1: GASTRO-INTESTINAL SYSTEM

ANTACIDS AHFS 56:04

Antacids taken by mouth to neutralize gastric acid include:
- magnesium salts
- aluminum hydroxide
- hydrotalcite/aluminum magnesium carbonate (not USA)
- calcium carbonate
- sodium bicarbonate.

Magnesium salts *are laxative and can cause diarrhea*; ***aluminum salts*** *constipate*. Most proprietary antacids contain a mixture of **magnesium salts** and **aluminum salts** so as to have a neutral impact on intestinal transit. With doses of 100–200mL/24h or more, the effect of **magnesium salts** increasingly overrides the constipating effect of **aluminum**.

The sodium content of some antacids may be detrimental in patients on salt-restricted diets, e.g. those with hypertension or heart failure; Gaviscon® liquid and **magnesium trisilicate mixture USP** both contain 1.14mEq/10mL compared with 0.13mEq/10mL in Maalox® Antacid/AntiGas®. Regular use of **sodium bicarbonate** may cause sodium loading and metabolic alkalosis. **Calcium carbonate** may cause rebound acid secretion about 2h after each dose, and regular use may cause hypercalcemia, particularly if taken with **sodium bicarbonate**.

Aluminum hydroxide binds dietary phosphate. It is of benefit in patients with hyperphosphatemia in renal failure. Long-term complications of phosphate depletion and osteomalacia are not an issue in advanced cancer.

Hydrotalcite (not USA) binds bile salts and is of specific benefit in patients with bile salt reflux, e.g. after certain forms of gastroduodenal surgery.

In post-radiation esophagitis and candidosis which is causing painful swallowing, an **aluminum hydroxide-magnesium hydroxide** suspension containing **oxethazine** (Mucaine®; not USA), a local anesthetic, can be helpful. Give 5–10mL (without fluid) 15min a.c. & at bedtime, and p.r.n. before drinks.

This should be regarded as short-term symptomatic treatment while time and specific treatment of the underlying condition permits healing of the damaged mucosa. Alternatively, plain **benzocaine** suspension 150mg/mL can be used.

The following should be borne in mind:
- *the administration of antacids should be separated from the administration of EC tablets*; direct contact between EC tablets and antacids may result in damage to the enteric coating with consequential exposure of the drug to gastric acid, and of the stomach mucosa to the drug
- apart from **sodium bicarbonate**, antacids delay gastric emptying and may thereby modify drug absorption
- some proprietary products contain peppermint oil which masks the chalky taste of the antacid and helps belching by decreasing the tone of the lower esophageal sphincter
- most antacid tablets feel gritty when sucked; some patients dislike this
- some proprietary products are fruit-flavored, e.g. Tums® (chewable tablet)
- the cheapest products are **magnesium trisilicate mixture USP** and **aluminum hydroxide gel USP** given alone or as a mixture
- some antacids contain additional substances for use in specific situations, e.g. **sodium alginate** (see below), **simethicone** (see p.3).

Nowadays, antacids are generally only used p.r.n. for occasional dyspepsia; H_2-receptor antagonists (see p.13) and PPIs (see p.17) are used when continuous gastric acid reduction is indicated.

COMPOUND ALGINATE PRODUCTS AHFS 56:04

Included for general information. Alginate products are generally *not recommended* as antacids in palliative care patients.

Class: Alginate.

Indications: Acid reflux ('heartburn').

Pharmacology
Alginates prevent esophageal reflux pain by forming an inert low-density raft on the top of the acidic stomach contents. Both acid and air bubbles are necessary to produce the raft. Alginate products may thus be less effective if used with an H_2-receptor antagonist or a PPI (reduces acid) and/or an antiflatulent (reduces air bubbles). Gaviscon®, a sodium alginate product, is a weak antacid; most of the antacid content adheres to the alginate raft. This neutralizes acid which seeps into the esophagus around the raft but does nothing to correct the underlying causes, e.g. lax lower esophageal sphincter, hyperacidity, delayed gastric emptying, obesity. Indeed, sodium alginate products are no better than simethicone-containing antacids in the treatment of acid reflux.[1] Sodium alginate products have been largely superseded by acid suppression with H_2-receptor antagonists and PPIs.
Onset of action <5min.
Duration of action 1–2h.

Cautions
Regular strength Gaviscon® liquid and tablets contain Na^+ 1.7mEq/15mL and Na^+ 0.8mEq/tablet respectively, and Gaviscon® Extra Strength liquid and tablets contain Na^+ 2.7mEq/15mL and Na^+ 1.3mEq/tablet respectively. They should not be used in patients requiring a salt-restricted diet, e.g. those with fluid retention, heart failure or renal impairment.

Dose and use
Several products are available but none is recommended. For patients already taking Gaviscon® and who are reluctant to change to Maalox® Antacid/AntiGas (or similar option), prescribe Gaviscon® 2–4 tablets or Gaviscon® liquid 15–30mL p.c. & at bedtime, and p.r.n.

Supply
Gaviscon® products are generally available OTC.

1 Pokorny C *et al.* (1985) Comparison of an antacid/dimethicone mixture and an alginate/antacid mixture in the treatment of oesophagitis. *Gut.* **26**: A574.

SIMETHICONE AHFS 56:10

Class: Antifoaming agent (antiflatulent).

Indications: Acid dyspepsia (including acid reflux), gassy dyspepsia, bloating, flatulence, †hiccup (if associated with gastric distension).

Pharmacology

Simethicone (silica-activated dimethicone or dimethylpolysiloxane) is a mixture of liquid dimethicones with silicon dioxide. It is an antifoaming agent present in several proprietary antacids, e.g. Maalox® Antacid/AntiGas. By facilitating belching, simethicone eases flatulence, distension and postprandial gastric discomfort. Simethicone-containing antacids are as effective as Gaviscon® in the treatment of acid reflux.[1] Maalox® Antacid/AntiGas should be used in preference to Gaviscon® liquid because it is cheaper and contains much less sodium.
Onset of action <5min.
Duration of action 1–2h.

Cautions

Although Maalox® Antacid/AntiGas contains both **aluminum** and **magnesium**, at higher doses (e.g. 30–60mL q.i.d. or more) the laxative effect of **magnesium** will override the constipating effect of **aluminum**.[2]

Dose and use

- Start with Maalox® Antacid/AntiGas regular strength suspension 10mL p.r.n., or 10mL q.i.d. & p.r.n.
- if necessary, double dose to 20mL.

Supply

Simethicone (generic)
Tablets chewable 80mg, 28 days @ 80mg q.i.d. = $9.

Mylanta Gas® (Johnson and Johnson/Merk)
Tablets chewable 40mg, 80mg,125mg, 28 days @ 80mg q.i.d. = $18.

Combination products
Maalox® Antacid/AntiGas (Novartis)
Oral suspension regular strength (simethicone 20mg, dried **aluminum hydroxide** 200mg, **magnesium hydroxide** 200mg/5mL), 28 days @ 10mL q.i.d. = $17; *low* Na^+.
Oral suspension maximum strength (simethicone 40mg, dried **aluminum hydroxide** 400mg, **magnesium hydroxide** 400mg/5mL), 28 days @ 10mL q.i.d. = $17; *low* Na^+.

1 Pokorny C *et al.* (1985) Comparison of an antacid/dimethicone mixture and an alginate/antacid mixture in the treatment of oesophagitis. *Gut.* **26**: A574.
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ANTIMUSCARINICS (ANTICHOLINERGICS) AHFS 12:08

Indications: Smooth muscle spasm (e.g. bladder, intestine), prevention of motion sickness (**scopolamine *hydrobromide*** TD), prevention of opioid-induced nausea and vomiting (**scopolamine *hydrobromide*** TD), adjunctive treatment of peptic ulcer, reduction of GI motility to aid diagnostic procedures (**hyoscyamine** and **propantheline**), pancreatitis (**hyoscyamine** and **propantheline**), symptomatic treatment of Parkinson's disease (PO **hyoscyamine** and **scopolamine *hydrobromide***, including sialorrhea and hyperhidrosis for PO **hyoscyamine**), drying secretions (including surgical premedication to decrease salivation and airway secretions, †sialorrhea, †drooling, †death rattle and †inoperable intestinal obstruction), †paraneoplastic pyrexia and sweating/hyperhidrosis.

Contra-indications: See individual monographs.

Pharmacology

Antimuscarinics are classified chemically as tertiary amines or quaternary ammonium compounds. The naturally-occurring belladonna alkaloids, **atropine**, **hyoscyamine** (**l-atropine**) and **scopolamine *hydrobromide***, are all tertiary amines, whereas the numerous semisynthetic and synthetic derivatives fall into both categories. Thus, **dicyclomine**, **oxybutynin** and **tolterodine** are tertiary amines, and **glycopyrrolate**, **propantheline** and **scopolamine *butylbromide*** (not USA) are quaternary ammonium compounds.

Apart from **scopolamine**, which causes CNS depression at therapeutic doses, the tertiary amines stimulate the brain stem and higher centers, producing mild central vagal excitation and respiratory stimulation. At toxic doses, all the tertiary amines, including **scopolamine *hydrobromide***, cause CNS stimulation resulting in agitation and delirium. Synthetic tertiary amines generally cause less central stimulation than the naturally-occurring alkaloids. Quaternary ammonium compounds do not cross the blood–brain barrier in any significant amount, and accordingly do not have any central effects.[1] They are also less well absorbed from the GI tract.

Peripheral antimuscarinic effects are a class characteristic (Box 1.A), and have been summarized as:

'*Dry as a bone, blind as a bat, red as a beet, hot as a hare, mad as a hatter.*'

However, at least five different types of muscarinic receptors have been identified,[2] and newer drugs tend to be more selective in their actions. Thus, **oxybutynin** and **tolterodine** are relatively selective for muscarinic receptors in the urinary tract (see p.405).

Box 1.A Peripheral antimuscarinic effects

Visual
Mydriasis
Loss of accommodation
} blurred vision (and thus may impair driving ability)

Cardiovascular
Tachycardia, palpitations
Extrasystoles
Arrhythmias
} also related to norepinephrine potentiation and a quinidine-like action

Gastro-intestinal
Dry mouth
Heartburn (relaxation of lower esophageal sphincter)
Constipation

Urinary tract
Hesitancy of micturition
Retention of urine

Skin
Reduced sweating
Flushing

Except when a reduction of oropharyngeal secretions is intended, dry mouth is an almost universal *undesirable* effect with this class of drugs. The secretion of saliva is mainly under the control of the autonomic nervous system. Food in the mouth causes reflex secretion of saliva, and so does stimulation by acid of afferent vagal fibers in the lower esophagus. Stimulation of the parasympathetic nerves causes profuse secretion of watery saliva, whereas stimulation of the sympathetic nerve supply causes the secretion from only the submaxillary glands of small quantities of saliva rich in organic constituents.[3] If the parasympathetic supply is interrupted, the salivary glands atrophy, whereas interruption of the sympathetic supply has no such effect. The muscarinic receptors in salivary glands are very responsive to antimuscarinics and inhibition of

salivation occurs at lower doses than required for other antimuscarinic effects.[4] This reduces the likelihood of undesirable effects when antimuscarinics are given to reduce salivation. In some patients, a reduction in excess saliva results in improved speech.[5]

To reduce the risk of undesirable effects, e.g. the development of an agitated delirium (central antimuscarinic syndrome), the concurrent use of two antimuscarinic drugs should generally be avoided (Box 1.B). Likewise, the concurrent use of an antimuscarinic and an opioid should be avoided as far as possible. Both cause constipation (by different mechanisms) and, if used together, will result in an increased need for laxatives, and may even result in a paralytic ileus. On the other hand, **morphine** and **glycopyrrolate** are sometimes purposely combined in terminally ill patients with inoperable intestinal obstruction in order to prevent colic and to reduce vomiting.[6] **Scopolamine *hydrobromide*** TD patches are also approved for the prevention of opioid-induced nausea and vomiting.

