1: GASTRO-INTESTINAL SYSTEM

ANTACIDS

Antacids taken by mouth to neutralize gastric acid include:
- magnesium salts
- aluminum hydroxide
- 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, the effect of **magnesium salts** tends increasingly to override the constipating effect of **aluminum**.[1]

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 (available OTC) contains Na^+ 53mg/5mL (equivalent to 4.6mmol/10mL dose) compared with 0.1nmol/10mL in **aluminum hydroxide-magnesium hydroxide** suspension (e.g. Almagel®). 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.

In post-radiation esophagitis and candidosis which is causing painful swallowing, an **aluminum hydroxide-magnesium hydroxide** suspension containing **oxethazine**, 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, **lidocaine** viscous oral suspension 2% (or a compounded **lidocaine** suspension) can be used (see p.449).

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
- except for **sodium bicarbonate**, antacids delay gastric emptying and may thereby modify drug absorption.

- most antacid tablets feel gritty when sucked; some patients dislike this
- some proprietary products are fruit-flavoured, e.g. Tums® (chewable tablet)
- the cheapest single-ingredient product is **aluminum hydroxide** chewable tablets (Amphojel®)
- the cheapest single-ingredient **magnesium** product is **milk of magnesia liquid** (generic), containing **magnesium hydroxide** 80mg/mL
- the cheapest **aluminum-magnesium** combination product is a generic store brand liquid product
- some antacids contain additional substances for use in specific situations, e.g. alginates (see below), **simethicone** (see p.3)
- magnesium-containing antacids should be used with caution in patients with renal impairment (see p.491); **calcium carbonate** is preferable.

Antacids are now generally only used p.r.n. for occasional dyspepsia; H_2-receptor antagonists (see p.15) and PPIs (see p.19) are used when continuous gastric acid reduction is indicated.[2]

Supply

See also **Simethicone**, p.3.

Aluminum hydroxide
Amphojel® (Aurium Pharma)
Tablets chewable 600mg, 28 days @ 1 t.i.d. & at bedtime = $27; *mint flavour.*
Oral suspension (sugar-free) 320mg/5mL, 28 days @ 10mL t.i.d. & at bedtime = $38; *mint flavour.*

Aluminum hydroxide-magnesium hydroxide
Almagel 200® (Laboratoire Atlas)
Oral suspension (sugar-free) **aluminum hydroxide** 200mg, **magnesium hydroxide** 200mg/5mL, 28 days @ 10mL t.i.d. & at bedtime = $13; *low Na^+.*

Calcium carbonate
Tums® (GlaxoSmithKline)
Tablets chewable regular strength, 500mg; extra strength, 750mg; ultra strength, 1,000mg; 28 days @ 2 t.i.d. & at bedtime = $7, $13 and $19 respectively; *low Na^+, fruit flavour.*

With **oxethazine**
Mucaine® suspension (Aurium Pharma)
Oral suspension **aluminum hydroxide** 300mg, **magnesium hydroxide** 100mg, **oxethazine** 10mg/5mL, 28 days @ 10mL t.i.d. a.c. & at bedtime = $77.

1 Morrissey J and Barreras R (1974) Antacid therapy. *New England Journal of Medicine*. **290**: 550–554.
2 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

ALGINATE PRODUCTS

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

Class: Alginate.

Indications: Acid reflux ('heartburn').

Pharmacology

Antacid products containing alginic acid or sodium alginate 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. Compound alginate products may thus be less effective if used with drugs which reduce acid (e.g. an H_2-receptor antagonist or a PPI) or products which reduce air bubbles (i.e. an antifoaming agent/antiflatulent).

Gaviscon® Liquid, 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, alginate-containing products are no better than **simethicone**-containing antacids in the treatment of acid reflux.[1] Compound alginate products have been largely superseded by acid suppression with PPIs and H_2-receptor antagonists.

Onset of action <5min.
Duration of action 1–2h.

Cautions

Gaviscon® Liquid contains Na^+ 53mg/5mL (equivalent to 4.6mmol/10mL dose). It 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 an alginate product and who are reluctant to change to **aluminum hydroxide–magnesium hydroxide** (or similar option), and if there are grounds for limiting sodium intake, choose one with a low sodium content, e.g. Gaviscon Heartburn Relief Tablets® (22mg Na^+/tablet).

Supply

Gaviscon® Liquid and tablets are available OTC.

