

# Drugs and the gastrointestinal system

<b>11.1 Gastric acid-related conditions</b>	<b>149</b>
<b>11.2 Nausea and vomiting</b>	<b>153</b>
<b>11.3 Disorders of the bowel</b>	<b>155</b>
<b>11.4 Gallstones</b>	<b>156</b>
Self-assessment on Chapter 11: questions	<b>158</b>
Self-assessment on Chapter 11: answers	<b>161</b>

## Overview

Conditions related to excessive secretion of gastric acid are extremely common, and include peptic ulcer disease, gastro-oesophageal reflux and nonspecific dyspepsia. Acid-suppressing drugs are very important and widely used in treating these conditions. *Helicobacter pylori* is associated with peptic ulcer disease but to only a very limited extent with simple dyspepsia and not at all with reflux oesophagitis. Eradication of *H. pylori* drastically reduces the relapse rate in peptic ulcer disease.

The causes and treatment of nausea and vomiting are considered. Constipation and diarrhoea are very common symptoms and some causes and symptomatic treatment are considered. Irritable bowel syndrome is a cause of both, and antispasmodics are available for treatment. Inflammatory bowel disease is commonly treated with anti-inflammatory drugs, either locally or systemically.

## 11.1 Gastric acid-related conditions

### Learning objectives

- At the end of this section you should:
- be able to explain the control of acid secretion in the stomach
  - be able to explain how drugs can affect acid secretion and the types of drug used, giving examples
  - know the role of *Helicobacter pylori* in acid-related diseases
  - be able to describe the regimens used for *H. pylori* eradication.

### Clinical sketch

A 28-year-old man goes to his GP complaining of pain in his epigastrium. The pain occurs whenever he eats spicy foods, but also at other times and, in particular, wakes him up at night.

*Comment: as many as one in ten of all GP consultations are for dyspepsia; this is a condition of epigastric pain and it is often difficult to work out from the history what the exact cause is. Causes include peptic ulcer disease, simple dyspepsia, irritable bowel syndrome or more serious pathologies such as gastric cancer. Reflux oesophagitis tends to have a more characteristic history. In at least half of all cases of dyspepsia there is no clear pathological cause. Treatment policies include early endoscopy for all patients, Helicobacter pylori screening to identify patients for endoscopy or specific treatment, or simple empirical treatment. In a young man presenting for the first time like this, simple empirical treatment is probably reasonable management in the first instance.*

## Control of gastric acid secretion

Gastric acid serves many purposes, including providing an optimal environment of proteolytic enzymes to work and enhancing the sterility of stomach contents. It is controlled by CNS and local endocrine effects.

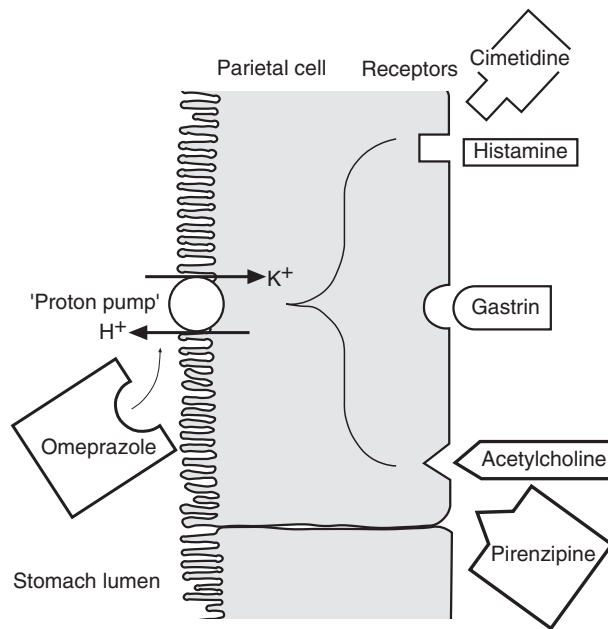
Acid secretion is increased by:

- the vagus nerve secreting acetylcholine
- local nerve endings secreting histamine, which acts on histamine type II receptors
- gastrin secreted by the antrum of the stomach.

Acid secretion is decreased by:

- prostaglandin receptors on the luminal surface of the cell.

All of these mechanisms act ultimately via the 'proton pump' (Fig. 40). Gastrin provides a negative feedback system: an acid environment in the stomach decreases gastrin output, shutting down acid



**Fig. 40** The pharmacology of acid secretion.

secretion, while an alkaline environment (e.g. after eating) stimulates acid secretion.

### Drugs and gastric acid

Drugs may:

- buffer acid secretion: antacids
- decrease acid secretion by
  - blocking acetylcholine receptors
  - blocking histamine H<sub>2</sub> receptors
  - stimulating prostaglandin receptors
  - blocking the final common pathway of all of these mechanisms, i.e. the proton pump.

The principal pathological conditions in which it is useful to reduce acid secretion are:

- simple dyspepsia
- peptic ulcers
- gastro-oesophageal reflux
- Zollinger–Ellison syndrome (a rare gastrin secreting tumour causing very high acid secretion and severe ulceration).

### Peptic ulcers

In peptic ulcers, the balance between protective elements (mucus secretion, gastric blood flow) and harmful elements (acid, exotoxins, drugs) is deranged.

### Duodenal ulcers

These are associated with:

- high acid output
- usually (95%+) *Helicobacter pylori* infection
- no risk of malignancy.

Duodenal ulcers can be cured by acid suppressant therapy alone but have a very high relapse rate (90% at 12 months); this can be reduced by eradication of *H. pylori* (see below).

