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Drug-Induced Acute Pancreatitis: A Review

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ABSTRACT

Background: The majority of drug-induced pancreatitis cases are mild to moderate in severity, but severe and even fatal cases can occur. Management of drug-induced pancreatitis requires withdrawal of the offending agent and supportive care.

Methods: This review focuses on differential diagnosis, clinical presentation, drug-mediated effects, treatments, and mechanisms of pancreatitis, with an emphasis on drug-induced pancreatitis.

Results: Although only a minority of cases associated with acute pancreatitis are linked to drugs, clinical presentation and mechanisms of injury to the pancreas are not well understood by clinicians in terms of individual drug effects in the mediation or modulation of injury to the pancreas. In recent years, a large number of commonly prescribed medications has been linked to drug-induced pancreatitis pathogenesis. Although mechanisms are proposed, the exact cause of injury is either not well understood or controversial.

Conclusion: Future investigation into the mechanisms of pancreatitis and an appreciation by clinicians of the drugs commonly linked to the condition will help establish earlier diagnosis and quicker cessation of offending drugs in the treatment of drug-induced acute pancreatitis.

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INTRODUCTION

Acute pancreatitis is the cause of up to 230,000 hospitalizations in the United States per year.[1] While mild acute pancreatitis carries a mortality of <1%, mortality rates for severe pancreatitis can reach as high as 30%.[2] Drugs are responsible for 0.1%-2% of acute pancreatitis incidents. The majority of drug-induced pancreatitis cases are mild to moderate in severity; however, severe and even fatal cases can occur. Management of drug-induced acute pancreatitis requires withdrawal of the offending agent and supportive care, and failure to identify a drug that is the offending agent can result in critical delays. Prevention of drug-induced pancreatitis requires an up-to-date knowledge of drugs with the strongest evidence connecting their use to the development of pancreatitis. Controversy exists about the precise mechanisms of drug-induced pancreatitis, and treatments have continued to evolve in recent years. In this article, we critically review the epidemiology, pathogenesis, diagnosis, and presentation of drug-induced pancreatitis. We also discuss drugs and classes of drugs strongly implicated in mediating or modulating acute pancreatitis based on well-documented case reports and laboratory investigation.[3,4]

PATHOGENESIS AND PRESENTATION

Acute pancreatitis is characterized by the onset of parenchymal and peripancreatic fat necrosis with associated inflammation in a previously healthy individual. Acute pancreatitis should be suspected in patients with acute severe abdominal pain and can be classified based on severity. The Atlanta classification divides acute pancreatitis into two groups: interstitial edematous acute pancreatitis and necrotizing acute pancreatitis. The first category is characterized by pancreatic parenchymal and peripancreatic inflammation without necrosis, while the latter category involves inflammation and some degree of necrosis. Another system classifies pancreatitis based on severity and extent of necrosis. Relatively little necrosis or organ failure is seen in mild acute

pancreatitis, but severe acute pancreatitis is characterized by extensive necrosis complicated by intrapancreatic thrombosis and vascular disruption, as well as intraparenchymal hemorrhage in the presence of persistent organ failure of one or multiple organs.[5,6]

PANCREATIC PHYSIOLOGY

The pancreas normally synthesizes and secretes several enzymes involved in digestion. These enzymes are produced in pancreatic acinar cells as inactive zymogens and secreted into the duodenum via the pancreatic duct and sphincter of Oddi where they are activated. The activation process begins as enterokinase, an enzyme produced in the duodenal crypts of Lieberkühn, encounters the pancreatic zymogen trypsinogen. Enterokinase binds to trypsinogen and cleaves an acidic propeptide, leaving active trypsin to initiate a cascade of proteolytic reactions. The reactions lead to the activation of other pancreatic zymogens such as chymotrypsinogen, proelastase, prophospholipase, and procarboxypeptidases that are necessary for digestion.[7,8]