Gaviscon Liquid® (GlaxoSmithKline)
Oral suspension (sugar-free) **sodium alginate** 250mg, **aluminum hydroxide** 100mg/5mL, 340mL bottle = $13 and 600mL bottle = $20; *53mg Na^+/5mL.*

Gaviscon Heartburn Relief Tablets® (GlaxoSmithKline)
Tablets chewable **alginic acid** 200mg, **magnesium carbonate** 40mg, 100 tablets = $20; *22mg Na^+/tablet.*

Gaviscon Heartburn Relief Extra Strength Tablets® (GlaxoSmithKline)
Tablets chewable **alginic acid** 313mg, **magnesium carbonate** 63mg, 60 tablets = $20; *35mg Na^+/tablet.*

Maalox Nighttime® (Novartis)
Oral suspension **sodium alginate** 275mg, calcium carbonate 300mg,
magnesium carbonate 125mg/5mL, 350mL bottle = $12; *45mg Na/5mL, mint flavour.*

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

Class: Antifoaming agent (antiflatulent).

Indications: Acid dyspepsia (including acid reflux), gassy dyspepsia, †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 single-agent products (e.g. Ovol®) and some combination antacids (e.g. Diovol Plus® and Maalox antacid with anti-gas®). By facilitating belching, simethicone eases flatulence, distension and postprandial gastric discomfort. Simethicone-containing antacids are as effective as alginate-containing

products in the treatment of acid reflux.[1] Simethicone-containing antacids should be used in preference to **alginate** products because they are more effective antacids, are cheaper, and contain less sodium.
Onset of action <5min.
Duration of action 1–2h.

Cautions

With high doses of mixed **aluminum–magnesium** antacids (>100–200mL/day), the laxative effect of **magnesium** tends to override the constipating effect of **aluminum**.[2]

Dose and use

Practice varies. Some centres initially prescribe simethicone alone; others use a combination antacid as a 'general purpose' antacid (and thus minimize the number of products kept in stock). Typical regimens include:

- simethicone alone:
  - 40–125mg t.i.d. p.c. and bedtime (plus p.r.n.)
  - maximum 500mg/day
- combination antacid:
  - Diovol Plus® or Maalox antacid with anti-gas® suspension 5mL t.i.d. p.c. and bedtime (plus p.r.n.)
  - if necessary, increase to 10–30mL/dose.

Supply

A selection of products only.
Simethicone
Ovol® (Church and Dwight)
Tablets chewable 80mg, 180mg, 28 days @ 80mg q.i.d. = $26.

Gas X® (Novartis)
Tablets chewable 80mg, 125mg, 28 days @ 80mg q.i.d. = $31.

Phazyme® (GlaxoSmithKline)
Capsule softgel 95mg, 180mg, 28 days @ 95mg q.i.d. = $35.

With antacids
Diovol Plus® (Church & Dwight)
Tablets simethicone 25mg, **aluminum hydroxide–magnesium carbonate** co-dried gel 300mg, **magnesium hydroxide** 100mg, 28 days @ 2 q.i.d. = $34.
Oral suspension simethicone 25mg, **aluminum hydroxide** 165mg, **magnesium hydroxide** 200mg/5mL, 28 days @ 20mL q.i.d. = $68.

Diovol Plus AF Tablets® (Church & Dwight)
Tablets chewable simethicone 25mg, **calcium carbonate** 200mg, **magnesium hydroxide** 200mg, 28 days @ 2 q.i.d. = $47.

Gelusil® (Wellspring)
Tablets chewable simethicone 25mg, **aluminum hydroxide** 200mg, **magnesium hydroxide** 200mg, 28 days @ 2 t.i.d. & at bedtime = $53.

Maalox Antacid Quick Dissolve with anti-gas® (Novartis)
Tablets chewable simethicone 60mg, **calcium carbonate** 1g, 28 days @ 2 q.i.d. = $40.
Oral suspension simethicone 20mg, **aluminum hydroxide** 200mg, **magnesium hydroxide** 200mg/5mL, 28 days @ 20mL q.i.d. = $74.

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.
2 Morrissey J and Barreras R (1974) Antacid therapy. *New England Journal of Medicine*. **290**: 550–554.

ANTIMUSCARINICS

Indications: Smooth muscle spasm (e.g. bladder, intestine), motion sickness (**scopolamine** (**hyoscine**) ***hydrobromide*** TD), drying secretions (including surgical premedication, †sialorrhea, †drooling, †death rattle (noisy respiratory secretions) and †inoperable intestinal obstruction), †paraneoplastic pyrexia and sweating.