### Gastric ulcers

These:

- often have low–normal acid output
- are related to *H. pylori* infection in 60–70% of cases
- carry a risk of malignancy
- can be related in some cases to use of non-steroidal anti-inflammatory drugs (NSAIDs; see Ch. 9).

### Complications of peptic ulcers

- pain
- anaemia
- severe bleeding
- perforation
- pyloric stenosis (caused by the fibrosis that follows the acute inflammatory process).

### *Helicobacter pylori* and peptic ulcer

*H. pylori* is spread by the faeco-oral route. It is highly prevalent and is associated with 95%+ of duodenal ulcers and 70% of gastric ulcers. It is less clearly associated with nonspecific dyspepsia and not with gastro-oesophageal reflux disease.

*H. pylori* colonises the antrum of the stomach, where it protects itself by secreting urease. This breaks down urea to ammonia and creates an alkaline microenvironment. Because it interferes with the normal control of acid secretion, acid output increases (Fig. 41). *H. pylori* also secretes exotoxins, directly damaging the mucosa.

Successful eradication of *H. pylori* heals duodenal ulcers and is associated with a very low relapse rate.

### Regimens for *H. pylori* eradication

The usual treatment is with a proton pump inhibitor and two antibiotics. Bismuth-based regimens are possibly slightly superior in effectiveness but they are less convenient and less well tolerated; consequently they usually form second line use only.

**Proton pump inhibitor regimen.** This usually comprises high-dose omeprazole and two antibiotics (any two of clarithromycin, amoxicillin and metronidazole) for 1 week. Clarithromycin regimens are probably slightly more effective.

**Bismuth-based regimen.** This is usually *chelated bismuth* and two antibiotics (*metronidazole* or *tinidazole*, and either *amoxicillin* or *tetracycline*, all in high doses), usually for 2 weeks.

**Clinical sketch**

A 45-year-old woman had peptic ulcer disease diagnosed 2 years ago. She was treated with ranitidine for 12 months, which settled her symptoms, but now they have recurred.

*Comment: peptic ulcer disease is most commonly caused by Helicobacter pylori. Simple acid suppression will allow the ulcer to heal but does not remove the underlying cause and relapse is likely, as in this patient.*

**Clinical sketch**

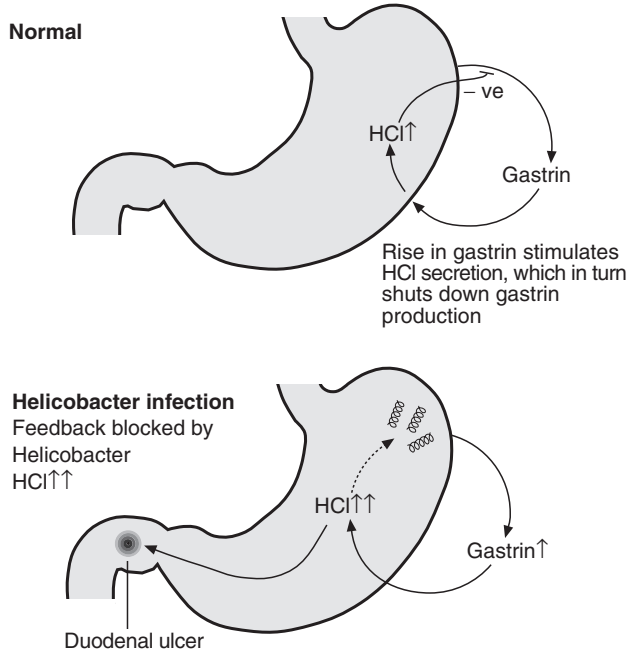
A 50-year-old man has peptic ulcer disease diagnosed as related to *Helicobacter pylori*. He is given an eradication course of treatment and his symptoms settle. However, a year later his symptoms recur and retesting shows the presence of *H. pylori*.

*Comment: re-infection with H. pylori occurs at the rate of about 1% per year. The alternative explanation in this patient is that eradication therapy was unsuccessful, either because the patient had resistant H. pylori or (as is frequently the case) the patient was not compliant with the full course of therapy to eradicate the infection.*

**NSAIDs and peptic ulcers**

NSAIDs (see Ch. 9) may cause peptic ulcer (especially gastric) by decreasing local prostaglandin secretion in the gastric mucosa and hence reducing mucosal blood flow, mucus secretion and other protective factors. This may occur regardless of the route of administration of the NSAID. Many NSAIDs may also have a direct irritant effect on the gastric mucosa. NSAIDs are a relatively common cause of gastrointestinal bleeding because of these effects.

Appropriate treatment is withdrawal of the NSAID if possible; if necessary, antisecretory drugs (see below) or the prostaglandin analogue *misoprostol* may be used.



**Fig. 41** *Helicobacter pylori* in peptic ulcer disease.

**Clinical sketch**

A 72-year-old woman taking diclofenac for her arthritis presents to hospital with haematemesis (vomiting blood).

*Comment: irritant drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) can also cause peptic ulcer disease or can cause a flare up in existing peptic ulcer disease. These gastrointestinal complications are among the most serious for NSAIDs. They may occur without any prior warning of dyspepsia and present with a serious complication, as in this case. This patient needs to have her NSAID withdrawn and needs an urgent endoscopy. She may also require blood transfusion or even surgery if the bleeding fails to stop spontaneously. She should avoid NSAIDs in the future, probably including Cox-2 selective drugs. Many patients receive acid-suppressant drugs such as proton pump inhibitors with their NSAIDs because they are considered to be at risk of such complications. A better approach, however, would be careful selection of those patients who receive NSAIDs, which are commonly overused.*

**Gastro-oesophageal reflux**

Gastric contents regurgitate into the oesophagus in some patients with an incompetent gastro-oesophageal sphincter, causing heartburn or severe pain. In severe cases, complications such as erosions,

## Eleven: Drugs and the gastrointestinal system

bleeding and stricture may occur. Management involves general measures (weight loss if obese, avoiding tight clothes around the waist, avoiding stooping, elevating the head of the bed to reduce nocturnal reflux) and, often, drug therapy.