If, however, the zymogens are activated prematurely before they exit the pancreatic interstitium, autodigestion of the peripancreatic tissue and pancreatic parenchyma can occur. To guard against premature activation, the pancreas has several defense mechanisms. The first is an enzyme, the pancreatic secretory trypsin inhibitor, that can bind to and inactivate 20% of trypsin activity. A second defense mechanism is autolysis of prematurely activated trypsin, and a third defense mechanism involves the action of nonspecific proteases such as alpha-1 antitrypsin.[9,10]

PANCREATITIS PATHOPHYSIOLOGY

For pancreatitis to occur, an initial event must overwhelm these defense mechanisms. Several well-known etiologies exist, with gallstone obstruction and ethanol abuse the two most prevalent causes. Gallstone obstruction of the ampulla of Vater, which is responsible for 35%-40% of acute pancreatitis cases in the United States, is thought to induce pancreatitis via stasis and reflux of bile into the pancreatic duct.[11] Prevailing theories posit that the blockage initiates the pancreatic zymogen cascade that then damages surrounding tissue. Cholecystectomy and bile duct clearance resolve the symptoms, confirming the cause-and-effect relationship.[12]

Ethanol abuse is the second most common cause of pancreatitis in the United States, responsible for approximately 30% of cases.[13] The pathogenic details of ethanol-induced pancreatitis are yet to be confirmed, but several mechanisms have been proposed. The first involves an oversensitization of pancreatic acinar cells to cholecystokinin and premature zymogen activation. The second suggests that ethanol induces acinar cells to overproduce enzymes that are activated prematurely because of buildup and stasis within the pancreas.[14,15]

Other etiologies involve smoking, scorpion venom, hypertriglyceridemia, endoscopic retrograde cholangiopancreatography (ERCP), hypercalcemia, steroids, malignancy, infection, trauma, and drugs.[16-25]

Regardless of the mechanism underlying an episode of pancreatitis, once activated, the enzymes will begin to digest the cell membranes of the pancreas, thereby activating an inflammatory response. This response increases the vascular permeability of the pancreas.[26] Hemorrhage, edema, ischemia, and necrosis can ensue.[26] The severity of acute pancreatitis can vary as it progresses to systemic inflammatory response syndrome, sepsis, and multiple organ failure.[27] Approximately 3%-13% of acute pancreatitis cases develop into chronic pancreatitis.[28]

PANCREATITIS SIGNS AND SYMPTOMS

Patients with pancreatitis typically present with abdominal pain, nausea, and vomiting. The symptoms depend on the severity of the pancreatitis; a patient with mild acute pancreatitis may experience only minimal tenderness to palpation. Nevertheless, the pain is constant, usually located in the epigastrium, and generally described as knifelike and radiating to the midcentral back. Patients are restless and may bend forward, bringing their knees to their chest in an effort to alleviate the pain.[29,30]

Jaundice is a common finding. In 3% of patients with severe acute pancreatitis, flank ecchymosis (Grey Turner sign) or periumbilical ecchymosis (Cullen sign) develops and is suggestive of retroperitoneal hemorrhage. Patients with severe acute pancreatitis can also develop fever, tachypnea, hypoxemia, and hypotension.[31,32]

Some patients display alterations in mental status. This symptom is more common in drug-induced acute pancreatitis and reflects exposure to drugs or to ethanol but may also result from hypotension, hypoxemia, or the massive release of toxic agents from the inflamed pancreas.[3,19]

Complications may arise that include local and systemic consequences. Local complications include fluid accumulation, pancreatic pseudocyst, necrotic collection, and walled-off necrosis. The fluids and necrotic tissue can become secondarily infected, leading to systemic inflammatory response syndrome and sepsis. Systemic complications include splanchnic vein thrombosis, abdominal compartment syndrome, pseudoaneurysm, acute respiratory distress syndrome, and exacerbation of underlying comorbid-

Table 1. Ranson Criteria for Acute Pancreatitis

At Admission	Within 48 Hours
Age >55 years	Serum calcium <8.0 mg/dL
WBC >16,000 cells/mm^3	Hematocrit drop >10%
Blood glucose >200 mg/dL	Pa_{O_2} <60 mmHg
Serum AST >250 IU/L	BUN increase >5 mg/dL
Serum LDH >350 IU/L	Base deficit >4 mEq/L
	Fluid sequestration >6 L