Contra-indications: See individual monographs.

Pharmacology

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

Except for **scopolamine hydrobromide**, which causes CNS depression at therapeutic doses, the tertiary amines stimulate the brain stem and higher centres, 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.411).

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 fibres 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 **hyoscine butylbromide** or **glycopyrrolate** are sometimes purposely combined in terminally ill patients with inoperable intestinal obstruction in order to prevent colic and to reduce vomiting.[6]

Box 1.B Drugs with antimuscarinic effects used in palliative care (Canada)[a]

- Antidepressants
  - TCAs, e.g. amitriptyline, imipramine
  - paroxetine (SSRI)
- Antihistamines, e.g.
  - chlorpheniramine
  - dimenhydrinate
  - promethazine
- Antiparkinsonians, e.g.
  - orphenadrine
  - procyclidine
- Antipsychotics (atypical)
  - olanzapine
- Antipsychotics (typical)
  - phenothiazines, e.g.
    - chlorpromazine
    - methotrimeprazine
    - prochlorperazine
- Antisecretory drugs
  - belladonna alkaloids
    - atropine
    - scopolamine (hyoscine)
  - glycopyrrolate
- Antispasmodics, e.g.
  - dicyclomine
  - oxybutynin
  - tolterodine

a. meperidine/pethidine, an opioid (not recommended), also has antimuscarinic effects.

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 details of antimuscarinic drugs used for death rattle

	Bio-availability	*Plasma halflife*	*Duration of action (antisecretory)*
Atropine	'readily absorbed' PO, SL	4h	no data
Glycopyrrolate	<5% PO	1.7h	7h
Hyoscine (scopolamine) butylbromide	8–10% PO	5–6h	<2h[a]
Scopolamine (hyoscine) hydrobromide	60–80% SL	5–6h	1–9h

a. in volunteers; possibly longer in moribund patients.

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**, **prednisone**, **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 SL tablets (e.g. **nitroglycerin**) may be reduced because of decreased saliva production.

Because antimuscarinics competitively block the final common (cholinergic) pathway through which prokinetics act,[8] concurrent prescription with **metoclopramide** and **domperidone** 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.411) and rectum.

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 and p.r.n. doses*	*CSCI dose/24 h*
Atropine	400microgram	1,000–2,000microgram
Glycopyrrolate	200microgram	600–1,200microgram
Hyoscine (scopolamine) butylbromide	20mg	20–300mg[a]
Scopolamine (hyoscine) hydrobromide	400microgram	1,200–2,000microgram

a. death rattle 20–60mg, some centres use up to 120mg; intestinal obstruction 60–300mg.

Antisecretory

Sialorrhea and drooling

Indicated particularly in patients with ALS/MND, advanced Parkinson's disease or with various disorders of the head and neck. Several regimens have been recommended, including:

- **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)
- compounded **glycopyrrolate** PO (see p.465)
- **scopolamine hydrobromide** 1mg/3 days TD.[9]

A regimen of **atropine** 1% 500microgram (1 drop) SL b.i.d. has been reported[10] but a controlled trial found 500microgram (2 drops) SL 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 (noisy respiratory secretions)

In Canada, antimuscarinic drugs for death rattle are generally given SC.[17] See Table 1.2 and Guidelines, p.10. In some countries the SL route is preferred, particularly in home care because it circumvents the need for injections. Treatment regimens, all off-label, are based mainly on local clinical experience, e.g.:

- **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)
- **glycopyrrolate** 100microgram SL q6h p.r.n. (see p.465)

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 500–1,000mg 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 antimuscarinic 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.405).

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.561). Anti-arrhythmics are not advisable if arrhythmias develop; but hypoxia and acidosis should be corrected.

Supply

See individual monographs: **glycopyrrolate** (p.465), **hyoscine (scopolamine) butylbromide** (p.11), **scopolamine (hyoscine) hydrobromide** (p.195), **oxybutynin** (p.411).

Atropine sulfate (generic)
Injection 400microgram/mL, 1mL ampoule = $1.50; 600microgram/mL, 1mL ampoule = $1.50.
Ophthalmic solution 1%, 5mL bottle = $3.50.

Minims® atropine sulfate (Chauvin)
Ophthalmic solution (single-dose units) 1%, 0.5mL single-dose unit = $2.