Therapy includes:

- antacids: particularly antacids combined with alginate, which coats the oesophagus and reduces the contact with acid
- antisecretory drugs: proton pump inhibitors are usually highly effective in severe cases. Long-term use may be necessary in some patients. Histamine H<sub>2</sub> blockers are effective in less severe cases
- prokinetic drugs. *Metoclopramide* and *domperidone* are discussed under antiemetics (see below) but both increase lower oesophageal sphincter pressure and increase gastric clearance, in addition to their central effects.

### Acid-modifying drugs

#### Antacids

Antacids are weak alkalis used for symptomatic relief. They:

- neutralise the acid secreted by the parietal cells
- are generally not absorbed and so cause no systemic effects
- may also reduce the absorption of other drugs, e.g. tetracyclines or digoxin.

#### Examples

*Aluminium hydroxide* (tends to cause constipation) or *magnesium trisilicate* (diarrhoea). *Sodium bicarbonate* is sometimes taken as a popular home remedy for dyspepsia. It is not recommended because it is absorbed and if used in large amounts can cause systemic alkalosis.

#### Histamine receptor antagonists

These drugs act by antagonising histamine at H<sub>2</sub> receptors. They:

- decrease acid secretion, especially at night and during fasting
- heal almost all duodenal ulcers after 4–8 weeks: gastric ulcers heal more slowly and may require higher doses for longer. There is a high relapse rate unless *H. pylori* is treated also
- are also effective in reflux oesophagitis, but here high-dose long-term therapy is often necessary
- relieve symptoms in many patients who have dyspepsia without any clear organic lesion.

Many patients take H<sub>2</sub> receptor antagonists indefinitely, or in repeated courses.

#### Clinical sketch

A 47-year-old woman has severe reflux oesophagitis confirmed on endoscopy. Initial treatment with ranitidine is partly successful, but she continues to have a lot of pain.

*Comment: in severe cases of reflux oesophagitis, proton pump inhibitors are more effective. In general, proton pump inhibitors decrease acid secretion to a greater extent than histamine H<sub>2</sub>-blockers, even in a high dose. Such intense acid suppression is not always necessary in acid-related conditions.*

#### Examples

*Cimetidine* and *ranitidine* are both well absorbed after oral administration, but both can also be given i.v. They are excreted unchanged by the kidney.

#### Adverse effects

*Cimetidine* has weak antiandrogen effects and occasionally causes gynaecomastia in long-term use. This is less common with *ranitidine*. Either may cause confusion and drowsiness in the elderly.

#### Interactions

*Cimetidine* inhibits drug-metabolising enzymes in the liver and may increase the effects and toxicity of many drugs (see Ch. 21).

#### Proton pump inhibitors

The H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme ('proton pump') is irreversibly inhibited by these drugs, and so acid production ceases. Acid secretion can only resume when new enzyme has been formed. They:

- are the most effective acid suppressants: heal acid-related diseases faster and to a greater extent than other drugs
- have a high relapse rate in peptic ulcers unless *H. pylori* is eradicated
- form long-term therapy in reflux oesophagitis commonly
- are used, in high doses, to treat Zollinger–Ellison syndrome.

#### Examples

*Omeprazole* is metabolised by the liver. Because of the irreversible inhibition of the proton pump, its duration of action is considerably longer than its half-life and *omeprazole* is usually administered once per day. *Lansoprazole* is similar. *Esomeprazole* is

a stereo-isomer of omeprazole and is used for intermittent treatment of gastro-oesophageal reflux disease.

### Adverse effects

- headache
- nausea, vomiting and diarrhoea.

### Interactions

Omeprazole can inhibit some hepatic drug-metabolising enzymes.

### Prostaglandin E<sub>1</sub> analogues: misoprostol

Prostaglandin E<sub>1</sub> decreases acid secretion by an action on a receptor on the surface of the parietal cell. It may have an effect in protecting the mucosa of the stomach, perhaps by increasing mucosal blood flow and mucus and duodenal bicarbonate secretion.

### Example

*Misoprostol* is an analogue of prostaglandin E<sub>1</sub> with a half-life of 2 hours. It is well absorbed and is metabolised to active metabolites. While misoprostol can heal peptic ulcers, H<sub>2</sub>-blockers or proton pump inhibitors are better and easier to take. Misoprostol is also used in the induction of abortion as it causes uterine contractions.

### Contraindication

In pregnant women, it may cause miscarriages.

### Adverse effects

- crampy abdominal pains
- diarrhoea.

### Prophylaxis in patients taking NSAIDs (see Ch. 9)

Prophylactic therapy may be advisable in patients at high risk (e.g. those who require a NSAID despite a previous history of peptic ulcer disease); its routine use in all patients taking NSAIDs is not justified. Misoprostol may have a role in the treatment and prophylaxis of ulcers caused by NSAIDs. However, proton pump inhibitors are more pleasant to take and more widely used as prophylaxis than misoprostol.

### Drugs with no effect on acid secretion

These drugs are believed to enhance the protective elements by forming a protective coating over the ulcer crater and allowing healing to occur under-

neath. They may also have a separate action in stimulating local prostaglandin release. They are not used often today.

### Chelated bismuth

This has some activity against *H. pylori* infection and also protects the ulcer crater and allows healing.