Box 1.B Drugs with antimuscarinic effects associated with palliative care

- Analgesics
  - meperidine (not recommended)
  - nefopam (mostly postoperative; not USA)
- Antidepressants
  - TCAs
  - paroxetine (SSRI)
- Antihistamines, e.g.
  - chlorpheniramine
  - cyclizine (not USA)
  - dimenhydrinate
  - promethazine
- Antiparkinsonians, e.g.
  - orphenadrine
  - procyclidine (not USA)
- Antipsychotics (atypical)
  - olanzapine
- Antipsychotics (typical)
  - phenothiazines, e.g.
    - chlorpromazine
    - methotrimeprazine (not USA)
    - prochlorperazine
- Antisecretory drugs
  - belladonna alkaloids
    - atropine
    - scopolamine
    - hyoscyamine (l-atropine)[a]
  - glycopyrrolate
- Antispasmodics, e.g.
  - dicyclomine
  - mebeverine
  - oxybutynin
  - propantheline
  - tolterodine

a. because the d-isomer is virtually inactive, hyoscyamine is twice as potent as racemic atropine.

Antimuscarinics used as antispasmodics and/or antisecretory drugs differ in their pharmacokinetic characteristics (Table 1.1). Availability and fashion are probably the main influences in choice of drug.

Table 1.1 Pharmacokinetic features of antimuscarinic drugs used for death rattle

	Bio-availability	*Plasma halflife*	*Duration of action (antisecretory)*
Atropine	readily absorbed	4h	no data
Hyoscyamine (l-atropine)	readily absorbed	3–5h	no data
Scopolamine *hydrobromide*	60–80% SL	5–6h	1–9h
Glycopyrrolate	<5% PO	1.7h	7h

Cautions

Concurrent treatment with two antimuscarinic drugs will increase the likelihood of undesirable effects, and of central toxicity, i.e. restlessness, agitation, delirium. Children, the elderly, and patients with renal or hepatic impairment are more susceptible to the central effects of antimuscarinics.

Various drugs not generally considered antimuscarinic have been shown to have detectable antimuscarinic activity by means of a radioreceptor assay, including **codeine**, **digoxin**, **dipyridamole**, **isosorbide**, **nifedipine**, **prednisolone**, **ranitidine**, **theophylline**, **warfarin**.[7] Theoretically, these drugs could exacerbate toxicity, particularly in debilitated elderly patients.

The increased GI transit time produced by antimuscarinics may allow increased drug absorption from some formulations, e.g. **digoxin** and **nitrofurantoin** from tablets and **potassium** from SR tablets, but reduced absorption from others, e.g. **acetaminophen** tablets. Dissolution and absorption of **nitroglycerin** SL tablets may be reduced because of decreased saliva production.

Because antimuscarinics competitively block the final common (cholinergic) pathway through which prokinetics act,[8] concurrent prescription should be avoided if possible.

Use with caution in myasthenia gravis, conditions predisposing to tachycardia (e.g. thyrotoxicosis, heart failure, β-adrenergic receptor agonists), and bladder outflow obstruction (prostatism). Use in hot weather or pyrexia may lead to heatstroke. Likely to exacerbate acid reflux. Narrow-angle glaucoma may be precipitated in those at risk, particularly the elderly.

Dose and use

Antispasmodic

Antimuscarinics are used to relieve smooth muscle spasm in the bladder (see **oxybutynin**, p.405) and rectum (**opium** and **belladonna** suppositories).

Antispasmodic and antisecretory

Antimuscarinics are used to reduce intestinal colic and intestinal secretions, particularly gastric, associated with inoperable organic intestinal obstruction in terminally ill patients (Table 1.2).

Table 1.2 Antisecretory and antispasmodic drugs: typical SC doses

Drug	*Stat dose*	*CSCI dose/24h*
Atropine	400microgram	1,200–2,000microgram
Scopolamine *hydrobromide*	400microgram	1,200–2,000microgram
Hyoscyamine (l-atropine)	200microgram	600–1,000microgram
Glycopyrrolate	200microgram	600–1,200microgram

Antisecretory

Sialorrhea and drooling

Indicated particularly in patients with motor neuron disease (amyotrophic lateral sclerosis/ALS), advanced Parkinson's disease or with various disorders of the head and neck. Several regimens have been recommended, including:

- **glycopyrrolate** PO, solution and tablets (see p.455)
- **scopolamine *hydrobromide*** 1mg/3 days TD[9]
- **hyoscyamine** drops 125microgram/mL, 2mL SL q4h p.r.n. but the relatively large volume makes this less preferable
- **hyoscyamine** SL tablets 125–250microgram q4h p.r.n.
- **atropine** 1% ophthalmic solution, 4 drops SL q4h p.r.n. (Note: drop size varies with applicator and technique, dose per drop may vary from 200–500microgram, i.e. 800microgram–2mg/dose).

A regimen of **atropine** 1% 500microgram (1 drop) b.i.d. has been reported[10] but a controlled trial found 500microgram (2 drops) q.i.d. no better than placebo.[11]

When antimuscarinics are contra-indicated, not tolerated or ineffective, **botulinum toxin** injections (with ultrasound guidance) into the parotid and submandibular glands offer an alternative approach. Generally effective in ⩽1–2 weeks, with benefit lasting 3–4 months.[12–16]

Death rattle

Many centers use antimuscarinics SL for death rattle, thereby avoiding the need for injections. Treatment regimens, all off-label, are based mainly on local clinical experience:

- **atropine** 1% ophthalmic solution, 4 drops SL q4h p.r.n. (Note: drop size varies with applicator and technique, dose per drop may vary from 200–500microgram, i.e. 800microgram–2mg/dose)
- **hyoscyamine** drops 125 microgram/mL, 2mL SL q4h p.r.n. but relatively large volume and thus less preferable
- **glycopyrrolate** 100microgram SL q6h p.r.n.

However, with some patients injections may be preferable (Table 1.2; also see Guidelines for management of death rattle, p.9).[17]

Paraneoplastic pyrexia and sweating

Antimuscarinic drugs are used in the treatment of paraneoplastic pyrexia (Box 1.C).

Box 1.C Symptomatic drug treatment of paraneoplastic pyrexia and sweating

Prescribe an antipyretic:
- acetaminophen 500mg–1g q.i.d. or p.r.n. (generally less toxic than an NSAID)
- NSAID, e.g. ibuprofen 200–400mg t.i.d. or p.r.n. (or the locally preferred alternative).

If the sweating does not respond to an NSAID, prescribe an antimuscarinic drug:
- amitriptyline 25–50mg at bedtime (may cause sedation, dry mouth and other anti-muscarinic effects)
- scopolamine *hydrobromide* 1mg/3 days TD[18]
- glycopyrrolate up to 2mg PO t.i.d.[19]

If an antimuscarinic fails, other options include:
- propranolol 10–20mg b.i.d.–t.i.d.
- cimetidine 400–800mg b.i.d.[20]
- olanzapine 5mg b.i.d.[21]
- thalidomide 100mg at bedtime.[22,23]

Thalidomide is generally seen as the last resort even though the response rate appears to be high.[22] This is because it can cause an irreversible painful peripheral neuropathy, and may also cause drowsiness (see p.398).

Overdose

In the past, **physostigmine**, a cholinesterase inhibitor, was sometimes administered to correct antimuscarinic toxicity/poisoning. This is no longer recommended because **physostigmine** itself can cause serious toxic effects, including cardiac arrhythmias and seizures.[24–26] A benzodiazepine can be given to control marked agitation and seizures. Phenothiazines should not be given because they will exacerbate the antimuscarinic effects, and could precipitate an acute dystonia (see Drug-induced movement disorders, p.547). Anti-arrhythmics are not advisable if arrhythmias develop; but hypoxia and acidosis should be corrected.

Supply

See individual monographs: **glycopyrrolate** (p.455), **oxybutynin** (p.405), **propantheline** (p.10), **scopolamine hydrobromide** (p.199).

Atropine sulfate (generic)
Ophthalmic solution 1%, 2mL bottle = $6, 5mL bottle = $7, 15mL bottle = $6.

Isopto® Atropine (Alcon)
Ophthalmic solution 1%, 5mL bottle = $4.50, 15mL bottle = $6.

Hyoscyamine sulfate (generic)
Tablets 125microgram, 28 days @ 125microgram q4h = $49.
Tablets orodispersible 125microgram, 28 days @ 125microgram q4h = $85.
Tablets SL 125microgram, 28 days @ 125microgram q4h = $52.
Tablets SR 375microgram, 28 days @ 375microgram b.i.d. = $29.

Levsin® (Schwarz Pharma)
Tablets 125microgram, 28 days @ 125microgram q4h = $126.
Tablets SL 125microgram, 28 days @ 125microgram q4h = $122.
Oral solution 125microgram/5mL and 125microgram/mL, 28 days @ 125microgram q4h = $210 and $352 respectively.
Injection 500microgram/mL, 1mL amp = $21.

NuLev® (Schwarz Pharma)
Tablets orodispersible 125microgram, 28 days @ 125microgram q4h = $142.

Levbid® (Schwarz Pharma)
Tablets SR 375microgram, 28 days @ 375microgram b.i.d. = $68.

Levsinex Timecaps® (Schwarz Pharma)
Tablets SR 375microgram, 28 days @ 375microgram b.i.d. = $77.

Cystospaz® (Polymedica)
Tablets 150microgram, 28 days @ 150microgram q.i.d. = $57.

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Guidelines: Management of death rattle

Death rattle is a term used to describe noisy rattling breathing which occurs in about 50% of patients near the end of life. It is caused by fluid pooling in the hypopharynx, and arises from one or more sources:

- saliva (most common)
- respiratory tract infection
- pulmonary edema
- gastric reflux.

Rattling breathing can also occur in patients with a tracheostomy and infection. Because the patient is generally semiconscious or unconscious, drug treatment for death rattle is mainly for the benefit of relatives, other patients and staff.

Non-drug treatment

- ease the family's distress by explaining that the semiconscious/unconscious patient is not distressed by the rattle
- position the patient semiprone to encourage postural drainage; but upright or semirecumbent if the cause is pulmonary edema or gastric reflux
- oropharyngeal suction but, because it is distressing to many moribund patients, generally reserve for unconscious patients.

Drug treatment

Saliva

Because they do not affect existing secretions, an antisecretory drug should be given SC (see Table) or SL (see Box A), as soon as the onset of the rattle is detected. SL use is off-label and less well supported by the literature. Even so, SL administration is standard practice at many centers.

Table Antimuscarinic antisecretory drugs for death rattle: typical SC doses

Drug	*Stat SC dose*	*CSCI dose/24h*
Hyoscyamine (l-atropine)	200microgram	600–1,000microgram
Glycopyrrolate	200microgram	600–1,200microgram
Atropine	400microgram	1,200–2,400microgram
Scopolamine *hydrobromide*	400microgram	1,200–2,400microgram

Box A Antimuscarinic antisecretory drugs for death rattle: typical SL doses

Glycopyrrolate 0.01% oral solution, 1mL (100microgram) SL q6h p.r.n.; can be compounded from glycopyrrolate powder (see Box B).

Atropine 1% ophthalmic solution, 4 drops SL q4h p.r.n. (Note: drop size varies with applicator and technique, dose per drop may vary from 200–500microgram, i.e. 800microgram–2mg/dose).

Hyoscyamine drops 125microgram/mL, 2mL (250microgram) SL q4h p.r.n.

Box B Compounded oral solution of glycopyrrolate

Dissolve 100mg of glycopyrrolate powder (obtainable from Gallipot) in 100mL of sterile or distilled water (= 1mg/mL concentrated solution).

This concentrate is stable for approximately 28 days if stored in a refrigerator.

Dilute the required volume of the concentrate 1 part with 9 parts sterile or distilled water (i.e. for every 1mL of concentrate, add 9mL of water).

To avoid microbial contamination, store in a refrigerator and discard any unused diluted solution after 1 week.

Guidelines continued

Note:
- by injection, the efficacy of the different drugs is broadly similar; the rattle is reduced in 1/2–2/3 of patients
- the onset of action of glycopyrrolate is slower compared with scopolamine *hydrobromide*
- scopolamine *hydrobromide* crosses the blood-brain barrier and possesses anti-emetic and sedative properties, but there is also a risk of developing or exacerbating delirium
- atropine and hyoscyamine also cross the blood-brain barrier but tend to stimulate rather than sedate; concurrent use with midazolam or haloperidol is more likely to be necessary.

Respiratory tract infection

Occasionally it is appropriate to prescribe an antibiotic in an imminently dying patient if death rattle is caused by profuse purulent sputum associated with an underlying chest infection:
- e.g. ceftriaxone, mix 1g ampule with 2.1mL lidocaine 1% (total volume 2.6–2.8mL), and give 250–1,000mg SC/IM once daily
- some centers use larger volumes of lidocaine 1% (up to 4mL) and administer a divided dose at separate SC/IM sites once daily or give b.i.d.