AST, aspartate aminotransferase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; Pa_{O_2}, partial pressure of oxygen in arterial blood; WBC, white blood cell count.
(Table adapted by permission from Macmillan Publishers Ltd: [Journal of Perinatology],[36] copyright 2014.)

ities such as coronary artery disease and chronic lung disease.[33-35]

The majority of severe complications occur within 48 hours of onset. The Ranson criteria identify a number of factors that, if positive, predict a poor prognosis. These criteria are divided into categories based on a diagnosis of gallstone pancreatitis vs non–gallstone pancreatitis. For drug-induced pancreatitis, which falls under the non–gallstone pancreatitis umbrella, the Ranson criteria are listed in Table 1.[36]

Each category that is positive for the patient equates to a point. The final point total indicates a prognosis for the patient as follows: 0-2: 2% mortality, 3-4: 15% mortality, 5-6: 40% mortality, and 7-8: 100% mortality.[36]

DIAGNOSIS OF DRUG-INDUCED PANCREATITIS

The diagnosis of drug-induced acute pancreatitis first requires a diagnosis of acute pancreatitis. Elevations in several biomarkers are indicative of pancreatitis, including serum lipase and amylase that are secreted in bulk by pancreatic acinar cells and thus are the most commonly measured. Other laboratory tests with diagnostic implications include serum trypsinogen, pancreatic proteases, C-reactive protein, interleukin-6, and interleukin-8. The next step in diagnosing drug-induced pancreatitis requires ruling out more common etiologies such as gallstone pancreatitis and ethanol-induced acute pancreatitis. A thorough medical history and the patient's medications must be recorded. The history should focus on previous symptoms and any record of gallstones, ethanol abuse, hypercalcemia, hypertriglyceridemia, and trauma. Serum amylase, lipase, triglyceride level, calcium level, and liver function tests should be ordered. Abdominal and endoscopic ultrasounds should be performed to evaluate for gallstones and other obstructive possibilities such as tumors of the pancreas head. ERCP should not be performed after an episode of acute pancreatitis in the absence of imaging or chemical evidence of choledocholithiasis.[24,35,37,38]

Any drugs with the potential to cause pancreatitis should be discontinued or exchanged for a drug of a different class, if possible. If the pancreatitis resolves after discontinuation of the drug, suspicion for drug-induced pancreatitis increases. This connection proves difficult to establish, however, as the resolution of disease may be linked coincidentally with cessation of the inciting agent. A firm diagnosis can be reasonably established with a rechallenge of the offending drug that results in the recurrence of pancreatitis symptoms.[3,18,19,39]

GENERAL MECHANISMS OF DRUG-INDUCED ACUTE PANCREATITIS

Drug-induced acute pancreatitis mechanisms are currently based on theories extracted from case reports, case-control studies, animal studies, and other experimental data. Drugs and drug classes associated with acute pancreatitis are summarized in Table 2.[26] 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.[40] 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.[26]

Angiotensin-Converting Enzyme Inhibitors

A possible mechanism of action for angiotensin-converting enzyme (ACE) inhibitor–induced acute pancreatitis is proposed to follow the mechanism of local angioedema of the pancreatic duct.[26] ACE inhibitors decrease the degradation of bradykinin that is linked to the development of angioedema.[26,41] Demonstrations show that bradykinins are released during acute pancreatitis, which is in concordance with observed increased vascular permeability in the pancreas during acute pancreatitis. This release can result in pancreatic edema, causing enzymes and other toxic substances to be trapped within the pancreas and leading to tissue damage in the pancreas and acute pancreatitis.[26,41] In addition, angiotensin II receptors may be important in regulating secretion and microcirculation within the pancreas.[41]

Table 2. Drugs, Drug Classes, and Other Agents Associated with Acute Pancreatitis