It is given orally and a small quantity is absorbed; this is later excreted through the kidney.

### Adverse effects

- metallic taste
- blackening of faeces
- encephalopathy, if used in high doses for prolonged periods; bismuth should not be used repeatedly or for more than 2 months at a time.

### Sucralfate

Sucralfate is an aluminum salt of sucrose. It heals peptic ulcers as effectively as histamine H<sub>2</sub>-blockers but is less convenient.

It causes constipation.

### Carbenoxolone

Carbenoxolone is a derivative of licorice. It stimulates gastric mucus secretion as well as protecting the ulcer. It is also used in treatment for reflux oesophagitis.

### Adverse effects

Carbenoxolone has mineralocorticoid effects and may cause sodium retention and hypokalaemia; this could be serious in patients with cardiac failure.

## 11.2 Nausea and vomiting

### Learning objectives

- At the end of this section you should:
  - understand the mechanisms that may cause nausea and vomiting
  - be able to describe the drugs that can be used to prevent or treat nausea and vomiting.

### Clinical sketch

A patient with migraine is unable to take simple analgesics because of the associated nausea and vomiting from the migraine.

*Comment: combined use of analgesic and a simple antiemetic such as metoclopramide is appropriate. This also has effects overcoming the gastric stasis common in migraine treated with an analgesic.*

## Eleven: Drugs and the gastrointestinal system

Nausea and vomiting are common nonspecific features of disease or drug toxicity and the cause should be diagnosed and treated where possible. Drugs to treat nausea and vomiting may be given orally or parenterally (i.m. or i.v.).

Vomiting is caused by activation of the vomiting centre in the brainstem, mainly via the vagus nerve. The vomiting centre is also influenced by the vestibular apparatus, by the cerebral cortex, by afferents from the gastrointestinal tract and by the chemoreceptor trigger zone, through muscarinic and histamine ( $H_1$ ) receptors. The chemoreceptor trigger zone is another region of the brainstem and is activated by afferents (often  $D_2$  dopaminergic) similar to those of the vomiting centre. In addition it is activated by toxins, including drugs.

### Antiemetics

Antiemetics may act in several different ways (Fig. 42).

**Anticholinergic drugs.** These act on the vomiting centre especially but also affect the gastrointestinal tract directly, for example *hyoscine*. Adverse effects are typical of anticholinergic drugs and include dry mouth, occasionally confusion and agitation.

**Antihistamines.** These act on  $H_1$  receptors in the vomiting centre and also have weak anticholinergic and sedating effects. Newer non-sedating antihistamines are not effective. The antihistamines are frequently used to treat motion sickness or vestibular disease (often inappropriately in the elderly). Example: *promethazine*.

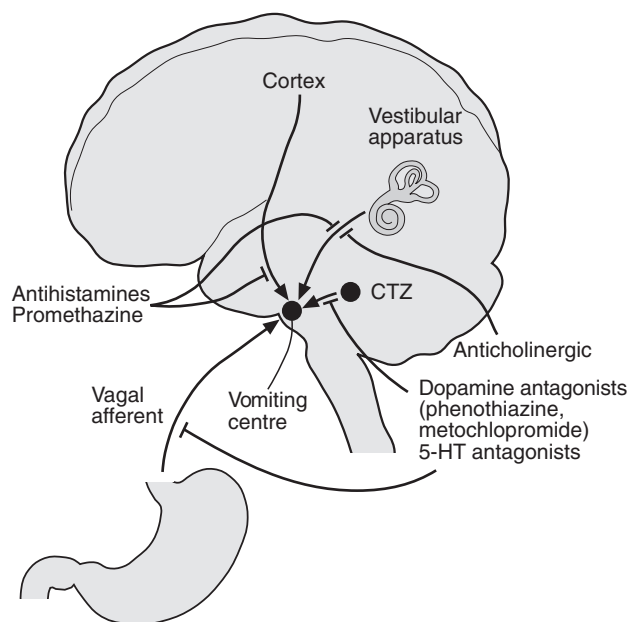


Fig. 42 Central actions of antiemetics.

**Phenothiazines.** In addition to anticholinergic, sedative and  $H_1$ -blocking effects, the phenothiazines also block dopamine receptors in the chemoreceptor trigger zone. Example: *prochlorperazine*.

*Adverse effects* include parkinsonism (see Ch. 6 for fuller description).

**Dopamine receptor antagonists.** *Metoclopramide* acts in the chemoreceptor trigger zone and has direct effects on the gastrointestinal tract (see above). It is given orally or parenterally for most causes of vomiting, although it is not effective for motion sickness.

*Adverse effects* include acute extrapyramidal reactions, such as oculogyric crisis, especially in children or young women (treat with parenteral anticholinergic such as benztropine). Increased prolactin concentrations and gynaecomastia can occur in prolonged use.

**Domperidone** is similar to metoclopramide but is less likely to cause extrapyramidal reactions; it can, however, cause cardiac arrhythmias when given parenterally in high dose.

**5-Hydroxytryptamine (5-HT) antagonists.** *Ondansetron* is one of several  $5-HT_3$  antagonists, which are very effective in treating severe nausea and vomiting, particularly after anticancer chemotherapy but also postoperatively. They are often reserved for cases where other drugs are ineffective.

*Adverse effects* include constipation and headache.

### Other drugs

*Aprepitant* is a neurokinin receptor antagonist and *nabilone* is a cannabinoid, both used orally to treat nausea and vomiting associated with chemotherapy which does not respond to other drugs.