Pulmonary edema

Consider furosemide 20–40mg SC/IM/IV q2h p.r.n.
Note: beware precipitating urinary retention.

Gastric reflux

Consider metoclopramide 20mg SC/IV q3h p.r.n., but do not use concurrently with an antimuscarinic because the latter blocks the prokinetic effect of the former.

Rattling breathing causing distress to a patient

In a semiconscious patient, if rattling breathing is associated with breathlessness, supplement the above with an opioid (e.g. morphine) ± an anxiolytic sedative (e.g. midazolam).

PROPANTHELINE AHFS 12:08.08

Class: Antimuscarinic.

Indications: Smooth muscle spasm (e.g. bladder, intestine), adjunctive treatment of peptic ulcer, reduction of GI motility to aid diagnostic procedures, †urinary frequency and incontinence, †hyperhidrosis, †gustatory sweating in diabetic neuropathy, †paraneoplastic sweating.

Contra-indications: Narrow-angle glaucoma (unless moribund), myasthenia gravis (unless moribund).

Pharmacology

Propantheline is a quaternary antimuscarinic (see p.3); it does not cross the blood-brain barrier and thus does *not* cause central effects. It doubles gastric emptying half-time[1] and slows GI transit generally. It has variable effects on drug absorption (see Cautions). Propantheline is extensively metabolized in the small intestine before absorption. *If taken with food, the effect of propantheline by mouth is almost abolished.*[2]

Bio-availability <50% PO (much reduced if taken after food).
Onset of action 30–60min.
Time to peak plasma concentration no data.
Plasma halflife 3–4h.
Duration of action 4–6h.

Cautions

Competitively blocks the prokinetic effect of **metoclopramide** and **domperidone** (not USA).[3] May reduce the rate of absorption of **acetaminophen**, thereby delaying the onset of analgesia.[4]

Increases the peripheral antimuscarinic toxicity of antihistamines, phenothiazines and TCAs (see Antimuscarinics (anticholinergics), p.3). Use with caution in conditions predisposing to tachycardia (e.g. thyrotoxicosis, heart failure, β_2-agonists), and bladder outflow obstruction (prostatism). Likely to exacerbate acid reflux. Narrow-angle glaucoma may be precipitated in those at risk, particularly the elderly. Use in hot weather or pyrexia may lead to heatstroke.

Undesirable effects

For full list, see manufacturer's PI.
Peripheral antimuscarinic effects (see p.4).

Dose and use

Antisecretory adjunct in peptic ulcer

Included because it is an approved indication, but not relevant for palliative care:
- start with 15mg t.i.d. 1h a.c. & 30mg at bedtime
- half the above dose may suffice in the elderly
- maximum dose 60mg q.i.d.

Intestinal colic

- start with 15mg t.i.d. 1h a.c. & 30mg at bedtime
- maximum dose 30mg q.i.d.

Urinary frequency

- same as for colic, but largely replaced by **oxybutynin** (see p.405) and **amitriptyline** (see p.160).

Sweating

Used as one of several alternatives to reduce paraneoplastic sweating (for other options, see Box 1.C, p.7):
- 15–30mg b.i.d.–t.i.d.

Supply

Propantheline (generic)
Tablets 7.5mg,15mg, 28 days @ 15mg t.i.d. & 30mg at bedtime = $66.

1 Hurwitz A *et al.* (1977) Prolongation of gastric emptying by oral propantheline. *Clinical Pharmacology and Therapeutics.* **22**: 206–210.
2 Ekenved G *et al.* (1977) Influence of food on the effect of propantheline and L-hyoscyamine on salivation. *Scandinavian Journal of Gastroenterology.* **12**: 963–966.
3 Schuurkes JAJ *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
4 Baxter K (ed) (2008) *Stockley's Drug Interactions* (8e). Pharmaceutical Press, London.

PROKINETICS AHFS 56:32

Prokinetics accelerate GI transit by a neurohumoral mechanism. The term is restricted to drugs which co-ordinate antroduodenal contractions and accelerate gastroduodenal transit (Table 1.3). This excludes other drugs which enhance intestinal transit such as bulk-forming agents and other laxatives, and drugs which cause diarrhea by increasing GI secretions, e.g. **misoprostol**. Some drugs increase contractile motor activity but not in a co-ordinated fashion, and so do not reduce transit time, e.g. **bethanechol**. Such drugs are promotility but not prokinetic.

Apart from **erythromycin**, prokinetics act by triggering a cholinergic system in the wall of the GI tract (Table 1.4, Figure 1.1).[2] This action is impeded by opioids. Further, antimuscarinic drugs competitively block cholinergic receptors on the intestinal muscle fibers (and elsewhere).[3] Thus, all drugs with antimuscarinic properties reduce the impact of prokinetic drugs; the extent of this depends on several factors, including the respective doses of the interacting drugs and times of

Table 1.3 Gastric prokinetics[1]

Class	*Examples*	*Site of action*
D_2-receptor antagonist	Domperidone Metoclopramide	Stomach Stomach
$5HT_4$-receptor agonist	Metoclopramide	Stomach → jejunum
Motilin agonist	Erythromycin	Stomach

Table 1.4 Comparison of prokinetic drugs[2]

Drug	*Erythromycin*	*Domperidone*	*Metoclopramide*
Mechanism of action			
Motilin agonist	+	−	−
D_2-receptor antagonist	−	+	+
$5HT_4$-receptor agonist	−	−	+
Response to treatment[a]			
Gastric emptying (mean % acceleration)	45	30	20
Symptom relief (mean % improvement)	50	50	40

a. all percentages rounded to nearest 5%.

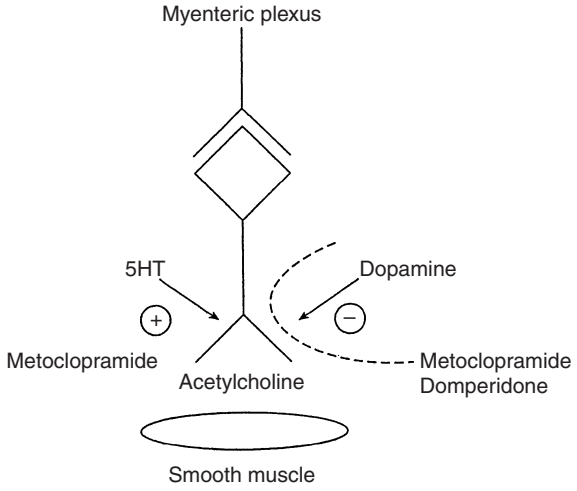

Figure 1.1 Schematic representation of drug effects on antroduodenal co-ordination via a postganglionic effect on the cholinergic nerves from the myenteric plexus.

⊕ stimulatory effect of 5HT triggered by metoclopramide; ⊖ inhibitory effect of dopamine; - - - blockade of dopamine inhibition by metoclopramide and domperidone.

administration. Thus, generally, the concurrent administration of prokinetics and antimuscarinic drugs is best avoided. On the other hand, even if the peripheral prokinetic effect is completely blocked, **domperidone** (not USA) and **metoclopramide** will still exert an anti-emetic effect at the dopamine receptors in the area postrema (see p.181).

Erythromycin, an antibacterial, is the only available motilin agonist.[4] It has been used mainly in diabetic gastroparesis when other prokinetics have proved inadequate.[5,6] A systematic review suggests that, overall, its prokinetic effect is greater than that of **metoclopramide** (Table 1.4). However, it may cause intestinal colic and, in healthy people, it often causes diarrhea. There is also

concern about bacterial resistance developing. In some patients, tolerance to its prokinetic effects develops over time.[7] However, some patients have taken **erythromycin** 250mg b.i.d. for more than a year without apparent loss of its prokinetic effect.[8]

Prokinetics are used in various conditions in palliative care (Box 1.D). D_2-receptor antagonists block the dopaminergic 'brake' on gastric emptying induced by stress, anxiety and nausea from any cause. In contrast, $5HT_4$-receptor agonists have a direct excitatory effect which in theory gives them an advantage over the D_2-receptor antagonists particularly for patients with gastric stasis or functional intestinal obstruction. However, when used for dysmotility dyspepsia, **metoclopramide** is no more potent than **domperidone** in standard doses.[9,10]

Box 1.D Indications for prokinetics in palliative care

Gastro-esophageal reflux

Gastroparesis
- dysmotility dyspepsia
- paraneoplastic autonomic neuropathy
- spinal cord compression
- diabetic autonomic neuropathy

Functional GI obstruction
- drug-induced, e.g. opioids
- cancer of head of pancreas
- neoplastic mural infiltration (linitis plastica)

1 Debinski H and Kamm M (1994) New treatments for neuromuscular disorders of the gastrointestinal tract. *Gastrointestinal Journal Club*. **2**: 2–11.
2 Sturm A *et al.* (1999) Prokinetics in patients with gastroparesis: a systematic analysis. *Digestion*. **60**: 422–427.
3 Schuurkes JAJ *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
4 Janssens J *et al.* (1990) Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. *New England Journal of Medicine*. **322**: 1028–1031.
5 Erbas T *et al.* (1993) Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. *Diabetes Care*. **16**: 1511–1514.
6 Smith DS and Ferris CD (2003) Current concepts in diabetic gastroparesis. *Drugs*. **63**: 1339–1358.
7 Dhir R and Richter JE (2004) Erythromycin in the short- and long-term control of dyspepsia symptoms in patients with gastroparesis. *Journal of Clinical Gastroenterology*. **38**: 237–242.
8 Hunter A *et al.* (2005) The use of long-term, low-dose erythromycin in treating persistent gastric stasis. *Journal of Pain and Symptom Management*. **29**: 430–433.
9 Loose FD (1979) Domperidone in chronic dyspepsia: a pilot open study and a multicentre general practice crossover comparison with metoclopramide and placebo. *Pharmatheripeutica*. **2**: 140–146.
10 Moriga M (1981) A multicentre double blind study of domperidone and metoclopramide in the symptomatic control of dyspepsia. In: G Towse (ed) *International Congress and Symposium Series: Progress with Domperidone, a Gastrokinetic and Anti-Emetic Agent* (No. 36). Royal Society of Medicine, London, pp. 77–79.

H_2-RECEPTOR ANTAGONISTS AHFS 56:28.12

Class: Gastroprotective drugs.

Indications: Acid dyspepsia, chronic episodic dyspepsia, acid reflux, erosive esophagitis (**ranitidine**), prevention and treatment of peptic ulceration (including NSAID-induced ulceration), *Helicobacter pylori* eradication (**ranitidine**, as part of multidrug regimen), acid reduction in pathological hypersecretory conditions, prevention of upper GI bleeding in critically ill patients (**cimetidine**), †reduction of malabsorption and fluid loss in short bowel syndrome, †prevention of degradation of pancreatin supplements.

Pharmacology

H_2-receptor antagonists reduce both gastric acid output and the volume of gastric secretions.[1] **Ranitidine** is a good choice in terms of convenience and safety. **Cimetidine**, alone among

H_2-receptor antagonists, can cause serious cytochrome P450-related drug interactions (see Cautions below and Cytochrome P450, p.537). None of the H_2-receptor antagonists, including **cimetidine**, alters the metabolism of **morphine**.[2]

Prophylactic treatment with a standard dose of an H_2-receptor antagonist reduces the incidence of NSAID-induced *duodenal* ulcers.[3] Prevention of *gastric* erosions and ulcers is seen only with a double dose.[4] In patients taking NSAIDs, **ranitidine** (compared with **omeprazole**) is less effective and slower in *healing* gastroduodenal ulcers (63% vs. 80% at 8 weeks) and in *preventing* relapse (59% vs. 72% over 6 months) (Table 1.5).[3,5]

Bio-availability **cimetidine** 60–70% PO; **ranitidine** 50% PO.
Onset of action <1h.
Time to peak plasma concentration **cimetidine** 1–3h PO, 15min IM; **ranitidine** 2–3h PO.
Plasma halflife **cimetidine** 2h; **ranitidine** 2–3h.
Duration of action **cimetidine** 7h; **ranitidine** 8–12h.