1 Sweetman SC (ed) (2005) *Martindale: The Complete Drug Reference* (34e). Pharmaceutical Press, London, p. 475.
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23 Calder K and Bruera E (2000) Thalidomide for night sweats in patients with advanced cancer. *Palliative Medicine*. **14**: 77–78.
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25 Caine ED (1979) Anticholinergic toxicity. *New England Journal of Medicine*. **300**: 1278.
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Guidelines: Management of death rattle (noisy respiratory secretions)

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.

Table Antimuscarinic antisecretory drugs for death rattle: typical SC doses

Drug	*Stat SC and p.r.n. doses*	*CSCI dose/24h*
Atropine	400microgram	1,200–2,000microgram
Glycopyrrolate	200microgram	600–1,200microgram
Hyoscine (scopolamine) *butylbromide*	20mg	20–120mg
Scopolamine (hyoscine) *hydrobromide*	400microgram	1,200–2,000microgram

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

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 *200–500*microgram, i.e. 800microgram–2mg/dose).

Glycopyrrolate 0.01% oral solution, 1mL (100microgram) SL q6h p.r.n.; A 0.05% solution (500microgram/mL) can be compounded from glycopyrrolate powder (see Box B).

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 (hyoscine) *hydrobromide*
- scopolamine (hyoscine) *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 also crosses the blood-brain barrier but tends to stimulate rather than sedate; concurrent use with midazolam or haloperidol is more likely to be necessary.

continued

Box B Examples of compounded oral solutions of glycopyrrolate

Based on glycopyrrolate injection
Glycopyrrolate 100microgram/mL (1mg/10mL)
Combine 25mL of Ora-Plus® and 25mL of Ora-Sweet®; add to 50mL preservative-free glycopyrrolate injection USP 200microgram/mL to make up to 100mL, and mix well.
Stable for 35 days at room temperature or in a refrigerator (refrigeration minimizes risk of microbial contamination).

Based on glycopyrrolate powder
Glycopyrrolate 500microgram/mL (5mg/10mL)
Add 5mL of glycerin to 50mg of glycopyrrolate powder and mix to form a smooth paste. Add 50mL of Ora-Plus® in portions and mix well. Add sufficient Ora-Sweet® or Ora-Sweet SF® to make a total volume of 100mL.
This solution is stable for 90 days at room temperature or in a refrigerator.

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 ampoule with 2.1mL lidocaine 1% (total volume 2.6–2.8mL), and give 250mg–1g SC/IM once daily
- some centres use larger volumes of lidocaine 1% (up to 4mL) and administer a divided dose at separate SC/IM sites once daily or 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).

HYOSCINE (SCOPOLAMINE) BUTYLBROMIDE

Class: Antimuscarinic.

Indications: Smooth muscle spasm (e.g. bladder, GI tract), †drying secretions (including sialorrhea, drooling, death rattle/noisy respiratory secretions and inoperable bowel obstruction), †paraneoplastic pyrexia and sweating.

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

Pharmacology

Hyoscine (scopolamine) butylbromide is an antimuscarinic (see p.5) and has both smooth muscle relaxant (antispasmodic) and antisecretory properties. It is a quaternary compound and, unlike **scopolamine (hyoscine) hydrobromide**, it does not cross the blood-brain barrier. In consequence, it does not have a central anti-emetic effect or cause drowsiness.

Oral bio-availability, based on urinary excretion, is <1%.[1] Thus, any antispasmodic effect reported after PO administration probably relates to a local contact effect on the GI mucosa.[2] In an RCT, hyoscine butylbromide 10mg t.i.d. PO and **acetaminophen** (**paracetamol**) 500mg t.i.d. both significantly reduced the severity of intestinal colic by >50%.[3] However, the difference between the benefit from these two drugs (both given in suboptimal doses) and placebo was only 0.5cm on a 10cm scale of pain intensity. This is of dubious clinical importance.[4] Thus the therapeutic value of PO hyoscine butylbromide for intestinal colic remains debatable.

The main uses for hyoscine butylbromide in palliative care are as an antispasmodic and antisecretory drug in inoperable GI obstruction, and as an antisecretory drug for death rattle. In an open non-randomized trial of hyoscine butylbromide 60mg/24h CSCI vs. **octreotide** 300microgram/24h CSCI, **octreotide** resulted in a more rapid reduction in the volume of gastric aspirate (by 75% vs. 50%) and improvement in nausea, although it was possible to remove nasogastric tubes in both groups after about 5 days.[5,6] However, higher doses of hyoscine butylbromide, e.g. 120–200mg/24h, have not been compared with **octreotide**.