### Choice of drug

- Postoperatively: phenothiazines, metoclopramide or a 5-HT antagonist are used.
- Pregnancy: drugs should be avoided in pregnancy as much as possible. Simple rehydration (perhaps intravenously) is enough in many cases. If drugs are necessary, the antihistamine promethazine is usually recommended.
- After chemotherapy: in regimens which are highly likely to cause vomiting, 5-HT antagonists are usually recommended. In regimens less prone to cause vomiting, metoclopramide or domperidone may be used. Consider dexamethasone and lorazepam which are also used to treat nausea with some chemotherapeutic regimens.

- After opiates: a phenothiazine may be used.
- Motion sickness: hyoscine is best but phenothiazines or antihistamines (with some anticholinergic action) are also useful.

## 11.3 Disorders of the bowel

### Learning objectives

At the end of this section you should:

- be aware that disorders of the bowel are common, often resolve without treatment and can be secondary to drug therapy and inflammatory conditions as well as infections
- know the main treatment possibilities and when to use them.

Disturbances of bowel habit are common and often resolve spontaneously without treatment. The cause should be identified if possible and treated as necessary. Bowel disturbance may be an adverse effect of many drugs (e.g. opiates and tricyclics can cause constipation, antibiotics can cause diarrhoea).

### Treatment of constipation

Constipation can often be treated effectively with dietary modification, with increased fibre and fluids; and with careful education of the patient. Only if this fails should laxatives be used, adjusting the dose to achieve the desired effect (Fig. 43). In order of preference:

1. the bulking agents
2. osmotic laxatives
3. stimulant drugs (reserved for intermittent use)
4. the faecal softeners (used less often).

#### Bulking agents

Bulking agents absorb water, swell and increase the bulk of the stool. This increased bulk stimulates normal peristalsis and hence defaecation. They may take a few days to act fully and may cause flatulence and crampy abdominal pain at first. They are given orally.

Examples: *bran, ispaghula*.

#### Osmotic laxatives

The osmotic laxatives reduce absorption of water from the bowel. This softens the stool and increases its bulk, stimulating peristalsis.

*Lactulose* is a disaccharide that is broken down by colonic bacteria to acetic and lactic acid, which cause

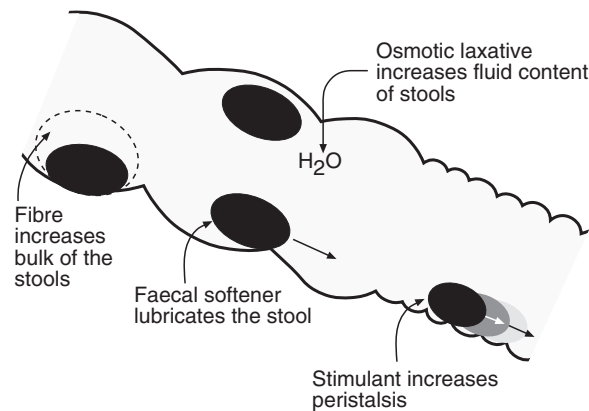


Fig. 43 Laxatives.

the osmotic effects. Polyethylene glycols are non-absorbed inert compounds. Both are taken orally. Adverse effects include abdominal pain and flatulence. *Phosphate* or *magnesium* salts are used as enemas.

#### Stimulants

Stimulants are drugs used to stimulate peristalsis and are indicated for severe chronic constipation or where a more rapid effect (within 6–8 hours) is required. They may cause atony of the bowel if used chronically, creating a vicious cycle of laxative use/constipation/laxative use for the patient. Stimulants are usually given orally.

Examples: *senna, bisacodyl, castor oil*.

#### Faecal softeners

The faecal softeners lubricate and soften the stool and are usually given orally.

Examples: *liquid paraffin*. (There is a risk of aspiration lipid pneumonia with liquid paraffin.)

### Treatment of diarrhoea

#### Clinical sketch

A 22-month-old child develops profuse diarrhoea. The GP tells the mother that this is infective gastroenteritis. The mother asks the GP for an antidiarrhoeal agent and an antibiotic.

*Comment: the priority in treating a child with diarrhoea is maintaining hydration of the child; oral rehydration therapy (dilute solutions of essential salts) is the correct therapy, but intravenous fluid administration in hospital may be necessary. Children die from dehydration in infective gastroenteritis. The use of antibiotics or antidiarrhoeal agents is entirely inappropriate in this setting.*

## Eleven: Drugs and the gastrointestinal system

In treating diarrhoea, especially in children, it is vitally important to replace fluid and electrolyte losses. Since most cases of diarrhoea are self-limiting, this is often all that is necessary, and the use of specific antidiarrhoeal drugs is often inappropriate.

### Antimotility drugs

Antimotility drugs reduce peristalsis by stimulating opioid receptors in the bowel. An adverse effect is constipation.

Examples: *loperamide*, *diphenoxylate* are pethidine derivatives that act only in the bowel. Diphenoxylate is often combined with atropine. *Codeine phosphate* and *morphine* (Ch. 7) are also occasionally used.

### Adsorbents

Some drugs absorb water without increasing stool bulk, so making the stool firmer and smaller, for example *kaolin*.

### Irritable bowel syndrome

Irritable bowel syndrome is common (30% of women, 15% of men) and is caused by dysmotility of the bowel. It overlaps in some cases with simple dyspepsia. Many new drugs are currently in development for this potentially large market.

Symptoms include intermittent diarrhoea and constipation, and abdominal pain.

Drug treatment is currently symptomatic, i.e. treat pain, constipation or diarrhoea as required.

### Antispasmodics

Anticholinergic drugs decrease bowel motility by reducing peristalsis and are used orally to treat painful spasm of the large bowel.