Table 1.5 Comparison of gastroprotective agents[3–7]

	Prevent NSAID-GU	*Prevent NSAID-DU*	*Heal NSAID-GU*	*Heal NSAID-DU*
Misoprostol	+	+	+	+
H_2-receptor antagonists	+[a]	+	+[b]	+[b]
Proton pump inhibitors	+	+	+[c]	+[c]

a. double dose necessary to protect against gastric ulcers
b. rate of healing decreased if NSAID continued
c. rate of healing unchanged if NSAID continued.

Cautions

Serious drug interactions: the increase in gastric pH caused by all H_2-receptor antagonists decreases the absorption of **itraconazole** and **ketoconazole**; an increased dose may be needed to avoid antifungal treatment failure. **Cimetidine** binds to microsomal cytochrome P450 and inhibits the metabolism of **warfarin**, IV **lidocaine** (but not ED **lidocaine** or **bupivacaine**), some calcium antagonists (**diltiazem**, **isradipine**, **nifedipine**), **pentoxifylline**, **theophylline**, **clomethiazole** (**chlormethiazole**; not USA), **diazepam**, TCAs, **moclobemide** (not USA), **phenytoin**, **methadone** and **fluorouracil**. **Cimetidine** inhibits the renal clearance of **procainamide** and **quinidine**.[8]

Hepatic impairment, renal impairment. **Cimetidine** causes a transient rise in the plasma concentrations of **carbamazepine**. It also increases plasma concentrations of some benzodiazepines (including **alprazolam** and **diazepam**), some SSRIs (including **citalopram**, **paroxetine** and **sertraline**), **mirtazapine**, **alfentanil**, **fentanyl**, **methadone**, **mefloquine**, **tacrine** and **zolmitriptan**.[8,9] There are inconsistent reports of **cimetidine** and **ranitidine** increasing the plasma concentration of **midazolam**.[8]

Undesirable effects

For full list, see manufacturer's PI.
Cimetidine occasionally causes gynecomastia.

Dose and use

Cochrane review: H_2-receptor antagonists (double-dose), **misoprostol** and PPIs are effective at *preventing* chronic NSAID-related endoscopic peptic ulcers. **Misoprostol** 400microgram/24h is less effective than 800microgram and is still associated with diarrhea. Of all these treatments, only **misoprostol** 800microgram/24h has been definitely shown to reduce the overall incidence of ulcer complications (perforation, hemorrhage or obstruction).[4] PPIs definitely reduce the incidence of re-bleeding from endoscopically confirmed peptic ulcers,[10] and may reduce the incidence of ulcer complications.[7]

Because **cimetidine** is responsible for several serious drug interactions, **ranitidine** is generally preferable in palliative care; generic tablets of **ranitidine** are also cheaper than generic tablets of **cimetidine** (see below). However, H_2-receptor antagonists have been largely superseded by PPIs as gastroprotective drugs of choice (see p.17).

H_2-receptor antagonists are second-line treatment for gastro-esophageal reflux disease, non-ulcer dyspepsia or uninvestigated dyspepsia, and an OTC measure for mild dyspepsia.[11]

The dose and duration of treatment is least with duodenal ulceration and most with reflux esophagitis and prophylaxis for NSAID-induced peptic ulcer, although the dose for ulcer healing can be doubled if the initial response is poor (Table 1.6). **Ranitidine** is more effective if taken at bedtime rather than with the evening meal.[12] Parenteral formulations are available for IM and for IV use if treatment is considered necessary in a patient with severe nausea and vomiting (see AHFS section 56:40).

Table 1.6 Recommended treatment regimens for H_2-receptor antagonists

Indication	*Cimetidine*	*Ranitidine*
Duodenal ulcer[a,b]	400mg b.i.d. or 800mg at bedtime for 4+ weeks	150mg b.i.d. or 300mg at bedtime for 4–8 weeks
Gastric ulcer[a,b]	400mg b.i.d. or 800mg at bedtime for 6+ weeks	150mg b.i.d. or 300mg at bedtime for 4–8 weeks
Prophylaxis for NSAID-associated peptic ulcer	800mg b.i.d. indefinitely	300mg b.i.d. indefinitely
Reflux esophagitis	400mg q.i.d. or 800mg b.i.d. for 4–8 weeks	150mg b.i.d. or 300mg at bedtime for 8–12 weeks
Short bowel syndrome	400mg b.i.d. or 800mg at bedtime indefinitely	–
To reduce degradation of pancreatin supplements	400mg 1h a.c.	150mg 1h a.c.

a. 8 weeks for NSAID-induced ulcer
b. dose can be doubled if initial response is poor.

The UK PI recommends that, in renal impairment, the dose of **cimetidine** should be adjusted according to creatinine clearance (Table 1.7). **Cimetidine** is removed by hemodialysis, but not by peritoneal dialysis.

For **ranitidine**, the dose should be reduced to 150mg at bedtime in severe renal impairment, but increased to 150mg b.i.d. if an ulcer fails to respond at the lower dose.

Table 1.7 Dose adjustment for cimetidine in renal impairment (UK manufacturer's recommendations)

Creatinine clearance (mL/min)	*Dose of cimetidine*
>50	No change in dose
30–50	200mg q.i.d.
15–30	200mg t.i.d.
0–15	200mg b.i.d.

Supply

Cimetidine (generic)
Tablets 300mg, 400mg, 800mg, 28 days @ 400mg b.i.d. or 800mg at bedtime = $80 and $72 respectively.
Oral solution 300mg/5mL, 28 days @ 400mg b.i.d. = $109.
Injection 150mg/mL, 2mL vial = $2.

Tagamet® (GSK)
Tablets 200mg, 300mg, 400mg, 28 days @ 400mg b.i.d. or 800mg at bedtime = $72.

Ranitidine (generic)
Capsules 150mg, 300mg, 28 days @ 150mg b.i.d. or 300mg at bedtime = $31 and $29 respectively.
Tablets 150mg, 300mg, 28 days @ 150mg b.i.d. or 300mg at bedtime = $11 and $13 respectively.

Zantac® (GSK)
Tablets 75mg, 150mg, 300mg, 28 days @ 150mg b.i.d. or 300mg at bedtime = $164 and $151 respectively.
Oral syrup 75mg/5mL, 28 days @ 150mg b.i.d. = $394; *contains 7.5% alcohol.*
Injection 25mg/mL, 2mL vial = $3.50.

1 Williams JG and Strunin L (1985) Pre-operative intramuscular ranitidine and cimetidine. Double blind comparative trial, effect on gastric pH and volume. *Anaesthesia.* **40**: 242–245.
2 Mojaverian P *et al.* (1982) Cimetidine does not alter morphine disposition in man. *British Journal of Clinical Pharmacology.* **14**: 809–813.
3 Hollander D (1994) Gastrointestinal complications of nonsteroidal anti-inflammatory drugs: prophylactic and therapeutic strategies. *American Journal of Medicine.* **96**: 274–281.
4 Rostom A *et al.* (2002) Prevention of NSAID-induced gastroduodenal ulcers. *The Cochrane Database of Systematic Reviews.* **10**: CD002296.
5 Yeomans N *et al.* (1998) A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs. Acid suppression trial. *New England Journal of Medicine.* **338**: 719–726.
6 Hawkins C and Hanks G (2000) The gastroduodenal toxicity of nonsteroidal anti-inflammatory drugs. A review of the literature. *Journal of Pain and Symptom Management.* **20**: 140–151.
7 Hooper L *et al.* (2004) The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. *British Medical Journal.* **329**: 948.
8 Baxter K (ed) (2008) *Stockley's Drug Interactions* (8e). Pharmaceutical Press, London.
9 Sorkin E and Ogawa C (1983) Cimetidine potentiation of narcotic action. *Drug Intelligence and Clinical Pharmacy.* **17**: 60–61.
10 Leontiadis GI *et al.* (2005) Systematic review and meta-analysis of proton pump inhibitor therapy in peptic ulcer bleeding. *British Medical Journal.* **330**: 568.
11 NICE (2004) *Dyspepsia. Management of dyspepsia in adults in primary care.* In: Clinical Guideline 17. National Institute for Clinical Excellence. Available from: www.nice.org.uk/page.aspx?o=CG017
12 Johnston DA and Wormsley KG (1988) The effect of food on ranitidine-induced inhibition of nocturnal gastric secretion. *Alimentary Pharmacology and Therapeutics.* **2**: 507–511.

MISOPROSTOL AHFS 56:28.28

Class: Prostaglandin analog, gastroprotective drug.

Indications: Healing of gastric or duodenal ulcers (including NSAID-induced ulcers), prevention of NSAID-induced gastroduodenopathy.

Contra-indications: Pregnancy (misoprostol increases uterine tone).

Pharmacology

Misoprostol is a synthetic PG analog with gastric antisecretory and protective properties. After oral administration, it is rapidly converted to an active free acid. Misoprostol helps *prevent* NSAID-related gastroduodenal erosions and ulcers.[1–3] In relation to *healing* NSAID-related gastroduodenal injury, misoprostol and PPIs are equally effective.[4] In one RCT, PPIs were more effective at preventing relapse (relapse rate: PPI 39%, misoprostol 52%, placebo 73%).[4] However, a systematic review indicates that the evidence for prophylactic benefit is much stronger for misoprostol than for PPIs.[3] The use of misoprostol is limited by its tendency to cause intestinal colic and diarrhea.
Bio-availability 90% PO.
Onset of action <30min.
Time to peak plasma concentration 30min.
Plasma halflife 1–2h for free acid.
Duration of action 2–4h.

Cautions
Women of childbearing age should use effective contraception.
Conditions where hypotension might precipitate severe complications, e.g. cerebrovascular disease, cardiovascular disease.

Undesirable effects
For full list, see manufacturer's PI.
Diarrhea (may necessitate stopping treatment), colic, dyspepsia, flatulence, nausea and vomiting, abnormal vaginal bleeding (intermenstrual, menorrhagia, postmenopausal), rashes, dizziness.

Dose and use

Cochrane review: Misoprostol, PPIs, and double-dose H_2-receptor antagonists are effective at *preventing* chronic NSAID-related endoscopic peptic ulcers. Misoprostol 400microgram/24h is less effective than 800microgram and is still associated with diarrhea. Of all these treatments, only misoprostol 800microgram/24h has been definitely shown to reduce the overall incidence of ulcer complications (perforation, hemorrhage or obstruction).[5] PPIs definitely reduce the incidence of re-bleeding from endoscopically confirmed peptic ulcers,[6] and may reduce the incidence of ulcer complications.[3]

NSAID-associated ulcers may be treated with an H_2-receptor antagonist, a PPI or misoprostol. In most cases, the causal NSAID need not be discontinued during treatment.[4,7] Consideration should be given to switching to a less toxic NSAID (see p.234).

Prophylaxis against NSAID-induced ulcers
200microgram b.i.d.–q.i.d. taken with the NSAID.

NSAID-associated ulceration
- 200microgram t.i.d. with meals & at bedtime *or*
- 400microgram b.i.d. (breakfast and bedtime) for 4–8 weeks.[1]

If causes diarrhea, give 200microgram t.i.d. & at bedtime and avoid **magnesium salts**.

Supply
Cytotec® (Searle)
Tablets 100microgram, 200microgram, 28 days @ 200microgram b.i.d. = $88.

1 Bardhan KD *et al.* (1993) The prevention and healing of acute NSAID-associated gastroduodenal mucosal damage by misoprostol. *British Journal of Rheumatology.* **32**: 990–995.
2 Silverstein FE *et al.* (1995) Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. *Annals of Internal Medicine.* **123**: 241–249.
3 Hooper L *et al.* (2004) The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. *British Medical Journal.* **329**: 948.
4 Hawkey C *et al.* (1998) Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. *New England Journal of Medicine.* **338**: 727–734.
5 Rostom A *et al.* (2002) Prevention of NSAID-induced gastroduodenal ulcers. *The Cochrane Database of Systematic Reviews.* **10**: CD002296.
6 Leontiadis GI *et al.* (2005) Systematic review and meta-analysis of proton pump inhibitor therapy in peptic ulcer bleeding. *British Medical Journal.* **330**: 568.
7 Hawkins C and Hanks G (2000) The gastroduodenal toxicity of nonsteroidal anti-inflammatory drugs. A review of the literature. *Journal of Pain and Symptom Management.* **20**: 140–151.

PROTON PUMP INHIBITORS — AHFS 56:40

Class: Gastroprotective drugs.

