Drug-Induced Acute Pancreatitis: Underdiagnosis and Overdiagnosis

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As the incidence of acute pancreatitis continues to rise, establishing the etiology in order to prevent recurrence is important [1, 2]. Although the etiology of acute pancreatitis is not difficult in the majority of patients, almost a quarter of patients are initially labeled as having idiopathic acute pancreatitis [3]. When confronted with a patient with acute pancreatitis and no clear etiology defined as an absence of a history of alcoholism, absence of imaging demonstrating gallstones (ultrasound and/or MRI), and a normal triglyceride level, it is reasonable to consider a drug as the cause of acute pancreatitis. When considering a particular medication as causing acute pancreatitis, often the first step is a literature search. Data from pharmaceutical companies and/or the Food and Drug Administration (FDA) is not helpful. Typically, these sources cite many medications as causing acute pancreatitis despite the fact that the evidence provided does not have sufficient detail as to demonstrate causation. Published case reports, if detailed properly, can give more definitive information as to the diagnosis of acute pancreatitis and whether other causes besides drugs have been properly ruled out.

A recent thorough review of the literature found over 100 drugs implicated in causing acute pancreatitis [4]. While some of these case reports are well written, many case reports represent poorly written experiences of the clinician simply implicating a drug without a careful evaluation. The case reports are plagued by a combination of failing to provide the definitive diagnosis of acute

pancreatitis and clarity in ruling out more common causes of acute pancreatitis such as alcoholism, gallstones, and hypertriglyceridemia. Due to problems in the literature, many patients with important causes of acute pancreatitis that need to be recognized such as gallstones, hypertriglyceridemia, and tumors, are falsely labeled as having drug-induced acute pancreatitis. This has resulted in the overdiagnosis of drug-induced pancreatitis. Conversely, some patients with idiopathic recurrent pancreatitis are not recognized as being on a medication that is causing their pancreatitis. This has resulted in the under-diagnosis of drug-induced pancreatitis.

There have been multiple attempts to critically review the literature and determine which drugs have the best evidence as causing acute pancreatitis [4–7]. The more recent critical reviews [4, 7] utilize a classification system of the published case reports based on the level of evidence for each drug implicated as causing acute pancreatitis. Both of these reviews describe the best evidence of a particular drug causing acute pancreatitis if there is either a positive rechallenge, a larger number of case reports for a particular drug and/or a consistent latency among the reports for a particular drug. A positive rechallenge is where the drug is stopped after a patient is found to have acute pancreatitis. After resolution of the pancreatitis, when the drug is restarted, acute pancreatitis develops again. This finding typically is reported as the clinicians caring for the patient made an error and did not blame the drug for causing acute pancreatitis. Despite a lack of a rechallenge, a drug may also be strongly suspected if there is a consistent latency among the case reports between initiating the drug and the onset of acute pancreatitis. A consistent latency may be a sign that the drug has a common mechanism of action. The Class I drugs, those with the most evidence causing acute pancreatitis, include mesalamine, amiodarone,

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azathioprine, 6-mercaptopurine, dexamethasone, enalapril, furosemide, isoniazide, lamivudine, metronidazole, omeprazole, sulfa, tetracycline, and valproic acid.

Although excellent critical reviews of the literature, there is a serious problem relying on these articles as a true assessment of drug-induced pancreatitis. As these reviews are largely based on small case series, or published case reports, the true epidemiology of drug-induced acute pancreatitis is not clear. The published classification systems are unable to quantify the risk of pancreatitis depending on the population exposure to the drugs. Population-based studies evaluating drug-induced pancreatitis would provide important information on the incidence, etiology, and severity of drug-induced pancreatitis.