Examples: *mebeverine*, which has little systemic anticholinergic effect; *propantheline*, which has more systemic effects and which is also used parenterally to relieve severe pain associated with spasm, e.g. in biliary colic.

### Inflammatory bowel diseases

The cause of the chronic inflammatory diseases is not known. Ulcerative colitis affects the large bowel; Crohn's disease affects mainly the small bowel but also the large bowel and other parts of the gastrointestinal tract. Both diseases typically undergo exacerbations and remissions.

The aim of treatment is to resolve the acute episodes and prolong remissions. In addition to

drug therapy, treatment involves correction of any nutritional deficiencies (enteral feeding may be effective in Crohn's) and sometimes surgery for complications or severe uncontrolled disease.

### Anti-inflammatory drugs

Drug treatment is with anti-inflammatory drugs, especially the corticosteroids, which are used systemically in severe acute attacks (e.g. *prednisolone* or *hydrocortisone*) (see Ch. 12). They may also be given locally by means of enemas for less severe acute attacks involving the large bowel, or as maintenance therapy. Other anti-inflammatories such as *azathioprine* or *ciclosporin* (see Ch. 9) are also occasionally used.

*Infliximab* is a monoclonal antibody which inhibits the actions of the inflammatory cytokine tumour necrosis factor (TNF)  $\alpha$ . It is used in refractory Crohn's disease. It is also used in rheumatoid arthritis.

### Aminosalicylates

5-Aminosalicylate (5-ASA) is the active drug, effective in treatment and maintenance of colonic disease in ulcerative colitis or Crohn's disease.

*Sulfasalazine* is a complex of a sulphonamide, *sulfapyridine*, and 5-ASA. The complex is taken orally or rectally and is broken down by bacteria in the large bowel to release the 5-ASA. It is also used as a disease-modifying drug in rheumatoid arthritis (see Ch. 9).

*Mesalazine* is another name for 5-ASA and can be given orally or rectally as an enema.

*Olsalazine* is two molecules of 5-ASA combined, given orally.

### Adverse effects

Adverse effects are mainly because of the sulfapyridine content: headache, nausea and vomiting, rashes and occasionally blood dyscrasias and renal dysfunction. Infertility in males can occur because of decreased sperm count.

Adverse effects of 5-ASA: diarrhoea, occasionally blood disorders (patients should be advised to report any purpura, unexplained bruising or sore throat or fever and a full blood count should then be done).

## 11.4 Gallstones

In the developed world, gallstones are usually made of cholesterol.

**Bile acids**

Bile acids may be used to gradually dissolve cholesterol gallstones. This is only suitable for small stones, as 3–6 months of treatment is required. Recurrence

is common. Bile acid treatment for gallstones is generally reserved for patients who are unfit for surgery. Diarrhoea is an adverse effect.

Examples: *chenodeoxycholic acid*, *ursodeoxycholic acid*.



## Self-assessment on Chapter 11: questions

### Multiple choice questions

- In duodenal ulcers:
  - H. pylori* is present in almost all cases
  - Relapse after treatment with omeprazole is rare
  - H. pylori* secretes a urease enzyme
  - Basal acid secretion is increased
  - Attempts to eradicate *H. pylori* are rarely successful
- In conditions where gastric acid secretion causes symptoms:
  - Antacids are mainly used for symptomatic relief
  - H<sub>2</sub> receptor antagonists block all acid secretion
  - Ranitidine may commonly cause drug interactions
  - The final common pathway of all stimuli to acid secretion is the proton pump
  - Omeprazole is very effective in reflux oesophagitis
- In treating peptic ulcer disease:
  - Misoprostol is used to treat the gastrointestinal adverse effects of NSAIDs
  - All patients taking NSAIDs should also take misoprostol
  - Chelated bismuth can be used
  - Long-term bismuth is used to maintain remission in peptic ulcer disease
  - Sucralfate may cause diarrhoea
- In the treatment of gastric motility disorders:
  - Metoclopramide may enhance drug absorption
  - Metoclopramide may cause severe dystonic reactions
  - Hyperprolactinaemia may be a result of taking antidopaminergic drugs
  - Domperidone increases large bowel motility
  - Bisacodyl inhibits peristalsis.
- Drugs used to treat nausea include:
  - Ondansetron
  - Prochlorperazine
  - Bromocriptine
  - Atropine
  - Dexamethasone
- Bowel disturbance may arise as a result of treatment with:
  - Disopyramide
  - Omeprazole
  - Erythromycin
  - Iron salts
  - Morphine
- In treating disturbances of bowel motility:
  - Rehydration is more important than using antidiarrhoeal drugs
  - Sulfasalazine is used to treat irritable bowel syndrome
  - Lactulose is most effective for treating morphine-induced constipation
  - In treating constipation, improving diet is often more important than drug therapy
  - Overdose of diphenoxylate may be treated with naloxone
- In treating inflammatory bowel disease:
  - Corticosteroids are the main anti-inflammatory drugs used to treat acute ulcerative colitis
  - Steroids are always used topically in inflammatory bowel disease
  - 5-ASA may cause male infertility
  - Patients may need to have their full blood count monitored
  - Infliximab is given orally or rectally

### Case history questions

#### Case history 1

A 30 year old patient complains of upper abdominal pain and is treated by his GP with omeprazole for a month. The pain recurs after the omeprazole is stopped and the patient is sent for a gastroscopy. This shows a duodenal ulcer. Antral biopsies show *Helicobacter pylori*.