Indications: Acid dyspepsia, acid reflux, erosive esophagitis, prevention and treatment of peptic ulceration (including prevention (**lansoprazole**) and †treatment of NSAID-induced ulceration), pathological hypersecretion of gastric acid (e.g. multiple endocrine adenomas, Zollinger-Ellison syndrome), eradication of *Helicobacter pylori* (in combination with antibacterials).

Pharmacology

Proton pump inhibitors (PPIs) reduce gastric acid output but, in contrast to H_2-receptor antagonists, do not reduce the volume of gastric secretions. Because **lansoprazole**, **omeprazole**, **pantoprazole** and **rabeprazole** are all rapidly degraded by acid, they are formulated as EC granules or tablets. These dissolve in the duodenum where the drug is rapidly absorbed to be selectively taken up by gastric parietal cells and converted into active metabolites. These irreversibly inhibit the proton pump (H^+/K^+-ATPase) and thereby block gastric acid secretion. Elimination is predominantly by metabolism in the liver to inactive derivatives excreted mainly in the urine. The plasma halflives of PPIs are all <2h but, because they irreversibly inhibit the proton pump, the antisecretory activity continues for several days until new proton pumps are synthesized.

When treating peptic ulceration **lansoprazole** 30mg/24h is as effective as **omeprazole** 40mg/24h, and **pantoprazole** 40mg/24h is as effective as **omeprazole** 20mg/24h.[1] However, **omeprazole** shows a dose-response curve above the standard dose of 20mg/24h, whereas no further benefit is seen by increasing the dose of **lansoprazole** and **pantoprazole** above 30mg and 40mg/24h respectively.[2,3] Thus, **omeprazole** 40mg/24h is superior to **lansoprazole** 60mg/24h and **pantoprazole** 80mg/24h in the management of severe gastro-esophageal reflux disease (esophagitis and stricture).[4]

The bio-availability of **lansoprazole** is reduced by food and the manufacturer recommends that it should be given each morning 1h before breakfast. However, the reduced bio-availability appears not to reduce efficacy.[5–7] In one study comparing **lansoprazole** given either before or after food, acid suppression was comparable with both regimens after 1 week (although on day 1 it was significantly less when taken after food).[8] Pharmacokinetic data are shown in Table 1.8.

Onset of action <2h.

Duration of action >24h.

Table 1.8 Pharmacokinetic features of PPIs given PO

	Bio-availability (%)	*Time to peak plasma concentration (h)*	*Plasma halflife (h)*
Lansoprazole	80–90	1.5–2	1–2
Omeprazole	60	3–6	0.5–3
Pantoprazole	77	2–2.5	1[a]

a. increases to 3–6h in cirrhosis.

Cautions

Serious undesirable drug reactions: ocular damage,[9] impaired hearing, angina, hypertension. Most cases of ocular damage have been reported with IV **omeprazole** (not USA).[10] PPIs possibly cause vasoconstriction by blocking K^+/H^+-ATPase. Because the retinal artery is an end-artery, anterior ischemic optic neuropathy may result. If the PPI is stopped, visual acuity may improve. Some patients have become permanently blind, in some instances after 3 days. Impaired hearing and deafness have also been reported, again mostly with IV **omeprazole**. A similar mechanism may be responsible for the angina and hypertension included in the manufacturer's list of undesirable effects for PO **omeprazole**.

Severe hepatic impairment. All PPIs increase gastric pH, and this can affect the absorption of other drugs. The EMEA recommends that PPIs should not be used concurrently with **atazanavir**, because of a study in which **omeprazole** reduced the trough plasma concentrations and AUC of **atazanavir** by 75%. Increasing the **atazanavir** dose by 33% did not compensate for this decrease.[11] **Omeprazole** also reduces **indinavir** levels, and should not be used concurrently.[12] Further, **omeprazole** and **rabeprazole** decrease the absorption of **ketoconazole**; **omeprazole** also reduces the absorption of **itraconazole** from capsules but not oral solution. Increased azole doses may be necessary to avoid treatment failure; alternatively, giving the azole with an acidic drink, e.g. Cola, minimizes the interaction.[12] Conversely, increased gastric pH with **omeprazole** increases the bio-availability of **digoxin** by 10%.[12]

PPIs are metabolized by the cytochrome P450 family of liver enzymes (see Cytochrome P450, p.537). However, clinically important interactions are rare with PPIs.[13,14] Sedation and gait disturbances have been reported when **omeprazole** was given with **diazepam**, **flurazepam**, or **lorazepam**. **Omeprazole** levels are increased by some macrolides (**clarithromycin**, **erythromycin**) and azole antifungals (**fluconazole**, **ketoconazole**, **voriconazole**).[12] No significant interactions between **pantoprazole** and other drugs have been identified.[12,15]

Undesirable effects

For full list, see manufacturer's PI.

Common (<10%, >1%): headache, abdominal pain, nausea, vomiting, diarrhea or constipation, flatulence.

Dose and use

Cochrane review: PPIs, **misoprostol**, and double-dose H_2-receptor antagonists are effective at *preventing* chronic NSAID-related endoscopic peptic ulcers. **Misoprostol** 400microgram/24h is less effective than 800microgram and is still associated with diarrhea. Of all these treatments, only **misoprostol** 800microgram/24h has been definitely shown to reduce the overall incidence of ulcer complications (perforation, hemorrhage or obstruction).[16] PPIs definitely reduce the incidence of re-bleeding from endoscopically confirmed peptic ulcers,[17] and may reduce the incidence of ulcer complications.[18]

UK guidelines state that PPIs are preferable to H_2-receptor antagonists for the treatment of dyspepsia, gastro-esophageal reflux disease and peptic ulcers, including NSAID-induced peptic ulcers (for comparison with H_2-receptor antagonists, see Table 1.5, p.14).[19] PPIs are used in combination with antibacterials for the eradication of *Helicobacter pylori* (see p.359).

Lansoprazole

- 30mg each morning for 4 weeks, followed by 15mg each morning indefinitely
- some patients may need 30mg each morning for 8 weeks.

A dose of 15–30mg b.i.d. is recommended when **lansoprazole** is being used with antibacterials to eradicate *Helicobacter pylori* (see p.359). In severe hepatic impairment, the total daily dose should be limited to 30mg.

The PI for **lansoprazole** states that administration should be a.c. in order to achieve 'optimal acid inhibition'. However, published data suggest that this precaution is unnecessary.[7,8] For patients with obstructive dysphagia and acid dyspepsia or with severe gastritis and vomiting, the rectal route can be used.[20]

Omeprazole

- 20mg each morning for both treatment and prevention of ulcer recurrence
- 40mg each morning in reflux esophagitis if poor response to standard dose
- 20mg b.i.d. when **omeprazole** is being used with antibacterials to eradicate *Helicobacter pylori* (see p.359).

In severe hepatic impairment, the total daily dose should be limited to 20mg.

For patients who cannot safely swallow tablets, **lansoprazole** can be given as orodispersible tablets (Prevacid Solutabs®) or oral suspension. Alternatively, **lansoprazole** or **omeprazole** capsules can be opened and the EC granules swallowed with water or fruit juice, or mixed with apple sauce or yoghurt. Specific procedures are available from the manufacturers for administration by enteral feeding tubes (see p.519).

Omeprazole has been used in the management of acute bleeding from an endoscopically proven peptic ulcer, either PO or IV.[17]

PPI injections and infusions are alkaline (pH 9–10.5) and should not be mixed with other drugs.

Supply

Omeprazole (generic)

Capsules enclosing EC granules 20mg, 28 days @ 20mg once daily = $88.

Prilosec® (AstraZeneca)
Capsules enclosing EC granules 10mg, 20mg, 40mg, 28 days @ 20mg once daily = $127.

Lansoprazole
Prevacid® (Tap)
Capsules enclosing EC granules 15mg, 30mg, 28 days @ 30mg once daily = $137.
Tablets orodispersible (Solutab®) 15mg, 30mg, 28 days @ 30mg once daily = $111.
Oral suspension (sachet of oral EC granules to mix with water) 15mg, 30mg/sachet, 28 days @ 30mg once daily = $138.

Prevacid IV® (Tap)
Injection (powder for reconstitution and use as an IV injection/infusion) 30mg vial = $25.

Pantoprazole
Protonix® (Wyeth)
Tablets EC 20mg, 40mg, 28 days @ 40mg once daily = $127.

Protonix IV® (Wyeth)
Injection (powder for reconstitution and use as an IV injection/infusion) 40mg vial = $20.

Esomeprazole
Nexium IV® (AstraZeneca)
Injection (powder for reconstitution and use as an IV injection/infusion) 20mg vial = $30, 40mg vial = $30.

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LOPERAMIDE AHFS 56:08

Class: Antidiarrheal.

Indications: Acute and chronic diarrhea, ileostomy (to improve fecal consistency).

Contra-indications: Colitis (ulcerative, infective, or antibiotic-associated).

Pharmacology

Loperamide is a potent μ-opioid receptor agonist.[1] Although well absorbed from the GI tract, it is almost completely metabolized by the liver where it is conjugated and excreted via the bile. Further, although highly lipophilic,[2] loperamide is a substrate for the efflux membrane transporter, P-glycoprotein, in the blood-brain barrier and it is actively excluded from the CNS.[3,4] Consequently, loperamide acts almost exclusively via a local effect in the GI tract[1] and the maximum therapeutic impact may not manifest for 16–24h, which has implications for dosing.[4]

Loperamide also has an effect on other peripheral μ-opioid receptors, including those which are activated in the presence of inflammation.[5] Accordingly, it is currently under investigation as a possible topical analgesic for painful skin ulcers.

Like **morphine** and other μ-receptor agonists, loperamide decreases propulsive intestinal activity and increases non-propulsive activity.[2,6] It also has an intestinal antisecretory effect mediated by calmodulin antagonism, which is a property not shared by other opioids.[7–9] Paradoxically, loperamide also reduces sodium-dependent uptake of glucose and other nutrients from the small bowel.[10] Tolerance does not occur. Unlike **diphenoxylate**, loperamide has no analgesic effect in therapeutic and supratherapeutic doses (but see Cautions). CNS effects have been observed rarely in children under 2 years of age who received excessive doses.[11,12] Loperamide is about 3 times more potent than **diphenoxylate** and 50 times more potent than **codeine**.[13] It is longer acting and, if used regularly, generally needs to be given only b.i.d. The following regimens are approximately equivalent:

- loperamide 2mg b.i.d.
- **diphenoxylate** 2.5mg q.i.d. (in combined **diphenoxylate** and **atropine** tablets)
- **codeine phosphate** 60mg q.i.d.

Bio-availability 10% PO.
Onset of action about 1h; maximum effect 16–24h.[14]
Time to peak plasma concentration 2.5h (syrup); 5h (capsules).[15]
Plasma halflife 11h.[15]
Duration of action up to 3 days.[16]

Cautions

Inhibitors of P-glycoprotein (e.g. **ketoconazole**, **quinidine**, **verapamil**) allow loperamide to cross the blood-brain barrier and thereby manifest central opioid effects.[3] Severe hepatic impairment leads to increased plasma concentrations with a risk of CNS effects.

Undesirable effects

For full list, see manufacturer's PI.

Excessive use of loperamide may cause symptomatic constipation or fecal impaction associated with overflow diarrhea and/or urinary retention.

A patient on **clozapine** (an atypical antipsychotic) died of toxic megacolon after taking loperamide during an episode of food poisoning. Additive inhibition of intestinal motility was considered the precipitating cause.[17]

Dose and use

Ensure that the diarrhea is not secondary to fecal impaction.

Acute diarrhea

- start with 4mg PO stat
- continue with 2mg after each loose bowel action for up to 5 days
- maximum recommended dose 16mg/24h.

Chronic diarrhea

If symptomatic treatment is appropriate, the same initial approach is used for 2–3 days, after which a prophylactic b.i.d. regimen is instituted based on the needs of the patient during the previous 24h, plus 2mg after each loose bowel action. The effective dose varies widely. In palliative care, it is occasionally necessary to increase the dose to as much as 32mg/24h; *this is twice the recommended maximum daily dose*.

Supply

Loperamide (generic)
Capsules 2mg, 28 days @ 2mg q.i.d. = $36.