In healthy volunteers, a bolus injection of 20mg has a maximum antisecretory duration of action of 2h.[7] However, the same dose by CSCI is often effective for 1 day in death rattle. Hyoscine butylbromide and **scopolamine hydrobromide** act faster than **glycopyrrolate** for this indication,[8,9] but the overall efficacy is generally the same[10] with death rattle reduced in 1/2–2/3 of patients.

Bio-availability <1% PO.[1]
Onset of action <10min SC/IM/IV; 1–2h PO.[11]
Time to peak plasma concentration 15min–2h PO.[1]
Plasma halflife 1–5h.[1]
Duration of action <2h in volunteers; probably longer in moribund patients.[7]

Cautions

Competitively blocks the prokinetic effect of **metoclopramide** and **domperidone**.[1,12] Increases the peripheral antimuscarinic effects of antihistamines, phenothiazines and TCAs (see Antimuscarinics, p.5).

Use with caution in conditions predisposing to tachycardia (e.g. thyrotoxicosis, heart failure, β-adrenergic receptor 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 Product Monograph.
Peripheral antimuscarinic effects (see p.5).

Dose and use

Inoperable intestinal obstruction with colic[13,14]
- start with 20mg SC stat and 60mg/24h CSCI
- if necessary, increase to 120mg/24h
- maximum reported dose 300mg/24h.

Some centres add **octreotide** 300–500microgram/24h if hyoscine butylbromide 120mg/24h fails to relieve symptoms adequately.

For patients with obstructive symptoms without colic, **metoclopramide** (see p.185) should be tried before an antimuscarinic because the obstruction is often more functional than organic.

Death rattle (noisy respiratory symptoms)
- start with 20mg SC stat, 20–60mg/24h CSCI, and/or 20mg SC q1h p.r.n.
- some centres use higher doses, namely 60–120mg/24h CSCI[9]

For use of alternative antimuscarinics, see Guidelines, p.10.

Supply

Buscopan® (Boehringer Ingelheim)
Tablets 10mg, 28 days @ 20mg q.i.d. = $79.
Injection 20mg/ml, 1ml amp = $5.

1 Boehringer Ingelheim GmbH *Data on file.*
2 Tytgat GN (2007) Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain. *Drugs*. **67**: 1343–1357.
3 Mueller–Lissner S *et al.* (2006) Placebo- and paracetamol-controlled study on the efficacy and tolerability of hyoscine butylbromide in the treatment of patients with recurrent crampy abdominal pain. *Alimentary Pharmacology & Therapeutics*. **23**: 1741–1748.
4 Farrar JT *et al.* (2000) Defining the clinically important difference in pain outcome measures. *Pain*. **88**: 287–294.
5 Mercadante S *et al.* (2000) Comparison of octreotide and hyoscine butylbromide in controlling gastrointestinal symptoms due to malignant inoperable bowel obstruction. *Supportive Care in Cancer*. **8**: 188–191.
6 Ripamonti C *et al.* (2000) Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: a prospective randomized trial. *Journal of Pain and Symptom Management*. **19**: 23–34.
7 Herxheimer A and Haefeli L (1966) Human pharmacology of hyoscine butylbromide. *Lancet*. **ii**: 418–421.
8 Back I *et al.* (2001) A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. *Palliative Medicine*. **15**: 329–336.
9 Bennett M *et al.* (2002) Using anti-muscarinic drugs in the management of death rattle: evidence based guidelines for palliative care. *Palliative Medicine*. **16**: 369–374.
10 Hughes A *et al.* (2000) Audit of three antimuscarinic drugs for managing retained secretions. *Palliative Medicine*. **14**: 221–222.
11 Sanches Martinez J *et al.* (1988) Clinical assessment of the tolerability and the effect of IK-19 in tablet form on pain of spastic origin. *Investigacion Medica International*. **15**: 63–65.
12 Schuurkes JAJ *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
13 De-Conno F *et al.* (1991) Continuous subcutaneous infusion of hyoscine butylbromide reduces secretions in patients with gastrointestinal obstruction. *Journal of Pain and Symptom Management*. **6**: 484–486.
14 Ripamonti C *et al.* (2001) Clinical-practice recommendations for the management of bowel obstruction in patients with end-stage cancer. *Supportive Care in Cancer*. **9**: 223–233.