ACE inhibitors	Cyproheptadine	Linagliptin	Liraglutide
Macrolides	Rifapentine	Acetaminophen	Cytosine
Mefenamic acid	Rivastigmine	ACTH	Danazol
6-MP	Ropinirole	Alendronate	Dapsone
Mesalamine	Saw palmetto	Saxagliptin	All-trans-retinoic acid
Alogliptin	DDP-4 inhibitors	Metformin	SSRIs
Alpha-methyldopa	Diazoxide	Methimazole	Sirolimus
Sitagliptin	Aminosalicylates	Diphenoxylate	Methyldopa
Sodium stibogluconate	Amiodarone	Dipyridamole	Divalproex sodium
Metronidazole	Somatropin	Amlodipine	Doxercalciferol
Mirtazapine	Statins	Ampicillin	Doxorubicin
Montelukast	Sulfamethoxazole	Antivirals	Ertapenem
Mycophenolate	Sulfasalazine	Aspirin	Estrogens
Exenatide	Nitrofurantoin	Sumatriptan	Atypical antipsychotics
Fibrates	NSAIDs	Tacrolimus	Azathioprine
Finasteride	Octreotide	Tamoxifen	Bupropion
Fluoroquinolones	Paclitaxel	Tetracyclines	Calcitriol
5-Fluorouracil	Pegaspargase	Thiazide diuretics	Cannabis
Furosemide	Penicillin	Thrombolytic agents	Capecitabine
Gabapentin	Pentamidine	TNF-alpha inhibitors	Carbamazepine
GLP-1 analogs	Pergolide	Topiramate	Ceftriaxone
Gold	Phenolphthalein	Valproic acid	Cimetidine
HAART agents	Pilocarpine	Venlafaxine	Cisplatin
Ifosfamide	Prazosin	Vincristine	Clomiphene
Indomethacin	Procainamide	Voriconazole	Codeine
Interferon/ribavirin	Propofol	Zolmitriptan	Colchicine
Interleukin-2	Propoxyphene	Corticosteroids	Irbesartan
PPIs	Co-trimoxazole	Isoniazid	Quinupristin/dalfopristin
COX-2 inhibitors	Isotretinoin	Ranitidine	Cyclophosphamide
Lamotrigine	Repaglinide	Cyclosporine	L-asparaginase
Rifampin			

6-MP, 6-mercaptopurine; ACE, angiotensin-converting enzyme; ACTH, adrenocorticotropic hormone; COX, cyclooxygenase; DDP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; HAART, highly active antiretroviral therapy; NSAIDs, nonsteroidal antiinflammatory drugs; PPI, proton pump inhibitor; SSRIs, selective serotonin reuptake inhibitors; TNF, tumor necrosis factor.
(Table adapted with permission from Kaurich.[26])

Statins

The onset of acute pancreatitis induced by statins has been observed from hours to years after treatment.[26,42] Because of the variance in the latency period, the mechanism may be related to a direct toxic effect to the pancreas and the accumulation of a toxic metabolite.[26,42] Other mechanisms of action of statin-induced acute pancreatitis are speculated to be associated with rhabdomyolysis, myalgia, and/or metabolism or drug interactions through cytochrome P-450 3A4 (CYP3A4).[26] In several case reports, either myalgia or rhabdomyolysis occurred before development of acute pancreatitis.[26] Because pravastatin does not metabolize CYP3A4, it may have fewer case reports of drug-induced acute pancreatitis than other statins.[26]

Oral Contraceptives/Hormone Replacement Therapy

Both of the proposed mechanisms for acute pancreatitis caused by estrogen are related to the negative effects of oral contraceptives and hormone replacement therapy (HRT). The first proposed mechanism is that patients develop hypertriglyceridemia as a new diagnosis, existing hypertriglyceridemia is exacerbated, patients are diagnosed with previously unknown familial hyperlipoproteinemia.[26] The second proposed mechanism is that pancreatic necrosis is induced by a hypercoagulable state.[26,40]