Imodium® (Janssen)
Caplets (capsule-shaped tablets) Imodium A-D®, 2mg, 28 days @ 2mg q.i.d. = $43.
Tablets chewable Imodium E-Z meltaways®, 2mg, 28 days @ 2mg q.i.d. = $45.
Oral syrup 1mg/5mL, 28 days @ 2mg q.i.d. = $38.

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LAXATIVES AHFS 56:12

Constipation is common in advanced cancer,[1] particularly in immobile patients with small appetites and those receiving constipating drugs such as opioids.[2,3] Exercise and increased dietary fiber are rarely feasible options.[4] Although some strong opioids are less constipating than **morphine** (e.g. **fentanyl**, **methadone**, **tramadol**), most patients receiving any opioid regularly will need a laxative concurrently.[1,5] Thus, as a general rule, all patients prescribed **morphine** (or other opioid) should also be prescribed a laxative (see Guidelines, p.24).

About 1/3 of patients also need rectal measures[6,7] either because of failed oral treatment or electively, e.g. in bedbound debilitated elderly patients, or patients with paralysis (see Guidelines, p.24).

There are several classes of laxatives (Box 1.E).[8,9] **Docusate sodium** is classed here as a surface-wetting agent, i.e. a fecal softener, and not a contact (stimulant) laxative. At doses

commonly used, it acts mainly by lowering surface tension, thus enabling water to percolate into the substance of the feces.

Opioids cause constipation by decreasing propulsive intestinal activity and increasing non-propulsive activity, and also by enhancing the absorption of fluid and electrolytes.[2,10] Colonic contact (stimulant) laxatives reduce intestinal ring contractions and thus facilitate propulsive activity. In this way, they provide a logical approach to the correction of opioid-induced constipation. In practice, a combination of a peristaltic stimulant and a fecal softener is often prescribed.[11–13]

Few RCTs of laxatives have been completed in palliative care patients:

- **senna** vs. **lactulose**[14]
- **senna** vs. **misrakasneham** (an Ayurvedic herbal remedy)[15]
- **senna** and **lactulose** vs. **magnesium hydroxide** and **mineral oil**.[16]

There were no significant differences between these treatments.

Box 1.E Classification of commonly used laxatives

Bulk-forming agents (fiber)
Methylcellulose
Psyllium husk (e.g. Metamucil®)
Sterculia (e.g. Normacol®)

Lubricants
Mineral oil

Surface-wetting agents
Docusate sodium

Osmotic laxatives
Lactulose syrup
Polyethylene glycol
Magnesium hydroxide suspension (Milk of Magnesia®)
Magnesium sulfate (Epsom Salts)

Contact (stimulant) laxatives
Bisacodyl
Senna

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Guidelines: Management of opioid-induced constipation

All opioids constipate, although to a varying extent. Morphine is more constipating than methadone and fentanyl. The aim of treatment is to achieve a regular bowel action without straining, generally every 1–3 days.

1. Ask about the patient's past (premorbid) and present bowel habit, and use of laxatives; record the date of last bowel action.
2. Palpate for fecal masses in the line of the colon; examine the rectum digitally if the bowels have not been open for >3 days or if the patient reports rectal discomfort or has diarrhea suggestive of fecal impaction with overflow.
3. For inpatients, keep a daily record of bowel actions.
4. Encourage fluids generally, and fruit juice and fruit specifically.
5. When an opioid is prescribed, prescribe docusate sodium 50mg-senna 8.6mg 2 tablets b.i.d. Note: it is sometimes appropriate to optimize a patient's existing laxative regimen, rather than change automatically to docusate sodium-senna.
6. Adjust the dose every 2–3 days according to results, up to 4 tablets t.i.d. (This is a total daily dose of docusate sodium 600mg and senna 103mg.)
7. During dose titration and subsequently: if >3 days since last bowel action, give suppositories, e.g. bisacodyl 10mg and glycerin 4g, or a micro-enema. If ineffective, administer a phosphate enema, and possibly repeat the next day.
8. If the maximum dose of docusate sodium-senna is ineffective, halve the dose and add lactulose 20mL b.i.d. or polyethylene glycol 1 sachet each morning, and titrate as necessary.
9. Alternatively, switch completely to an osmotic laxative, e.g. lactulose 20–40mL b.i.d.–t.i.d. or polyethylene glycol 1–3 sachets each morning.
10. Lactulose or polyethylene glycol may be preferable in patients with a history of colic with colonic stimulants (senna, bisacodyl).

Guidelines: Bowel management in paraplegia and tetraplegia

Theoretically, management is determined by the level of the spinal cord lesion:
- above T12–L1 = cauda equina intact → spastic bowel with preserved sacral reflex; generally responds to digital stimulation of the rectum; the presence of an anal reflex suggests an intact sacral reflex
- below T12–L1 = cauda equina involved → flaccid bowel; generally requires digital evacuation of the rectum
- a lesion at the level of the conus medullaris (the cone shaped distal end of the spinal cord, surrounded by the sacral nerves) may manifest a mixture of clinical features.

However, in practice, management tends to follow a common pathway.

Aims

Primary: to achieve the controlled regular evacuation of normal formed feces:
- every day in long-term paraplegia/tetraplegia, e.g. post-traumatic
- every 1–3 days in advanced cancer.

Secondary: to prevent both incontinence (feces too soft, over-treatment with laxatives) and an anal fissure (feces too hard, under-treatment with laxatives).

continued

Oral laxatives

In debilitated patients with a poor appetite, a bulking agent is unlikely to be helpful, and may result in a soft impaction.

Particularly if taking morphine or another constipating drug, an oral contact (stimulant) laxative should be prescribed, e.g. bisacodyl tablets 5–10mg b.i.d. The dose should be carefully titrated to a level which results in normal feces *in the rectum* but without causing an uncontrolled evacuation.

In relatively well patients with a good appetite (probably the minority):
- maintain a high fluid intake
- encourage a high roughage diet, e.g. wholegrain cereals, wholemeal foods, greens, bran or a bulk-forming laxative, e.g. psyllium (ispaghula) husk.

Beware:
- the prescription of docusate sodium, a fecal softener, may result in a soft fecal impaction of the rectum, and fecal leakage through a patulous anus
- oral bisacodyl in someone not on opioids may cause multiple uncontrolled evacuations, at the wrong time and in the wrong place.

Rectal measures

Initially, if impacted with feces, empty the rectum digitally. Then, develop a daily routine:
- as soon as convenient after waking up in the morning, insert 2 glycerin suppositories, or 1–2 bisacodyl suppositories (i.e. 10–20mg), or a micro-enema deep into the rectum, and wait 1.5–2h
- because the bisacodyl acts only after absorption and biotransformation, bisacodyl suppositories must be placed against the rectal wall, and not into feces
- the patient should be encouraged to have a hot drink after about 1h in the hope that it will stimulate a gastro-colonic reflex
- if there is a strong sacral reflex, some feces will be expelled as a result of the above two measures
- to ensure complete evacuation of the rectum and sigmoid colon, digitally stimulate the rectum:
  - insert gloved and lubricated finger (either soap or gel)
  - rotate finger 3–4 times
  - withdraw and wait 5min
  - if necessary, repeat 3–4 times
  - check digitally that rectum is fully empty.

Patients who are unable to transfer to the toilet or a commode will need nursing assistance. Sometimes it is easiest for a patient to defecate onto a pad while in bed in a lateral position.

If the above measures do not achieve complete evacuation of the rectum and sigmoid colon, proceed to digital evacuation (more likely with a flaccid bowel). A pattern will emerge for each patient, allowing the rectal measures to be adjusted to the individual patient's needs and response.

PSYLLIUM HUSK (ISPAGHULA HUSK) AHFS 56:12

Included for general information. Psyllium husk (synonym, ispaghula husk) is *not recommended* as a laxative in palliative care patients. It may sometimes be helpful in regulating the consistency of feces (making them more formed) in a patient with a colostomy/distal ileostomy.

Class: Bulk-forming laxative.

Indications: Chronic atonic or spastic constipation, constipation associated with rectal disorders (e.g. anal fissure, hemorrhoids), irritable bowel syndrome, †colostomy/ileostomy regulation, †diverticular disease, †ulcerative colitis.

Contra-indications: Dysphagia, intestinal obstruction, colonic atony, fecal impaction.

Psyllium is derived from the husks of an Asian plant, *Plantago ovata*. It has very high water-binding capacity, is partly fermented in the colon, and increases bacterial cell mass. Like other bulk-forming laxatives, psyllium stimulates peristalsis by increasing fecal mass. Its water-binding capacity also helps to make loose feces more formed in some patients with a colostomy/distal ileostomy.
Onset of action full effect obtained only after several days.
Duration of action best taken regularly to obtain a consistent ongoing effect; may continue to act for 2–3 days after the last dose.

Cautions

Adequate fluid intake should be maintained to avoid intestinal obstruction.

Undesirable effects

For full list, see manufacturer's PI.
Flatulence, abdominal distension, fecal impaction, intestinal obstruction.

Dose and use

Psyllium swells in contact with fluid and needs to be drunk quickly before it absorbs water. Stir the granules or powder briskly in 150mL of water and swallow immediately; carbonated water can be used if preferred. Alternatively, the granules can be swallowed dry, or mixed with a vehicle such as jelly, and followed by 100–200mL of water. Give 1 sachet each morning–t.i.d., preferably after meals; not immediately before going to bed.

Supply

Metamucil® (Procter & Gamble)
Oral powder 3.4g/sachet, 28 days @ 1 sachet b.i.d. = $14; *orange flavor.*
Oral powder bulk, 30oz = $10; *orange flavor.*

CONTACT (STIMULANT) LAXATIVES AHFS 56:12

Indications: Treatment and †prevention of constipation, colonic evacuation before examination or procedure.

Contra-indications: Large intestinal obstruction.

Pharmacology

Senna is a mixture of two naturally occurring plant glycosides (sennosides A and B). It is inactive and passes unabsorbed and unchanged through the small intestine; it is then hydrolyzed by *bacterial* glycosidases in the large intestine to yield an active metabolite.[1] Systemic absorption of sennosides or the active metabolite is small. The laxative effect is through direct contact with the submucosal (Meissner's) plexus and the deeper myenteric (Auerbach's) plexus, resulting in both a secretory and a motor effect in the large intestine. The motor effect precedes the secretory effect, and is the more important laxative action. There is a decrease in segmenting muscular activity and an increase in propulsive waves. Differences in bacterial flora may explain differences in individual response to **senna**.

Bisacodyl has a similar laxative effect to **senna**.[1] However, it is hydrolyzed by intestinal enzymes and thus acts on both the small and large intestines. When applied directly to the intestinal mucosa in normal subjects, **bisacodyl** induces powerful propulsive motor activity within minutes.[2]

Phenolphthalein is another contact laxative, and is present in some proprietary laxatives. **Phenolphthalein** exists in two forms: white and yellow. The yellow form contains several impurities produced during manufacture. These impurities enhance the laxative effect of **phenolphthalein** such that the comparable dose of the yellow form is only 2/3 that of the pure white form. The active constituent of **phenolphthalein** is released in two stages: by metabolism in the liver and subsequently in the colon, and it probably undergoes enterohepatic circulation.[3] Some people respond to small doses.

Few RCTs of laxatives have been completed in palliative care patients:

- **senna** vs. **lactulose**[4]
- **senna** vs. **misrakasneham** (an Ayurvedic herbal remedy)[5]
- **senna** and **lactulose** vs. **magnesium hydroxide** and **mineral oil**.[6]

There were no significant differences between these treatments.

Onset of action

Senna 8–12h.

Bisacodyl tablets 10–12h; suppositories 20–60min.

Undesirable effects

For full list, see manufacturer's PI.

Intestinal colic, diarrhea. **Bisacodyl** suppositories may cause local rectal inflammation. **Phenolphthalein** occasionally causes a drug rash or photosensitivity. Rarely, it causes encephalitis which can be fatal.

Dose and use

Because of the constipating effect of opioids (and other drugs), the doses recommended here for contact (stimulant) laxatives sometimes exceed those recommended in the AHFS and PIs. At many centers, the laxative of choice is **senna** with **docusate sodium** in a combination tablet.

All palliative care services should have a protocol for the management of opioid-induced constipation (see Guidelines, p.24).[7–10] Likewise, there is need for a protocol for patients with paraplegia and tetraplegia (see Guidelines, p.24).