1. Should this patient have received treatment to eradicate *H. pylori* on first presentation?
2. What treatment should be given to eradicate *H. pylori*?
3. What treatment might be given to heal the peptic ulcer?
4. If therapy to eradicate *H. pylori* is not given, what are the risks of recurrence?
5. Does the patient need a further endoscopy to check if the ulcer has in fact healed?
6. The patient later develops osteoarthritis of the knee; should he be given a non-steroidal anti-inflammatory drug (NSAID)?

### Case history 2

A patient has gastro-oesophageal reflux proven on endoscopy.

1. Apart from non-pharmacological treatments, what drugs might be considered?
2. How might metoclopramide be helpful?
3. What drugs might aggravate this condition?
4. How should severe cases be treated?
5. What are the adverse effects of omeprazole?

### Case history 3

An elderly patient resident in a nursing home is constipated, i.e. no bowel motion passed for 5 days.

1. What drugs might cause constipation?
2. What other causative factors should be considered in this patient's constipation?
3. If dietary treatment is unsuccessful in this patient, what drug treatment should be considered?
4. What are the harmful effects of long-term use of senna or other stimulant laxatives?
5. What drug therapies might be useful in acute severe constipation?

### Short note questions

Write short notes on:

1. Treatment of *Helicobacter pylori* infection
2. Acid-suppressant drugs
3. Drugs in the treatment of reflux oesophagitis.

### Extended matching items questions

Theme: Upper gastrointestinal disorders

#### Options

- A. Omeprazole
- B. Cimetidine
- C. Clarithromycin
- D. Ranitidine
- E. Metronidazole
- F. Lansoprazole
- G. Metoclopramide
- H. Erythromycin
- I. Loratadine

For each of 1–6 below, choose the most appropriate option from the list above. Each option may be used once, more than once, or not at all.

1. Select three drugs that might be used together in the eradication of *Helicobacter pylori*.
2. Select a drug to treat postoperative vomiting.
3. Select a drug that binds to histamine H<sub>2</sub> receptors.
4. Select a drug that increases gastric motility.
5. Which drugs might cause drug interactions by liver enzyme inhibition?
6. Which drug or drugs might be used to treat or prevent NSAID-induced ulceration?

Theme: Lower gastrointestinal disorders

#### Options

- A. Diphenoxylate
- B. Lactulose
- C. 5-ASA
- D. Infliximab
- E. Mebeverine
- F. Bisacodyl
- G. Metoclopramide

For each of the questions below, choose the most appropriate options from the list above. Each option may be used once, more than once, or not at all.

1. Which drug or drugs would be best to treat opiate-induced constipation?

## Questions

---

2. Which drug or drugs might cause diarrhoea?
3. Which drug or drugs might be used to treat Crohn's disease?
4. Which drug is most likely to be fatal in overdose (e.g. in children)?
5. Which drug or drugs can be used in irritable bowel syndrome?



## Self-assessment on Chapter 11: answers

### Multiple choice answers

1. a. **True.** Its association with gastric ulcers is less certain.  
 b. **False.** Relapse is frequent since the cause of the peptic ulcer, the *H. pylori* infection, persists.  
 c. **True.** This is how it protects itself from stomach acid.  
 d. **True.** As a result of blockage of negative feedback on gastrin.  
 e. **False.** Triple therapy with proton pump inhibitors, bismuth and antibiotics is successful in about 90% of cases, if the patient is compliant with therapy.
2. a. **True.** Very high but unpalatable doses can be used to heal ulcers also.  
 b. **False.** Acid production is reduced by about 70–80%.  
 c. **False.** Cimetidine, however, does, because of its effects on liver enzymes.  
 d. **True.** Hence omeprazole is the most effective of all antisecretory drugs.  
 e. **True.** Again, omeprazole is the most effective treatment.
3. a. **True.** By replacing the decreased mucosal prostaglandins.  
 b. **False.** It is unnecessary in many patients, has adverse effects of its own and adds considerably to the costs.  
 c. **True.** Less widely used today because it is less pleasant than alternatives and because we now know of the importance of treating *H. pylori*.  
 d. **False.** There would be a serious risk of bismuth encephalopathy.  
 e. **False.** Sucralfate tends to cause constipation.
4. a. **True.** For instance, used with paracetamol in patients with migraine.  
 b. **True.** Especially in children or young women.  
 c. **True.** Because dopamine inhibits prolactin release from the pituitary.  
 d. **False.** Domperidone may stimulate upper gastrointestinal motility, but not lower.  
 e. **False.** Bisacodyl stimulates peristalsis and is used in the management of constipation.
5. a. **True.** A 5-HT<sub>3</sub> antagonist.  
 b. **True.** Widely and perhaps excessively used.  
 c. **False.** Bromocriptine is a dopamine agonist, and its adverse effects include nausea.  
 d. **False.** Although the anticholinergic hyoscine is used.  
 e. **True.** Especially after anticancer chemotherapy.
6. a. **True.** Anticholinergic, so may cause constipation.  
 b. **True.** Diarrhoea.  
 c. **True.** Diarrhoea (one of its most frequent effects), and so may many other antibiotics.  
 d. **True.** Constipation.  
 e. **True.** Constipation.
7. a. **True.** Often forgotten.  
 b. **False.** Sulfasalazine is used to treat inflammatory bowel disease of the colon.  
 c. **False.** A stimulant laxative is usually needed.  
 d. **True.** Very important and often forgotten. High fibre diets and improving fluid intake can be very effective.  
 e. **True.** Diphenoxylate is an opioid.
8. a. **True.** Either systemically or topically depending on the severity of the illness.  
 b. **False.** Topical use will limit adverse effects and is desirable wherever possible but systemic steroids will need to be used in many cases.  
 c. **False.** This is an adverse effect of sulfapyridine, part of sulfasalazine.  
 d. **True.** For several reasons: firstly because the disease itself may cause bleeding or in the case of Crohn's nutritional problems, but also because many of the drugs used (e.g. 5-ASA or more powerful immunosuppressants) may affect the blood.

