapy

It has been noted from various observational studies that aggressive fluid administration may lead to benefit like decreased mortality and organ failure as well as harm like abdominal compartment syndrome. Lactated Ringer's solution may be preferred over normal saline for fluid replacement therapy.[8]

Correction of electrolyte, glucose and lipid abnormalities

IV potassium and magnesium are used to correct electrolyte deficiency states. Calcium gluconate must be given intravenously if there is evidence of hypocalcaemia with tetany. Insulin is used to treat hyperglycaemia. Statins may be started to correct abnormal lipid levels.

Prevention of pancreatic necrosis and infection

Necrosectomy may improve survival in patients with necrotizing pancreatitis and is often indicated for infected necrosis, although a select group of relatively stable patients with infected pancreatic necrosis may be managed with antibiotics alone.

Prevention of drug-induced pancreatitis:

Prevention of drug-induced pancreatitis consists largely on recognition of which drug has strongest evidence of being causally associated with pancreatitis, high-risk groups, maintenance of high index of

suspicion. DIP can be prevented by extracting the detailed history like risk factors for pancreatitis, any history of drug intake, any previous such event, history of alcohol intake, gallstone etc. Knowledge of possible mechanisms of drug-induced pancreatitis may be helpful in prevention of this adverse drug reaction. DIP occurring as a result of idiosyncratic drug reaction is difficult to prevent.[9]

Conclusion:

The incidence of drug-induced pancreatitis is increasing globally. There are many drugs reported in literature to be causally associated with acute pancreatitis. Acute pancreatitis due to drug reactions is often overlooked because of difficulty in appreciating a drug as its cause. A careful clinical assessment, history and causality assessment of drug reaction will help in early diagnosis and management. There are many risk factors for drug-induced pancreatitis which should be taken in to consideration for proper diagnosis. Future studies are needed to identify which subset of the population is more prone for this adverse drug reaction.

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