Drug-induced gastrointestinal disorders

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Abstract

Adverse drug effects on the gastrointestinal (GI) tract can occur as a predictable result of a drug's mode of action, by direct injury, through compromising GI defences, or as a consequence of changes in colonic bacterial flora. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common cause of gastroduodenal injury, owing to inhibition of prostaglandin synthesis, and increase the risk of serious GI complications between twofold and fourfold. Low doses of aspirin are associated with an increased risk of upper GI haemorrhage. COX-2 inhibitors largely spare the GI mucosa from injury. Advancing technology for investigating the small bowel now allows identification of subtle changes to the small bowel mucosa (such as ulceration and erosions) secondary to drugs. This can lead to occult iron deficiency anaemia, hypoalbuminaemia and protein-losing enteropathy. Drug-induced colitis is an important problem, with antibiotics the most common drug cause. Drugs can also exacerbate pre-existing inflammatory bowel disease. Strategies to minimize the adverse GI effects of drugs include drug avoidance or minimization, using lowest doses for the shortest time, selective COX-2 inhibitors for high-GI/low-cardiovascular risk patients, and upper GI mucosal protection by co-prescription of proton pump inhibitors with GI irritants.

Keywords Adverse events; colon; drugs; gastrointestinal injury; NSAIDs; pill induced; small intestine

What's new?

- Treatment of head and neck cancer with radiotherapy and/or cytotoxic agents can cause mucositis affecting primarily the oral mucosa
- Warfarin and the newer oral anticoagulants such as dabigatran, have all been associated with acute upper GI bleeding
- The narcotic bowel syndrome is characterized by cycles of abdominal pain and increasing dose escalation of opiates in chronic users, and may be associated with hyperalgesia and constipation. It is an important diagnosis to exclude in these patients
- Microscopic colitis has been associated with use of NSAIDs and PPIs
- Elderly patients can be particularly susceptible to drug-related GI injury, in particular gastroduodenal ulceration and colitis

Introduction

Almost any drug can affect the gastrointestinal (GI) tract. Studies have shown up to 5% of admissions to hospital are associated with drug-induced disorders[1] and 40% of adverse drug reactions affect the GI tract. This contribution highlights drug-induced GI disorders that are common, important or often missed. It is useful to consider drug effects on the GI tract in the four categories below.

Consequences of pharmacological mode of action – adverse drug effects can occur as a predictable result of a drug's mode of action. Thus, drugs with anticholinergic effects (e.g. antidepressants) reduce oesophageal sphincter pressure, resulting in reflux and heartburn; they also reduce colonic transit, resulting in constipation.

Impairment of GI defences – the best-known examples are non-steroidal anti-inflammatory drugs (NSAIDs), which act principally by inhibiting prostaglandin synthesis.

Direct injury to the GI tract – examples include oesophageal damage by potassium preparations, gastroduodenal ulcers caused by cytotoxic drugs, and the ulceration and colitis associated with NSAIDs independent of prostaglandin inhibition.

Changes in colonic bacterial flora – widespread use of antibiotics, particularly cephalosporins, are associated with an increased incidence of *Clostridium difficile* infection and pseudomembranous colitis.

Oral disease

There are few drugs that cause significant problems to the oral mucosa. However, use of head and neck radiotherapy, or cytotoxic agents can lead to oral mucositis, which most commonly affects the oral mucosa but can affect the mucosal lining throughout the GI tract. Mucositis is diagnosed by temporal association and the presence of inflammatory or ulcerative lesions in the mucosal barrier. Therapy is largely conservative. Risk of sepsis is increased particularly in immunosuppressed patients due to loss of the mucosal barrier. Further damage to the mucosa should be minimized. Good oral and dental hygiene, topical and patient-controlled analgesia, and early nutritional assessment are recommended. In some cases injury can be so severe as to impair intake of nutrition owing to severe pain. In these cases nutritional support may be required.[2]

Oesophageal disease

Heartburn

Drugs commonly associated with heartburn and/or oesophageal injury are listed in Table 1. Drugs that relax the lower oesophageal sphincter are particularly likely to cause problems because of the increased acid exposure of the oesophagus (often without mucosal injury). For most drugs, the precise mechanism

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Common drug causes of oesophageal problems

Relax lower oesophageal sphincter causing heartburn
- Anticholinergic agents (e.g. procyclidine, trihexyphenidyl)
- Tricyclic antidepressants
- Calcium channel blockers
- Nitrates
- Phenothiazines

Direct mucosal injury
- Tetracyclines
- Bisphosphonates

Associated with strictures
- Potassium chloride[a]
- Quinidine[a]
- NSAIDs

[a] Particularly modified-release preparations.

