Ever-increasing diversity of drug-induced pancreatitis.

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With over 100000 hospital admissions per annum, acute pancreatitis remains the leading gastrointestinal cause of hospitalization in the United States and has far-reaching impact well beyond. It has become increasingly recognized that drug-induced pancreatitis (DIP), despite accounting for less than 3% of all cases, represents an important and growing though often inconspicuous cause of acute pancreatitis. Nevertheless, knowledge of DIP is often curtailed by the limited availability of evidence needed to implicate given agents, especially for non-prescription medications. Indeed, the majority of available data is derived from case reports, case series, or case control studies. Furthermore, the mechanism of injury and causality for many of these drugs remain elusive as a definitive correlation is generally not established (< 10% of cases). Several classification systems have been proposed, but no single system has been widely adopted, and periodic updates are required in light of ongoing

pharmacologic expansion. Moreover, infrequently prescribed medications or those available over-the-counter (including herbal and other alternative remedies) are often overlooked as a potential culprit of acute pancreatitis. Herein, we review the ever-increasing diversity of DIP and the potential mechanisms of injury with the goal of raising awareness regarding the nature and magnitude of this entity. We believe this manuscript will aid in increasing both primary and secondary prevention of DIP, thus ultimately facilitating more expedient diagnosis and a decrease in DIP-related morbidity.

Drug-induced pancreatitis

pmc-prop-legally-suppressed

pmc-prop-has-supplement

pmc-prop-suppress-copyright

pmc-prop-is-real-version

pmc-prop-is-scanned-article

Acute pancreatitis is an acute, inflammatory, potentially life-threatening condition of the pancreas. With over 100000 hospital admissions per annum, acute pancreatitis is the leading gastrointestinal cause of hospitalization in the United States and the 10

The World Health Organization database lists 525 different medications associated with acute pancreatitis (

PUBLIC HEALTH IMPORTANCE OF DIP

As there is no standardized approach to stratifying patients to determine their risk of developing acute pancreatitis, primary prevention for the majority of etiologies cannot be fully implemented. Secondary prevention of acute pancreatitis, on the other hand, can more easily be executed. For example, abstinence from alcohol reduces the risk of alcoholic pancreatitis, cholecystectomy reduces the risk of gallstone pancreatitis, and tight control of triglycerides reduces the risk of recurrent episodes of pancreatitis secondary to hypertriglyceridemia. On this notion, unique to DIP, is the fact that it can be prevented in both the primary and secondary fashion. Unfortunately, however, most of the available data in reference to DIP is derived from case reports, case series, or case control studies. In this vein, the causality between specific medications and acute pancreatitis has been established in only a minority of cases (< 10%)[

CHALLENGES IN ESTABLISHING A DIAGNOSIS OF DIP

Numerous factors limit the ability of clinicians to causally link acute pancreatitis with medications. First, the lack of mandatory adverse drug reporting systems allow many cases to go unreported[

Flow diagram to help identify the potential cause of acute pancreatitis, including cases of drug-induced pancreatitis. ERCP: Endoscopic retrograde cholangiopancreatography; FDA: Food and Drug Administration.

APPROACH AND AVAILABLE METHODS TO ESTABLISH DIP

In accordance with the aforementioned limitations, evidence implicating numerous medications is inconsistent and, at times, even contradictory. Hence, although not uniform, nor universally accepted, official tier systems exist to help quantify the likelihood of a drug to be established as a culprit of acute pancreatitis. The earliest classification system was developed in 1980 and was designed to include three classes; Class I: Included drugs that were implicated to induce pancreatitis in a minimum of 20 cases of which at least one case documented drug re-exposure, Class II: Included drugs that were implicated to induce pancreatitis in 10-20 cases with or without documented drug re-exposure, and Class III: Included all drugs implicated in pancreatitis[

The earliest classification system of drug-induced pancreatitis, as proposed by Trivedi et al[

≥ 1 case documenting a positive re-challenge

With or without drug re-challenge

All drugs associated with drug induced pancreatitis

The most recent classification system was developed by Badalov et al[

The more recent classification system of drug-induced pancreatitis, proposed by Badalov et al[

Minimum No. of case reports

Re-challenge required

Alternative causes of pancreatitis excluded

In greater than 75% of cases. N/A: Not applicable.

Additionally, the Naranjo adverse drug reaction probability scale can be helpful in establishing the degree of association between a drug and an adverse reaction[

The Naranjo adverse drug reaction probability scale[

Finally, and most recently, our proposed specific drug-induced pancreatitis probability scale (modified from the Naranjo scale to be more pancreatitis-specific) can serve as a standardized tool for determining the likelihood of drug-induced pancreatitis based on the aggregate score from a series of 10 questions. A score of < 2 suggests doubtful DIP, 3-5 possible DIP, 6-8 probable DIP, and > 9 highly

probable DIP (Figure

Proposed drug-induced pancreatitis probability assessment scale in which a total summative score of > 9: highly probable, 6-8: probable, 3-5: possible, and ≤ 2: doubtful. ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography.