Bisacodyl

- start with 10–20mg PO at bedtime
- if necessary, increase by stages to 20mg PO t.i.d.
- by suppository: 10–20mg PR once daily.

Senna

- start with 2 tablets at bedtime but 4 tablets if taking opioids (or 2 tablets b.i.d.)
- if necessary, increase to 2–4 tablets t.i.d.

Docusate sodium and senna

• see Guidelines referred to above, p.24.

Supply

Bisacodyl (generic)
Tablets EC 5mg, 28 days @ 10mg at bedtime = $3.
Suppositories 10mg, 28 days @ 10mg once daily = $6.

Dulco-lax® (Boehringer Ingelheim)
Tablets EC 5mg, 28 days @ 10mg at bedtime = $15.
Suppositories 10mg, 28 days @ 10mg once daily = $31.

Senna (generic)
Tablets total **sennosides**/tablet 8.6mg, 28 days @ 2 tablets at bedtime = $7.

Senokot® (Purdue Frederick)
Tablets total **sennosides**/tablet 8.6mg, 28 days @ 2 tablets at bedtime = $12.
Oral syrup total **sennosides** 8.8mg/5mL, 28 days @ 10mL at bedtime = $22.

Combination products
Docusate sodium and senna (generic)
Tablets **docusate sodium** 50mg + **sennosides** 8.6mg, 28 days @ 2 b.i.d. = $6.

Senokot-S® (Purdue)
Tablets **docusate sodium** 50mg + **sennosides** 8.6mg, 28 days @ 2 b.i.d. = $47.

1 Jauch R *et al.* (1975) Bis-(p-hydroxyphenyl)-pyridyl-2-methane: the common laxative principle of bisacodyl and sodium picosulfate. *Arzneimittel-Forschung Drug Research*. **25**: 1796–1800.
2 De Schryver AM *et al.* (2003) Effects of a meal and bisacodyl on colonic motility in healthy volunteers and patients with slow-transit constipation. *Digestive Diseases and Sciences*. **48**: 1206–1212.
3 Godding EW (1975) Constipation and allied disorders: 3. Therapeutic agents-chemical laxatives (section 2). *Pharmaceutical Journal*. **215**: 60–62.
4 Agra Y *et al.* (1998) Efficacy of senna versus lactulose in terminal cancer patients treatment with opioids. *Journal of Pain and Symptom Management*. **15**: 1–7.
5 Ramesh P *et al.* (1998) Managing morphine-induced constipation: a controlled comparison of an Ayurvedic formulation and senna. *Journal of Pain and Symptom Management*. **16**: 240–244.
6 Sykes N (1991) A clinical comparison of lactulose and senna with magnesium hydroxide and liquid paraffin emulsion in a palliative care population. [cited in Miles CL *et al.* (2006) Laxatives for the management of constipation in palliative care patients. The Cochrane Database of Systematic Reviews. CD003448].
7 Levy MH (1996) Pharmacologic treatment of cancer pain. *New England Journal of Medicine*. **335**: 1124–1132.
8 Pappagallo M (2001) Incidence, prevalence, and management of opioid bowel dysfunction. *American Journal of Surgery*. **182 (suppl 5A)**: 11s–18s.
9 Bouvy ML *et al.* (2002) Laxative prescribing in relation to opioid use and the influence of pharmacy-based intervention. *Journal of Clinical Pharmacy and Therapeutics*. **27**: 107–110.
10 Herndon CM *et al.* (2002) Management of opioid-induced gastrointestinal effects in patients receiving palliative care. *Pharmacotherapy*. **22**: 240–250.

DOCUSATE SODIUM AHFS 56:12

Class: Surface-wetting agent (fecal softener).

Indications: Constipation (particularly where straining during defecation must be avoided), †hemorrhoids, †anal fissure, †bowel preparation before abdominal radiography, †partial bowel obstruction.

Pharmacology

Although sometimes classified as a stimulant laxative, docusate sodium (docusate) is principally an emulsifying and wetting agent and has a relatively weak effect on GI transit. Docusate lowers surface tension, thereby allowing water and fats to penetrate hard, dry feces. It also stimulates fluid secretion by the small and large intestines.[1,2] Docusate does not interfere with protein or fat absorption.[3] Docusate has been evaluated in several groups of elderly patients; frequency of

defecation increased and the need for enemas decreased almost to zero.[4–6] Given these clinical results, it is surprising that, in a study in normal subjects, docusate did not increase fecal weight.[7] In palliative care, docusate is not recommended as the sole laxative except in patients with partial bowel obstruction.[8] The routine combination of docusate and a contact (stimulant) laxative has been criticized because of a lack of published data supporting such a regimen.[9] However, in the USA, such a combination is widely used with good effect in patients with opioid-induced constipation (see Guidelines, p.24).

Onset of action 12–72h.

Cautions

Docusate enhances the absorption of **mineral oil**;[10] combined products containing these substances are prohibited in some countries.

Undesirable effects

For full list, see manufacturer's PI.

Diarrhea, nausea, abdominal cramp, rashes. Docusate solution may cause an unpleasant aftertaste or burning sensation, minimized by drinking plenty of water after taking the solution.

Dose and use

Docusate combined with **senna** is widely used as the laxative of choice for opioid-induced constipation (see Guidelines, p.24). Docusate is often used alone for patients with persistent partial bowel obstruction. Dose varies according to individual need:

- generally start with 100mg b.i.d.
- if necessary, increase to 200mg b.i.d.–t.i.d.

Supply

Docusate (generic)
Capsules 100mg, 28 days @ 100mg b.i.d. = $3.
Oral solution 50mg/5mL, 28 days @ 10mL b.i.d. = $16.

Colace® (Roberts)
Capsules 100mg, 28 days @ 100mg b.i.d. = $17.

Combination products
Docusate and **senna** (generic)
Tablets docusate 50mg + **sennosides** 8.6mg, 28 days @ 2 b.i.d. = $6.

Senokot-S® (Purdue)
Tablets docusate 50mg + **sennosides** 8.6mg, 28 days @ 2 b.i.d. = $47.

1 Donowitz M and Binder H (1975) Effect of dioctyl sodium sulfosuccinate on colonic fluid and electrolyte movement. *Gastroenterology.* **69**: 941–950.
2 Moriarty K *et al.* (1985) Studies on the mechanism of action of dioctyl sodium sulphosuccinate in the human jejunum. *Gut.* **26**: 1008–1013.
3 Wilson J and Dickinson D (1955) Use of dioctyl sodium sulfosuccinate (aerosol O.T.) for severe constipation. *Journal of the American Medical Association.* **158**: 261–263.
4 Cass L and Frederik W (1956) Doxinate in the treatment of constipation. *American Journal of Gastroenterology.* **26**: 691–698.
5 Harris R (1957) Constipation in geriatrics. *American Journal of Digestive Diseases.* **2**: 487–492.
6 Hyland C and Foran J (1968) Dicotyl sodium sulphosuccinate as a laxative in the elderly. *Practitioner.* **200**: 698–699.
7 Chapman R *et al.* (1985) Effect of oral dioctyl sodium sulfosuccinate on intake-output studies of human small and large intestine. *Gastroenterology.* **89**: 489–493.
8 Twycross RG and Wilcock A (2001) *Symptom Management in Advanced Cancer* (3e). Radcliffe Medical Press, Oxford.
9 Hurdon V *et al.* (2000) How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. *Journal of Pain and Symptom Management.* **19**: 130–136.
10 Godfrey H (1971) Dangers of dioctyl sodium sulfosuccinate in mixtures. *Journal of the American Medical Association.* **215**: 643.

LACTULOSE AHFS 40:10

Class: Osmotic laxative.

Indications: Constipation, hepatic encephalopathy.

Contra-indications: Intestinal obstruction, galactosemia.

Pharmacology

Lactulose is a synthetic disaccharide, a combination of galactose and fructose, which is not absorbed by the small intestine.[1] It is a 'small bowel flusher', i.e. through an osmotic effect, lactulose deposits a large volume of fluid into the large intestine. Lactulose is fermented in the large intestine to acetic, formic and lactic acids, hydrogen and carbon dioxide, with an increase in fecal acidity, which also stimulates peristalsis. The low pH discourages the proliferation of ammonia-producing organisms and thereby reduces the absorption of ammonium ions and other nitrogenous compounds; hence its use in hepatic encephalopathy.[2] Lactulose does not affect the management of diabetes mellitus. Although the calorific value of lactulose is about 1kcal/mL, because bio-availability is negligible, the number of calories absorbed is much lower.

Few RCTs of lactulose have been completed in palliative care patients:

- **senna** vs. lactulose[3]
- **senna** and lactulose vs. **magnesium hydroxide** and **mineral oil**.[4]

There were no significant differences between these treatments.

Onset of action up to 48h.

Undesirable effects

For full list, see manufacturer's PI.

Abdominal bloating, discomfort and flatulence, diarrhea, intestinal colic.

Dose and use

Lactulose is used particularly in patients who experience intestinal colic with contact (stimulant) laxatives, or who fail to respond to contact (stimulant) laxatives alone.

- starting dose 15mL b.i.d. and adjust according to need
- in hepatic encephalopathy, 30–50mL t.i.d.; adjust dose to produce 2–3 soft fecal evacuations per day.

Supply

Lactulose (generic)

Oral solution 10g/15mL, 28 days @ 15mL b.i.d. = $23.

1 Schumann C (2002) Medical, nutritional and technological properties of lactulose. An update. *European Journal of Nutrition*. **41 (suppl 1)**: 117–25.

2 Zeng Z *et al.* (2006) Influence of lactulose on the cognitive level and quality of life in patients with minimal hepatic encephalopathy. *Chinese Journal of Clinical Rehabilitation*. **10**: 165–167.

3 Agra Y *et al.* (1998) Efficacy of senna versus lactulose in terminal cancer patients treatment with opioids. *Journal of Pain and Symptom Management*. **15**: 1–7.

4 Sykes N (1991) A clinical comparison of lactulose and senna with magnesium hydroxide and liquid paraffin emulsion in a palliative care population. [cited in Miles CL *et al.* (2006) Laxatives for the management of constipation in palliative care patients. The Cochrane Database of Systematic Reviews. CD003448].

POLYETHYLENE GLYCOL

Class: Osmotic laxative.

Indications: Constipation, fecal impaction.

Contra-indications: Severe inflammatory conditions of the intestines, intestinal obstruction.

Pharmacology

Polyethylene glycol 3350 acts by virtue of an osmotic action in the intestines, thereby producing an increase in fecal volume which induces a laxative effect. Electrolytes present in the formulation ensure that there is virtually no net gain or loss of sodium and potassium. Polyethylene glycol 3350 is unchanged in the GI tract, virtually unabsorbed and has no known pharmacological activity. Any absorbed polyethylene glycol 3350 is excreted via the urine.

At some centers, it is the first-line laxative for opioid-induced constipation (often supplemented with a contact/stimulant laxative).[1] In an open study in 27 adults of its use in fecal impaction without concurrent rectal measures, polyethylene glycol 3350 cleared the impaction in 44% in ≤1 day, 85% in ≤2 days, and 89% in ≤3 days.[2,3]

Onset of action 1–2 days for constipation; 1–3 days for fecal impaction.

Undesirable effects

For full list, see manufacturer's PI.

Uncommon (<1%, >0.1%): abdominal bloating, discomfort, borborygmi, nausea.

Very rare (<0.01%): electrolyte shift (edema, shortness of breath, dehydration and heart failure).

Dose and use

Each sachet is taken in 240mL of water.

Fecal impaction

- 8 sachets on day 1, to be taken in <6h
- patients with cardiovascular impairment should restrict intake to not more than 2 sachets/h
- repeat on days 2 and 3 p.r.n.

Most patients do not need the full dose on the second day.

Constipation

- start with 1 sachet once daily
- if necessary, increase to 1 sachet t.i.d.

Although it is more expensive than **lactulose** (another osmotic laxative), it is more effective and better tolerated.[4]

Supply

MiraLax® (Braintree)

Oral powder polyethylene glycol 3350 17g/sachet, 28 days @ 1sachet once daily = $19; *available OTC.*

1 Wirz S and Klaschik E (2005) Management of constipation in palliative care patients undergoing opioid therapy: is polyethylene glycol an option? *American Journal of Hospice and Palliative Care.* **22**: 375–381.