Table 1

by which dyspepsia arises is unknown, though there are a few exceptions (e.g. erythromycin, which causes pain as a consequence of its prokinetic activity as a motilin receptor agonist). Drugs such as cytotoxic agents, oral gold and pivampicillin have been associated with peptic ulceration, though the evidence for the association is often informal. Recently, calcium channel antagonists have been implicated in peptic ulcer bleeding.

Patients should be managed by drug withdrawal when possible, though a few may require acid suppression. Endoscopy is not usually required if the onset is clearly related to the drug and the condition settles on drug cessation.

Candida oesophagitis is a common cause of dyspepsia (heartburn) or odynophagia (painful swallowing) in patients taking corticosteroids, antibiotics or immunosuppressive drugs. The characteristic appearance at endoscopy is the formation of discrete white plaques.

Mucosal injury and strictures

NSAIDs and tetracyclines are relatively common causes of erosive or 'pill' oesophagitis. There are case reports of other drugs such as fluoxetine,[3] rifampicin and oral contraceptives causing similar problems. Potassium chloride and quinidine are more strongly associated with stricture, often in the mid-oesophagus, with modified release preparations a particular problem. Bisphosphonates, now commonly prescribed, can cause reversible oesophagitis.[4] Risk of drug injury can be minimized by correct administration in the upright position, with plenty of fluids.

Dyspepsia and gastroduodenal ulcers

Virtually any drug can cause dyspepsia, most commonly without oesophagitis or gastroduodenal ulceration (non-ulcer dyspepsia). Some drugs have been associated with ulceration or ulcer complications. Most attention has focused on NSAIDs. In the past, realistic estimates from the UK attributed about 1000 deaths each year to the use of NSAIDs, but this burden may be reducing as use is declining and the use of protective measures (principally prescribing of PPIs) increasing. Aspirin is an NSAID at anti-inflammatory dosage, which is now hardly ever used. Use at low doses for cardiovascular protection and, more recently, cancer prophylaxis and therapy is growing so that aspirin is more widely prescribed than non-aspirin NSAIDs.

NSAID ulcers and non-ulcer dyspepsia

Non-ulcer dyspepsia is the most common GI adverse effect of NSAIDs, affecting about one-third of users. Uncomplicated ulceration is also common (Figure 1) but often (relatively) silent. Dyspepsia is thus a poor guide to management and patients often present with an unheralded ulcer complication. NSAIDs cause ulcers principally because of inhibition of prostaglandin synthesis.

Estimation of risk — the use of traditional NSAIDs increases the risk of serious GI complications.[5] Recent studies have shown that the cumulative incidence of upper GI complications is approximately 1%.[6]

Risk factors

Patient-associated risk factors: the main concomitant risk factors for ulcer complications are age and previous gastrointestinal bleeding. Some studies suggest that NSAID-induced dyspepsia is particularly common in patients infected with *Helicobacter pylori*. Whether the same is true for ulceration is controversial.

Drug-related risk factors: the main drug-related risk factors are dose and choice of NSAID, co-prescription of corticosteroids and co-prescription of warfarin. The risk of ulcer complications increases with dose. Several meta-analyses have suggested a hierarchy of risk from a low level, with low doses of ibuprofen, through an intermediate level, with diclofenac, to a high level with ketoprofen, piroxicam, naproxen, indometacin. In addition, there was an up to eightfold variation in risk across the recommended dose ranges for each drug.[7] It now seems likely that corticosteroids do not increase the risk of ulceration, except in patients taking NSAIDs.

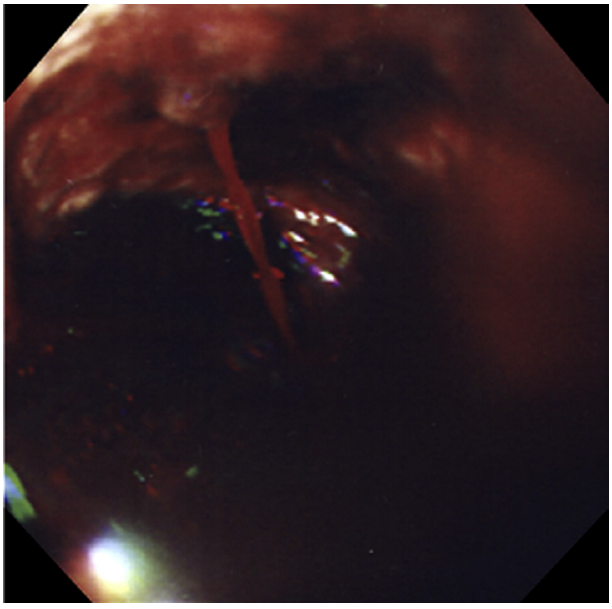

Figure 1 An NSAID-induced gastric ulcer with active bleeding. (Courtesy of *Clinical Gastroenterology and Hepatology*, Mosby, 2005).