DRUGS AND MECHANISMS INVOLVED

While consensus has yet to be reached regarding the cause of drug-induced pancreatitis in many cases, numerous potential mechanisms have been speculated. These include, pancreatic/biliary duct constriction, cytotoxic effects, metabolic effects, accumulation of a toxic metabolite or intermediary, and idiosyncratic and/or hypersensitivity reaction, with idiosyncratic response or direct toxic effect likely accounting for the majority of cases[

The proposed mechanisms leading to pancreatic insult in drug-induced pancreatitis.

Studies concerning the incidence of drug-induced pancreatitis have established a range of 0.3% to 1.4% of all acute pancreatitis cases being due to drugs[

Classes of medications implicated in drug-induced pancreatitis grouped according to the three-class system of classification

Alkylating antineoplastics

Angiotensin-converting enzyme inhibitors

Antimetabolite antineoplastics

Hormone replacement therapies

Antitubercular agents

Non-biologic immunosuppressives

Nonsteroidal anti-inflammatories

Reverse transcriptase inhibitors

Reverse transcriptase inhibitors

Antimetabolite antineoplastics

Atypical antipsychotics

Cholesterol lowering agents

Cyclooxygenase II inhibitors

Nonsteroidal anti-inflammatories

Parasympathetic agents

Proton pump inhibitors

Selective serotonin agonists

Statin-induced pancreatitis

Among the many drugs that have been associated with pancreatitis, statins have been increasingly reported as a cause of acute pancreatitis[

5-aminosalicylic acid-induced pancreatitis

Although rare, several 5-aminosalicylic acid (5-ASA)-induced acute pancreatitis cases have been published in the literature. Interestingly, both oral and enema mesalamine preparations have been implicated in causing pancreatitis within days[

Antibiotic-induced pancreatitis

Metronidazole has been reported in association with acute pancreatitis, although the mechanism is not fully known[

Steroid and non-steroidal anti-inflammatory drug-induced pancreatitis

Numerous steroids (dexamethasone, prednisone, prednisolone, cortisone acetate, and adrenocorticotropic hormone) have been associated with inducing acute pancreatitis nearly all with a short latency period[

Immunotherapy-induced pancreatitis

Immunotherapy agents have long been associated with acute pancreatitis, however their increased use in recent decades has led to a concomitant increase in im-munotherapy-associated pancreatitis. Interleukin-2 immunotherapy-associated pancreatitis in particular has been reported[

Angiotensin-converting-enzyme inhibitor-induced pancreatitis

There have been many well-documented case reports of acute pancreatitis due to Angiotensin-converting-enzyme inhibitors (ACE-Is)[

Anti-glycemic medication-induced pancreatitis

Although proven to be relatively safe for the management of type 2 diabetes mellitus, numerous classes of oral anti-glycemic agents including biguanides (metformin)[

Illicit drug-induced pancreatitis

Marijuana (cannabis) is the most common illicit drug globally with over 4% of the population using it per annum[

Highly active anti-retroviral therapy-induced pancreatitis

The highly active anti-retroviral therapy therapy drugs have long thought to be associated with the development of acute pancreatitis[

Diuretic-induced pancreatitis

Hormone replacement therapy and oral contraceptive-induced pancreatitis

Numerous cases have been reported in which estrogen-containing products were thought to induce acute pancreatitis[

Anti-acid-induced pancreatitis

Although both H2-blockers and proton-pump inhibitors have been reported in the literature to cause acute pancreatitis, the evidence regarding this relationship is controversial[

Anti-depressant medication-induced pancreatitis

Many cases have linked antidepressants (

Anti-seizure medication-induced pancreatitis

Numerous anti-seizure medications (clozapine, olanzapine, and valproic acid) have been associated with inducing pancreatitis, especially in the pediatric population[

Vitamin-induced pancreatitis

To our knowledge, two cases of vitamin-induced acute pancreatitis have been reported, both involving vitamin D. One involved oral vitamin D, wherein the injury was seemingly related to the hypercalcemic effect of vitamin D[

Herbal, supplement, and homeopathic medication-induced pancreatitis

Although seldom in nature, several herbal medications have been reported the in literature as being associated with DIP. These including: Sambucol (black elderberry extract), “Immune factors” [combination of

In the setting of an ever-increasing armamentarium of pharmacological agents, drug-induced adverse effects including acute pancreatitis are increasingly encountered. DIP is a difficult diagnosis to establish and is thus likely underreported, owing in part to its often unsuspected nature as well as the technical difficulty in causally linking a drug to acute pancreatitis. Criteria for definite DIP are many and generally include requiring that the drug cause acute pancreatitis during or predictably after initiating treatment with the drug, resolution of pancreatitis upon discontinuation of the drug, and reoccurrence of pancreatitis upon re-administration of the drug, granted that other likely causes of acute pancreatitis have been ruled out. With these caveats in mind, the current list of drugs associated with DIP is by no means complete nor fully understood, and further research is needed.

As cases of DIP are associated with higher morbidity, extended hospital stays, and increased healthcare costs, in large part due to delays in diagnosis, patients presenting with pancreatitis of unknown etiology should be carefully questioned regarding drugs that could be linked to DIP[

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