2 Culbert P *et al.* (1998) Highly effective oral therapy (polyethylene glycol/electrolyte solution) for faecal impaction and severe constipation. *Clinical Drug Investigation.* **16**: 355–360.

3 Culbert P *et al.* (1998) Highly effective new oral therapy for faecal impaction. *British Journal of General Practice.* **48**: 1599–1600.

4 Attar A *et al.* (1999) Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. *Gut.* **44**: 226–230.

MAGNESIUM SALTS AHFS 56:12

Class: Osmotic laxative.

Indications: Constipation, particularly in patients who experience intestinal colic with contact (stimulant) laxatives, or who fail to respond to the latter.

Pharmacology

Magnesium and sulfate ions are poorly absorbed from the gut. Their action is mainly osmotic but other factors may be important, e.g. the release of cholecystokinin.[1,2] Magnesium ions also decrease absorption or increase secretion in the small bowel. Total fecal PGE_2 increases

progressively as the dose of magnesium *hydroxide* is raised from 1.2 to 3.2g/24h.[3] Also see **Magnesium**, p.421.

An RCT of magnesium *hydroxide* and **liquid paraffin** vs. **senna** and **lactulose** failed to differentiate between the two combination treatments.[4]

Cautions

Risk of hypermagnesemia in patients with renal impairment.

Dose and use

Magnesium *hydroxide* mixture contains about 8% of hydrated magnesium *oxide* and the usual dose is 25–50mL. Magnesium *sulfate* is a more potent laxative which tends to produce a large volume of liquid stool. The compound is not popular with patients because it often leads to a sense of distension and the sudden passage of offensive liquid feces which is socially inconvenient; it is very difficult to adjust the dose to produce a normal soft stool. The usual dose is 4–10g of crystals each morning, preferably before breakfast, dissolved in warm water and taken with extra fluid.

Supply

All the products below are available OTC.

Magnesium *hydroxide*

Phillips Milk of Magnesia® (Bayer)

Oral suspension contains about 8% hydrated magnesium *oxide*, 415mg/5mL, 355mL = $7; *do not store in a cold place*.

Magnesium *sulfate* USP

Epsom Salts (Rite Aid)

Oral powder 1.8kg = $3 (ARP); available OTC.

Oral solution magnesium *sulfate* 4–5g/10mL can be compounded.

1 Donowitz M (1991) Magnesium-induced diarrhea and new insights into the pathobiology of diarrhea. *New England Journal of Medicine*. **324**: 1059–1060.

2 Harvey R and Read A (1975) Mode of action of the saline purgatives. *American Heart Journal*. **89**: 810–813.

3 Donowitz M and Rood R (1992) Magnesium hydroxide: new insights into the mechanism of its laxative effect and the potential involvement of prostaglandin E2. *Journal of Clinical Gastroenterology*. **14**: 20–26.

4 Sykes N (1991) A clinical comparison of lactulose and senna with magnesium hydroxide and liquid paraffin emulsion in a palliative care population. [cited in Miles CL *et al.* (2006) Laxatives for the management of constipation in palliative care patients. The Cochrane Database of Systematic Reviews. CD003448].

RECTAL PRODUCTS AHFS 56:12

Indications: Constipation and fecal impaction if oral laxatives are ineffective.

Treatment strategy

One third of patients receiving **morphine** continue to need rectal measures (laxative suppositories, enemas and/or digital evacuation) either regularly or intermittently despite oral laxatives.[1,2] Sometimes these measures are elective, e.g. in paraplegics and in the very old and debilitated (Box 1.F; also see Guidelines, p.24).

In the USA, most patients needing laxative suppositories receive both **glycerin** and **bisacodyl**. **Glycerin** is hygroscopic, and draws fluid into the rectum, thereby softening and lubricating any feces in the rectum. The laxative effect of **bisacodyl** is the result of local direct contact with the rectal mucosa after dissolution of the suppository and after metabolism by intestinal bacteria to an active metabolite (see p.27). The minimum time for response is thus generally >20min, and may be up to 3h.[3] (Defecation a few minutes after the insertion of a **bisacodyl** suppository is the result of ano-rectal stimulation.) **Bisacodyl** suppositories occasionally cause fecal leakage, even after a successful evacuation.

Fecal softener mini-enemas contain **docusate sodium**, a wetting agent (see p.28), which allows water to permeate into hard feces. In contrast, osmotic standard enemas contain

phosphates, and draw fluid into the rectum by osmosis. Digital evacuation is the ultimate approach to fecal impaction; the need for this can be reduced by using **polyethylene glycol** (see p.30).[4,5]

Box 1.F Rectal measures for the relief of constipation or fecal impaction

Suppositories
Glycerin 4g, has a hygroscopic and lubricant action; also said to be a rectal stimulant but this is unsubstantiated.

Bisacodyl 10mg, after hydrolysis by enteric enzymes, stimulates propulsive activity.[6]

Enemas
Fecal softener mini-enema, contains docusate sodium 283mg per unit.

Lubricant enema (118mL), contains mineral oil; this is generally instilled and left overnight before giving a bisacodyl suppository or an osmotic enema.

Osmotic standard enema (118mL), contains phosphates.

Supply

Suppositories
Glycerin USP
Glycerin (CB Fleet)
Suppositories 2g, pack of 12 = $7.

Bisacodyl (generic)
Suppositories 10mg, 28 days @ 10mg once daily = $6.

Dulco-lax® (Boehringer Ingelheim)
Suppositories 10mg, 28 days @ 10mg once daily = $31.

Fecal softener enema
DocuSol® constipation relief mini-enema (Western Research Labs), **docusate sodium** 283mg, **polyethylene glycol** and **glycerin**, 1unit = $1.50.

Lubricant enema
Mineral Oil USP
Fleet® mineral oil enema (CB Fleet), 118mL = $1.

Osmotic enemas
Fleet® ready-to-use saline enema (CB Fleet), **monobasic sodium phosphate** 19g, **dibasic sodium phosphate** 7g in 118mL, *contains 4.4g Na^+/enema*, 1 enema = $2.

Rite-Aid® complete ready-to-use enema (Rite-Aid), **monobasic sodium phosphate** 19g, **dibasic sodium phosphate** 7g in 133mL, *contains 4.4g Na^+/enema*, pack of 2 = $3.50 (ARP); *available OTC*.

1 Twycross RG and Lack SA (1986) *Control of Alimentary Symptoms in Far Advanced Cancer.* Churchill Livingstone, Edinburgh, pp. 173–174.
2 Twycross RG and Harcourt JMV (1991) The use of laxatives at a palliative care centre. *Palliative Medicine*. **5**: 27–33.
3 Flig E *et al.* (2000) Is bisacodyl absorbed at all from suppositories in man? *International Journal of Pharmaceutics.* **196**: 11–20.
4 Goldman M (1993) Hazards of phosphate enemas. *Gastroenterology Today.* **3**: 16–17.
5 Culbert P *et al.* (1998) Highly effective oral therapy (polyethylene glycol/electrolyte solution) for faecal impaction and severe constipation. *Clinical Drug Investigation*. **16**: 355–360.
6 von Roth W and von Beschke K (1988) Pharmakokinetik und laxierende wirkung von bisacodyl nach gabe verschiedener zubereitungsformen. *Arzneimittel Forschung Drug Research*. **38**: 570–574.

PRODUCTS FOR HEMORRHOIDS AHFS 53:08

Because hemorrhoids are often more troublesome if associated with the evacuation of hard feces, constipation must be corrected (see Laxatives, p.22). Peri-anal pruritus, soreness and excoriation are best treated by the application of a bland ointment or cream. Soothing products containing mild astringents such as **bismuth subgallate**, **zinc oxide** and **witch hazel** (**hamamelis**) all give symptomatic relief in hemorrhoids. Many proprietary products also contain lubricants, vasoconstrictors and antiseptics.

Local anesthetics relieve pruritus ani as well as pain associated with hemorrhoids. **Lidocaine** ointment can be used before defecation to relieve pain associated with an anal fissure. Local anesthetic ointments are absorbed through the rectal mucosa and could produce a systemic effect if applied excessively. They should be used for only a few days because, apart from **lidocaine**, they can cause contact dermatitis. Corticosteroids can be combined with local anesthetics and astringents; suitable for short-term use after exclusion of infection, such as *Herpes simplex*. Pain associated with spasm of the internal anal sphincter may be helped by topical **nitroglycerin** ointment (see p.52).

Dose and use

- apply cream or ointment topically b.i.d. and after defecation for 5–7 days (t.i.d.–q.i.d. on first day if necessary), then once daily for a few days after symptoms have cleared
- insert suppository after defecation and at bedtime for 5–7 days (in severe cases initially b.i.d.–t.i.d.).

Supply

Anusol® (Warner Lambert)
Ointment pramoxine hydrochloride 1%, zinc oxide 12.5%, mineral oil, 28g = $6.
Suppositories topical starch 51%, 7 days @ 1 once daily = $40.

Preparation H® (Whitehall Robins)
Cream glycerin 12%, petrolatum 18%, phenylephrine hydrochloride 0.25%, shark liver oil 3%, 51g = $10 (ARP); *available OTC*.
Ointment mineral oil 14%, petrolatum 72%, phenylephrine hydrochloride 0.25%, shark liver oil 3%, 28g = $7 (ARP); *available OTC*.
Gel phenylephrine hydrochloride 0.25%, witch hazel 50%, 51g = $11 (ARP); *available OTC*.
Suppositories cocoa butter 85.5%, phenylephrine hydrochloride 0.25%, shark liver oil 3%, pack of 48 = $20 (ARP); *available OTC*.

With corticosteroids
Preparation H® (Whitehall Robins)
***Ointment* hydrocortisone acetate** 1%, 26g = $6 (ARP); *available OTC*.

PANCREATIN AHFS 56:16

Class: Enzyme supplement.

Indications: †Symptomatic steatorrhea caused by biliary and/or pancreatic obstruction, e.g. cancer of the pancreas.

Pharmacology

Steatorrhea (the presence of undigested fecal fat) typically results in pale, bulky, offensive, frothy and greasy feces which flush away only with difficulty; associated with abdominal distension, increased flatus, loss of weight, and mineral and vitamin deficiency (A, D, E and K).

Pancreatin is a standardized preparation of porcine lipase, protease and amylase. Pancreatin hydrolyzes fats to glycerol and fatty acids, degrades protein into amino acids, and converts starch into dextrin and sugars. Because it is inactivated by gastric acid, pancreatin is best taken with food (or immediately before or after food). Gastric acid secretion may be reduced by giving **ranitidine** an hour before meals or a PPI once daily. Concurrent use of antacids further reduces gastric acidity. EC products, such as Creon®, deliver a higher enzyme concentration in the duodenum provided the granules are swallowed whole without chewing.

Cautions

Fibrotic strictures of the colon have developed in children with cystic fibrosis who have used high-strength preparations of pancreatin. This has not been reported in adults or in patients without cystic fibrosis. Creon® has not been implicated.

If mixing with food or drinks:

- avoid very hot food or drinks because heat inactivates pancreatin
- take immediately after mixing because the EC coating starts to dissolve if left to stand.

Undesirable effects

For full list, see manufacturer's PI.

Very common (>10%): abdominal pain.

Common (<10%, >1%): nausea and vomiting, constipation or diarrhea, allergic skin reactions.

Dose and use

There are several different pancreatin products, of which Creon® is a good choice. Capsule strength denotes lipase unit content. Thus, Creon® 10 contains 10,000units and Creon 20® contains 20,000units.

In adults, start with Creon® 10. The granules in the capsules are EC and, if preferred, may be added to fluid or soft food and *swallowed without chewing*:

- Creon® 10, initially give 1–2 capsules with each meal
- Creon® 20, initially give 1 capsule with each meal.

The dose is adjusted upwards according to fecal size, consistency, and number. Extra capsules may be needed if snacks are taken between meals. If the pancreatin continues to seem ineffective, prescribe a PPI or H_2-receptor antagonist concurrently, and review.

Supply

Creon® (Solvay)

A standardized preparation obtained from pigs; *there is no non-porcine alternative*.

Capsules enclosing EC granules Creon® 5, 28 days @ 2 t.i.d. = $90.

Capsules enclosing EC granules Creon® 10, 28 days @ 2 t.i.d. = $175.

Capsules enclosing EC pellets Creon® 20, 28 days @ 1 t.i.d. = $167.