## Answers

- e. **False.** Infliximab is a monoclonal antibody, or protein; it will be digested if given orally. It is not absorbed across mucous membranes.

## Case history answers

### Case history 1

1. In general, current opinion is that he should not. The link between *H. pylori* and simple dyspepsia is not strong and anti-*H. pylori* treatment will benefit relatively few patients while causing adverse effects in some. There is an argument for endoscopy all patients with dyspepsia early to make a definitive diagnosis, especially in older patients (over 55) where the possibility of finding serious pathology is increased. However, in a young person like this, symptomatic treatment in the first instance is reasonable. However, once he is known to have a duodenal ulcer, more specific treatment is certainly warranted.
2. Triple therapy with omeprazole or other proton pump inhibitor, metronidazole, and amoxicillin or clarithromycin is the standard therapy at present: many other, perhaps more acceptable, regimens are also suitable.
3. The ulcer will heal if *H. pylori* is eradicated but more slowly. Giving a longer course of a proton pump inhibitor beyond the usual *H. pylori* course will speed healing up.
4. The recurrence rate at 1 year is 80–90%.
5. This is not usually necessary. Many would do a noninvasive hydrogen breath test to confirm eradication of the *H. pylori* and if not eradicated first time, treat again with an alternative regimen.
6. NSAIDs should be avoided wherever possible in patients with peptic ulcer disease, even if healed. Patients with osteoarthritis often need only analgesia and not an anti-inflammatory, so paracetamol used regularly might be sufficient. If the patient had a true inflammatory arthropathy, a Cox-2 selective NSAID or a standard NSAID might be necessary and prophylactic therapy with misoprostol or omeprazole should be considered.

### Case history 2

1. Drug treatment would normally be an antacid with alginate, drugs to suppress acid secretion,

or occasionally prokinetic agents – or combinations of these.

2. Metoclopramide increases the tone of the lower oesophageal sphincter and increases gastric emptying.
3. Drugs with an anticholinergic adverse effect decrease lower oesophageal tone, as do smooth muscle relaxants (e.g. calcium-channel blockers).
4. The drug of choice in severe cases is omeprazole, which is exceedingly effective and may be needed for long-term maintenance in some patients.
5. Omeprazole may cause headache, diarrhoea and drug interactions.

### Case history 3

1. Drugs with anticholinergic adverse effects, such as tricyclic anticonvulsants or phenothiazines, also opiate analgesics.
2. Hypothyroidism and depression should be excluded. Other factors include poor diet (deficient in fibre), immobility and dehydration.
3. The first line of drug treatment is usually supplementation of fibre intake, either by diet or by use of a bulking agent, followed by an osmotic laxative and finally intermittent use of a stimulant laxative.
4. Atony of the bowel and laxative dependency.
5. Local treatment with suppositories (e.g. glycerin or bisacodyl) or by enema (e.g. phosphate enema) may be useful in acute severe cases: serious pathology, e.g. intestinal obstruction, should be excluded first.

## Short note answers

1. This should mention regimens including 2 weeks with a proton pump inhibitor with two antibiotics. Reserve schemes should include mention of bismuth-based preparations in combination with antibiotics.
2. This should discuss histamine H<sub>2</sub>-blockers, proton pump inhibitors and, for the very perceptive student, anticholinergics, although these are no longer used therapeutically.
3. This might describe antacids with alginates, histamine H<sub>2</sub>-blockers and proton pump inhibitors (PPIs). Description of the drugs alone would not suffice here; a student would

also be expected to show an awareness of how the drugs are used, and which are the most effective approaches, etc. An alternative would be a step-up approach – using antacids, H<sub>2</sub>-blockers if not resolved, and then PPIs if still not resolved – or a step-down approach – using high-dose PPIs to heal inflammation and then settling down to a maintenance dose, possibly given intermittently in mild cases. Both regimens have their advocates. In severely affected patients, PPIs are by far the most effective.

### Extended matching items answers

#### Theme: Upper gastrointestinal disorders

1. A, C, E or F, C, and E. These are standard regimens, a proton pump inhibitor with two antibiotics, for 2 weeks.
2. G. Metoclopramide is a standard antiemetic.
3. B or D. (Loratadine binds to histamine H<sub>1</sub> receptors; see Ch. 10 on hypersensitivity.)
4. G or H (surprisingly). Metoclopramide increases gastric motility. So too does erythromycin, which seems to act at specific receptors. This is partly the basis of its common adverse effects. It is used as a gastric stimulant occasionally, for instance in patients

with severe gastric stasis secondary to diabetic autonomic neuropathy.

5. A and B (and H). Omeprazole and cimetidine inhibit the metabolism of drugs such as warfarin and phenytoin, among others.
6. A or F would be best. B and D could be used but are less effective.

#### Theme: Lower gastrointestinal disorders

1. F. A stimulant laxative would be most useful.
2. B or F. This may seem incredibly obvious but is often overlooked.
3. C or D. C is used to treat mild Crohn's of the colon, just as it is in ulcerative colitis. D is used in refractory disease, especially where there are fistulas that fail to heal.
4. A. It is an opiate. A propriety preparation containing diphenoxylate and atropine is available over the counter and might be misused to treat diarrhoea in children – this is a problem for two reasons: first the proper treatment for diarrhoea in children is usually rehydration; second, the combination can be very dangerous in overdose in children.
5. A, B, E, D. The choice depends on what symptoms are the most prominent in individual patients: pain, diarrhoea or constipation.