PROKINETICS

Prokinetics accelerate gastro-intestinal 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.

Table 1.3 Gastric prokinetics[1]

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

Except for **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 fibres (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 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** and **metoclopramide** will still exert an anti-emetic effect at the dopamine receptors in the area postrema (see p.187).

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%.

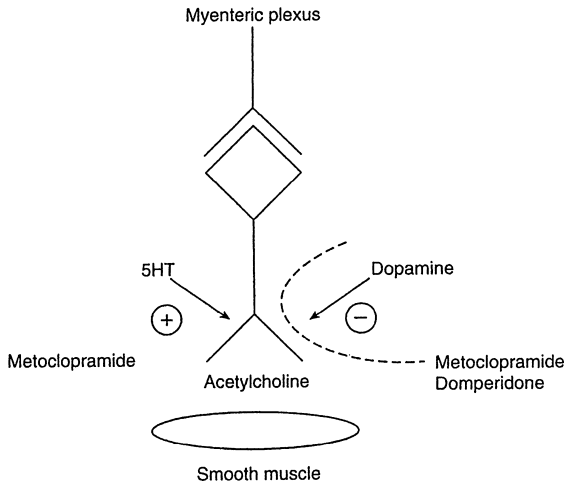

Figure 1.1 Schematic representation of drug effects on antroduodenal co-ordination via a postganglionic effect on the cholinergic nerves from the myenteric plexus.

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

Erythromycin, an antibiotic, 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 gastro-intestinal 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

Class: Gastroprotective drugs.

Indications: Chronic episodic dyspepsia, acid reflux, prevention and treatment of peptic ulceration (including NSAID-induced ulceration), †reduction of malabsorption and fluid loss in short bowel syndrome (**cimetidine**), †prevention of degradation of pancreatin supplements (**cimetidine**).

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.551). 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**, **nifedipine**), **pentoxifylline**, **theophylline**, **chlormethiazole** (not Canada), **diazepam**, TCAs, **moclobemide**, **phenytoin**, **methadone** and **fluorouracil**. **Cimetidine** inhibits the renal clearance of **procainamide** and **quinidine**.[8]

Hepatic impairment, renal impairment (see Table 1.7). **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** (not Canada) and **zolmitriptan**.[8,9] There are inconsistent reports of **cimetidine** and **ranitidine** increasing the plasma concentration of **midazolam**.[8]

Undesirable effects

See manufacturer's Product Monograph.
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 daily is less effective than 800microgram and is still associated with diarrhea. Of all these treatments, only **misoprostol** 800microgram daily 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 preferable in palliative care. However, H_2-receptor antagonists have been largely superseded by PPIs as the gastroprotective drugs of choice (see p.19).[11] H_2-receptor antagonists are second-line treatment for gastro-esophageal reflux disease, non-ulcer dyspepsia and uninvestigated dyspepsia.

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 IV use if treatment is considered necessary in a patient with severe nausea and vomiting. Some centres use 50mg SC b.i.d.–q.i.d. (off-label route) without evidence of local inflammation.

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**, reduce the dose to 150mg at bedtime in severe renal impairment, (creatinine clearance $<$30mL/min) but increase to 150mg b.i.d. if an ulcer fails to respond at the lower dose.

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. 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	200–400mg 1h a.c.	150mg 1h a.c.

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

Table 1.7 Dose adjustment for cimetidine in renal impairment

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 200mg, 300mg, 400mg, 600mg, 800mg, 28 days @ 400mg b.i.d. or 800mg at bedtime = $8 and $7 respectively.

Ranitidine (generic)
Tablets 150mg, 300mg, 28 days @ 150mg b.i.d. or 300mg at bedtime = $23 and $22 respectively.
Oral solution 75mg/5mL, 28 days @ 150mg b.i.d. = $66.
Injection 25mg/mL, 2mL amp = $2.50.

Zantac® (GSK)
Tablets 150mg, 300mg, 28 days @ 150mg b.i.d. or 300mg at bedtime = $11; *a 75mg Zantac® tablet is available OTC.*
Oral solution (sugar-free) 75mg/5mL, 28 days @ 150mg b.i.d. = $125; contains 7.5% alcohol, mint flavour.
Injection 25mg/mL, 2mL amp = $3.