In this issue, Vinklerova et al. [8] from University Hospital, Palacky University, in the Czech Republic add to our knowledge of drug-induced acute pancreatitis by evaluating the incidence, etiology, and severity of drug-induced acute pancreatitis in a single tertiary care facility. The authors used the Hospital Information System over a 2-year period to identify patients with acute pancreatitis. Cases of drug-induced pancreatitis were defined after a careful analysis using an algorithm previously published [7] and then each case was confirmed by the WHO probability scale for the evaluation of causality between acute pancreatitis and the suspected drug. In their population-based retrospective analysis over a 2-year period, these investigators found the incidence of drug-induced pancreatitis to be 5.3%, the third most frequent cause of acute pancreatitis after gallstones and alcohol. With the exception of azathioprine, seen in two patients, all cases of drug-induced pancreatitis in their series are single cases related to agents previously shown to cause acute pancreatitis, such as mesalamine, ramipril, valproate, and dexamethasone. Similar to the findings of prior reviews, this population-based study found that drug-induced pancreatitis is typically not a severe disease.

Although the conclusion of the authors is limited by the fact that only nine cases of drug-induced acute pancreatitis were identified, there are several important issues to recognize. As the authors point out, drug-induced acute pancreatitis appears to be underestimated. The disease may be more common in younger patients, in women, and in those with Crohn's disease as demonstrated by the patients identified in their study. For reasons not entirely clear, azathioprine-induced acute pancreatitis appears to be more common in patients with Crohn's disease compared to those with autoimmune hepatitis who are taking the same drug. Although it may be possible that there is some genetic or disease-specific predisposition that these patients possess, which increases their risk for developing drug-induced pancreatitis, it is more likely that other factors are involved. It must be remembered that these patient populations, young, women, and Crohn's disease, include

patients who typically utilize the medications more commonly associated with drug-induced acute pancreatitis, such as mesalamine, metronidazole, azathioprine, 6-mercaptopurine, and estrogens. Additionally, both women and those patients with Crohn's disease are inherently at an increased risk for the most common cause of acute pancreatitis, gallstones. This brings up another important issue that must be remembered when dealing with patients with suspected drug-induced acute pancreatitis. What is more likely? That the patient has a rare drug-induced disease, or a more common underlying etiology, such as gallstones, that is not presenting in its more common form (e.g., with gallstones in the gallbladder on ultrasound).

The cause of drug-induced pancreatic injury remains unclear. The pathophysiology is likely idiosyncratic and different among the medications depending on their chemical structure. There is little evidence that intrinsic toxicity of a drug is a cause of pancreatitis in humans. For example, there are only four cases of acetaminophen causing acute pancreatitis in the setting of an overdose. Considering the number of cases of acetaminophen overdoses and the rarity of pancreatitis in this setting, it is much more likely that an idiosyncratic reaction is occurring. Many of these drugs have latencies from the time drug is started to the development of acute pancreatitis of 1–6 weeks [4]. This time frame suggests a hypersensitivity reaction. However, classically, hypersensitivity reactions are accompanied by a rash, fever, joint pain, eosinophilia, and/or lymphadenopathy. In such patients, when rechallenge occurs, one would expect a shorter latency. There are several medications that fulfill this characteristic, including azathioprine, 6-mercaptopurine, and mesalamine. Idiosyncratic reactions may also be related to the accumulation of a toxic metabolite with long latencies. Some medications may merely exacerbate the known causes of pancreatitis, such as estrogens which increase the triglyceride level and increase the risk of gallstones and microlithiasis (cholesterol monohydrate crystals). Similarly, codeine has been postulated as causing acute pancreatitis by causing constriction of the sphincter of Oddi in susceptible patients.

Our current understanding of drug-induced acute pancreatitis unfortunately is largely based on case reports and critical reviews. The current method of case reporting in the literature, to the FDA, and to the pharmaceutical company is not only ineffective, but also often inaccurate. The study by Vinklerova and colleagues is a step in a new direction which adds not only to our knowledge of the disease, but more important, shows us the importance of population-based studies in understanding drug-induced pancreatitis. As the authors correctly point out, larger pharmaco-epidemiology-based studies are needed. These studies should be prospective, include patients only where acute pancreatitis has been clearly established, and include patients only where the

common causes of acute pancreatitis, gallstones, alcohol, and hypertriglyceridemia, have been ruled out. These studies will be challenging as they would require multiple institutions working together and require the integration of medical records in a large database. Until clinicians have the information from these larger population-based studies, drug-induced acute pancreatitis will continue to be underdiagnosed and overdiagnosed, thus contributing to the growing morbidity of this disease.

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