Canterbury District Health Board
Te Poari Hauora ō Waitaha

Clinical Pharmacology Bulletin

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Drug-induced pancreatitis

Background
Acute pancreatitis is a severe disease with an overall mortality of around 5%. Mortality may be as high as 17% and 30% with necrotising pancreatitis or infected necrosis, respectively. Drug-induced pancreatitis is very rare with a reported incidence of up to 2% of all acute pancreatitis cases. Only a small number of drugs have been proven to cause this reaction. However, many more have been anecdotally associated with it. The aim of this bulletin is to highlight drugs (see Table below) that are associated with this potentially life-threatening condition.

Risk factors for drug-induced pancreatitis
There are several possible risk factors for drug-induced pancreatitis based on epidemiological data. These include:

- young age
- advanced age coupled with polypharmacy
- female sex
- advanced HIV disease (CD4 count<200 cells/mm^3)
- inflammatory bowel disease
- treatment with cancer chemotherapy agents

Diagnosis
Acute pancreatitis is usually confirmed by the presence of two of the following features:

- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase > 3 times the upper limit of normal
- characteristic findings on CT scan

Diagnosis of drug-induced pancreatitis is often difficult due to the lack of unique features distinguishing it from the other forms of the disease. Presence of the following may indicate causes other than drugs: alcohol use, biliary tract disease, gallstones, abdominal trauma (including surgery), personal or family history of pancreatitis and weight loss.

Management of drug-induced pancreatitis
If drug-induced pancreatitis is suspected, possible causative agents should be discontinued immediately. Patients should receive standard treatment (see Blue Book) with fluids, opioid analgesia and referral to intensive care in severe cases.

Oral intake should be withheld in patients with significant abdominal pain, distension, nausea and vomiting until symptoms resolve. In most cases this occurs within 3 to 7 days. Nutritional support may be needed in more severe cases.

Pathogenesis
Several mechanisms (see Table below) have been proposed for drug-induced pancreatitis. However, for many drugs the actual mechanism is unknown. Time to onset of this reaction is highly variable, from a few weeks with immunological causes to several months to years with other mechanisms such as angioedema.

Proving an association with a particular drug may not always be straightforward. Use of an adverse drug reaction probability scale (see page 167 of 14th ed. of PML) may be helpful in determining the likelihood of a drug cause. Rechallenge with suspected causal agents can sometimes be undertaken using low doses, close monitoring and prompt discontinuation if symptoms recur. However, rechallenge may not be wise if pancreatitis was severe on the first occurrence.

Table: Drugs associated with drug-induced pancreatitis that recurred on rechallenge

Drug	Proposed mechanism	Time to reaction	Time to recurrence on rechallenge
azathioprine	likely idiosyncratic, possibly immune or metabolic	3 - 4 weeks	hours - 2 days
5-aminosalicylic acid drugs	increased duct permeability	2 days - 1 month (1 report after 1 year)	hours - 2 days
codeine	transient, rapid spasm of sphincter of Oddi	1.5 - 3 hours	1 - 2 hours
enalapril	angioedema of pancreatic duct	5 weeks - 1 year	6 hours - 10 days
isoniazid	hypersensitivity reaction	11 - 21 days	6 hours - 21 days
losartan	unknown	3 - 7 days	1 - 3 days
metronidazole	unknown, possible direct toxic effect on pancreatic cells	12 hours - 7 days	12 hours - 7 days
oestrogens	related to hypertriglyceridaemic or prothrombotic effects	2 months - 5 years (3 months most common)	2 - 4 months
simvastatin	unknown	within 6 months	7 days
sulindac	idiosyncratic reaction to active metabolite	3 weeks - 5 years	1 - 2 months
tetracycline	possible accumulation of toxic metabolite	5 days - 2 months	4 days - 3 months
valproate	possible accumulation of metabolite	3 - 17 months	6 - 12 weeks

Other drugs associated with reports of drug-induced pancreatitis

amiodarone	clarithromycin	ifosfamide	methyldopa	perindopril
atorvastatin	clomifene	interferon/ribavirin	nelfinavir	pravastatin
carbimazole	clozapine	isotretinoin	nitrofurantoin	propofol quinapril
captopril	cytarabine	lisinopril	omeprazole	tamoxifen
chlorothiazide	dapsone	marijuana	pentamidine	