Abstract

Drugs are a relatively rare cause of acute pancreatitis, with an estimated incidence of 0.1–2%. Many drugs have been suspected of causing pancreatitis, but the true incidence is not known as the evidence is derived mainly from random case reports. Case reports with the strongest evidence are those that clearly diagnose pancreatitis and exclude common aetiologies, provide the dose and time interval between the start of treatment with the suspected drug and the development of pancreatitis, document response to withdrawal of the drug, and demonstrate recurrent pancreatitis upon rechallenge with the drug. Few data exist on the mechanisms of drug-induced pancreatitis. Certain subpopulations such as children, women, the elderly and patients with advanced HIV infection or inflammatory bowel disease may be at higher risk. The diagnosis of drug-induced pancreatitis is often challenging because there are no unique clinical characteristics to distinguish drugs from other causes of pancreatitis. The majority of cases are mild, but severe and even fatal cases may occur, thus making identification of the offending agent critical. Management of drug-induced acute pancreatitis requires withdrawal of the offending agent and supportive care. Prevention of
Drug-induced pancreatitis requires an up-to-date knowledge of drugs that have the strongest evidence linking their use to the development of pancreatitis as well as the proposed mechanisms through which they may cause the reaction. In this paper, the epidemiology, diagnosis, management and prevention of drug-induced pancreatitis is reviewed. Drugs and classes of drugs strongly implicated as causing acute pancreatitis, based on well documented case reports, are discussed in detail.

Acute pancreatitis is a severe disease with an overall mortality of approximately 5%, though in subpopulations with necrotizing pancreatitis and infected necrosis, mortality may be as high as 17% and 30%, respectively.\textsuperscript{11} The most common aetiologies are excessive alcohol use and gallstone disease, comprising 70–80% of all cases. Other aetiologies include autoimmune disease, iatrogenic injury, inflammatory bowel disease, infections, inherited disorders, neoplasia, structural abnormalities, toxins, trauma, ischaemia and some drugs.\textsuperscript{2} Drug-induced pancreatitis is remarkably rare, given the large number of drugs prescribed. Due to its rarity and the lack of unique clinical characteristics, the true epidemiology and risk factors for drug-induced pancreatitis remain unknown, and diagnosis of this adverse effect is challenging.

The first cases of drug-induced pancreatitis were reported with chlortalidone and cortisol in the 1950s.\textsuperscript{3,4} Since then, over 500 medications have been associated with pancreatitis,\textsuperscript{5} and the list continues to expand. Most of the evidence comes from random case reports. These reports are often incomplete, with inadequate data regarding drug dose, latency between initiating the drug to development of pancreatitis and exclusion of other common causes. Many case reports do not meet sufficient criteria to diagnose acute pancreatitis, and most do not provide evidence of rechallenge with the drug. Furthermore, random case reports are subject to selection and publication bias. Selection bias is influenced by the reporting and prescribing behaviours of clinicians. Publication bias may be present because the more severe adverse reactions are reported, whereas many cases of mild pancreatitis may not be reported or come to clinical attention.

In this paper, the epidemiology, diagnosis, management and prevention of drug-induced pancreatitis are reviewed. Drugs and classes of drugs strongly implicated as causing acute pancreatitis, based on well documented case reports, are discussed in detail.

1. Literature Search Methodology

A MEDLINE search (1950–2007) of the English language literature was conducted using the search terms ‘drug-induced pancreatitis’ and ‘\textit{x} and pancreatitis’, where ‘\textit{x}’ was the name of any drug that has been proposed to cause pancreatitis based on previous clinical reviews.\textsuperscript{6–11} The references in these papers were used to obtain additional case reports. Case reports were considered well documented if they met the criteria established by Mallory and Kern.\textsuperscript{6} These criteria stipulate that pancreatitis develops during treatment with the drug, resolves upon discontinuing the drug, recurs upon re-administration of the drug, and other likely causes of pancreatitis are not present. Additionally, case reports were required to contain adequate criteria for the diagnosis of pancreatitis.\textsuperscript{11} These case reports are considered to provide the best evidence for drug-induced pancreatitis and are further discussed in section 6. For a number of commonly used drugs, such as corticosteroids, furosemide and omeprazole, the available case reports fail to meet criteria established by Mallory and Kern and are therefore not discussed in this paper. Extensive reviews of drug-induced pancreatitis have been published recently, highlighting both common and uncommon drugs that may cause pancreatitis.\textsuperscript{17–12} Drug classes and individual drugs frequently associated with pancreatitis are listed in table I.

2. Epidemiology

Determining the true incidence of drug-induced pancreatitis is difficult because of the lack of adequate and consistent reporting. Epidemiological studies suggest an overall incidence of 0.1–2%,\textsuperscript{127–131} and that the risk may be increas-