Diuretics

Suggested mechanisms of action for furosemide-induced acute pancreatitis include a direct toxic effect to the pancreas, diuretic-induced stimulation of pan-

creatic secretion, and ischemia.[26,41] An experimental study demonstrated that a decreased volume of extracellular fluid lessens pancreatic blood flow, thereby leading to ischemia.[43] Two of the negative effects of hydrochlorothiazides are hypercalcemia and hyperlipidemia. Because hydrochlorothiazides cause increased calcium resorption from bone and increased levels of serum calcium, hydrochlorothiazides create an increased risk for acute pancreatitis.[43] Hydrochlorothiazides also may be involved in the development of hyperparathyroidism that can lead to hypercalcemia and acute pancreatitis.[26,41] Finally, hydrochlorothiazides can increase serum triglyceride levels, putting a patient at increased risk for acute pancreatitis.[43]

Highly Active Antiretroviral Therapy

Human immunodeficiency virus (HIV) infection is a proposed mechanism for acute pancreatitis because HIV directly causes inflammation of the pancreas.[26,40] Highly active antiretroviral therapy may also be involved in the development of acute pancreatitis because the antiretroviral therapy could potentially cause a toxic effect directly to the pancreas or induce negative effects associated with acute pancreatitis. Protease inhibitors (PIs) can cause metabolic disturbances, including development of insulin resistance, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia. However, triglyceride levels need not be elevated, as cases have been reported in which levels were normal. According to several studies, no significant increase of acute pancreatitis risk occurs after the introduction of PIs to treatment.[26]

Valproic Acid

The proposed mechanisms of action of valproic acid–induced acute pancreatitis are a direct toxic effect of free radicals on the pancreatic tissue and a depletion of superoxide dismutase, catalase, and glutathione peroxidase.[26] Valproic acid–induced acute pancreatitis can result from an individual's distinct reaction to a drug against the norm of other adverse effects associated with the drug. This risk increases in patients with a history of drug sensitivity.[44]

Hypoglycemic Agents

Various oral hypoglycemic agents used in the treatment of diabetes are linked to acute pancreatitis. While some association exists between the occurrence of pancreatitis and biguanide agents such as metformin, as well as with dipeptidyl peptidase 4 inhibitors, including sitagliptin, vildagliptin, and saxagliptin, current research suggests that the only oral hypoglycemic agents with a disproportionately increased risk of pancreatitis are the glucagon-like peptide-1 (GLP-1) mimetics. Of particular concern is exenatide that was linked to 36 postmarketing reports of acute pancreatitis soon after its introduction. Further inquiry has estimated a 6-fold increase in the risk of pancreatitis with the use of exenatide compared to other therapies.[45,46]

The pathogenesis of GLP-1 analog-induced pancreatitis is unclear, but current evidence suggests an additive or synergistic exacerbation of pancreatitis when GLP-1 analogs are used in the presence of a high fat diet. The sequence of injury appears to begin with acinar cell hypertrophy, progress to proinflammatory cytokine induction, and culminate in pancreatic vascular injury.[47]

MOLECULAR MECHANISMS OF PANCREATITIS

Role of Triglycerides

Based on studies of the effect of triglycerides and free fatty acids in the dog pancreas, rapid accumulation of triglyceride-containing lipoproteins, mostly chylomicrons, are believed to lead to ischemic events in the microcirculation of the pancreas. In addition, proinflammatory nonesterified free fatty acids generated from the esterification of chylomicron triglycerides may lead to the release of inflammatory mediators and free radicals, further contributing to pancreatic damage.[48]

Autoimmune Pancreatitis

A link is postulated to exist between abnormal human leukocyte antigen expression on both acinar and ductal cells of the pancreas and the presentation of autoantigens that would then lead to autoimmune pancreatitis, but this mechanism is not proven. For now, the pathophysiologic mechanisms of autoimmune pancreatitis remain unknown.[49]

CONCLUSION

Pancreatitis is a serious condition with significant potential morbidity and mortality. Although drug-induced acute pancreatitis is relatively rare, a firm understanding of the drugs associated with the condition should alert the clinician to appropriately diagnose and treat patients. An early diagnosis can facilitate prompt cessation of the offending agent, thereby reducing complications and length of hospital stay. Ongoing research is focused on determining the molecular mechanisms behind drug-induced acute pancreatitis and its clinical sequelae.

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