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. *Cochrane Database Systematic Review*. **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) (2006) *Stockley's Drug Interactions* (7e). 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

Class: Prostaglandin analogue, gastroprotective drug.

Indications: Healing of duodenal ulcers, prevention and healing of NSAID-induced gastric and duodenal ulcers.

Contra-indications: Women of childbearing potential should not be started on misoprostol until pregnancy is excluded (misoprostol increases uterine tone).

Pharmacology

Misoprostol is a synthetic PG analogue 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 diarrhea and intestinal colic.

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 Product Monograph.
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 daily is less effective than 800microgram and is still associated with diarrhea. Of all these treatments, only misoprostol 800microgram daily 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.248).

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; avoid **magnesium salts**.

Supply
Misoprostol (generic)
Tablets 200microgram, 28 days @ 200microgram b.i.d. = $25.

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. *Cochrane Database 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

Class: Gastroprotective drugs.

Indications: Licensed indications vary between products; consult the manufacturers' product monographs for details; they include acid dyspepsia, acid reflux, peptic ulceration, prevention and treatment of NSAID-induced ulceration, eradication of *Helicobacter pylori* (with antibiotics).

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 they 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 mostly <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 daily is as effective as **omeprazole** 40mg daily, and **pantoprazole** 40mg daily is as effective as **omeprazole** 20mg daily.[1] However, **omeprazole** shows a dose-response curve above the standard dose of 20mg daily, whereas no further benefit is seen by increasing the dose of **lansoprazole** and **pantoprazole** above 30mg and 40mg daily respectively.[2,3] Thus, **omeprazole** 40mg daily is superior to **lansoprazole** 60mg daily and **pantoprazole** 80mg daily 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 >1 day.

Table 1.8 Pharmacokinetic details of PPIs given PO[9]

	Bio-availability (%)	*Time to peak plasma concentration (h)*	*Plasma halflife (h)*
Esomeprazole	64 (40mg single dose) 89 (40mg once daily for 5 days)	1–2	1.2 for 20mg 1.5 for 40mg
Lansoprazole	80–90	1.5–2	1–2
Omeprazole	60	3–6	0.5–3
Pantoprazole	77	2–2.5	1[a]
Rabeprazole	52	1.6–5	1

a. increases to 3–6h in cirrhosis.

Cautions

Serious undesirable drug reactions: ocular damage,[10] impaired hearing, angina, hypertension. Most cases of ocular damage have been reported with IV **omeprazole**.[11] PPIs possibly cause vasoconstriction by blocking H^+/K^+-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 US manufacturer's list of undesirable effects for **omeprazole**.

Severe hepatic impairment. Note: concern about serious cardiac events (infarction, death) with esomeprazole and omeprazole is now considered to be groundless.[12]

All PPIs increase gastric pH, and this can affect the absorption of other drugs. The European Medicines Agency (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.[13] **Omeprazole** also reduces **indinavir** levels, and should not be used concurrently.[14] 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.[14] Conversely, increased gastric pH with **omeprazole** increases the bio-availability of **digoxin** by 10%.[14]

PPIs are metabolized by the CYP450 family of liver enzymes (see Cytochrome P450, p.551). However, clinically important interactions are rare with PPIs.[15,16] 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**).[14]

The antithrombotic effect of **clopidogrel** (a pro-drug activated by CYP2C19) is reduced by concurrent administration with a PPI, including **rabeprazole**.[17–19] The evidence in relation to **pantoprazole** is equivocal.[17,18] Although **pantoprazole** is said not to inhibit CYP2C19,[18] and thus could be safe in this respect, the safest option would be to prescribe an H_2-receptor antagonist instead. e.g. **ranitidine**. No other significant CYP450 drug–drug interactions have been identified with **pantoprazole** or **rabeprazole**.[14,20]

Undesirable effects

For full list, see manufacturer's Product Monograph.
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 daily is less effective than 800microgram and is still associated with diarrhea. Of all these treatments, only **misoprostol** 800microgram daily has been definitely shown to reduce the overall incidence of ulcer complications (perforation, hemorrhage or obstruction).[21] PPIs definitely reduce the incidence of re-bleeding from endoscopically confirmed peptic ulcers,[22] and may reduce the incidence of ulcer complications.[23]

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.16).[24] PPIs are used together with antibiotics for the eradication of *Helicobacter pylori* (see p.367).

The choice of PPI is often determined by the local Drug and Therapeutics Committee, with cost being the overriding consideration. However, **pantoprazole** (available in PO and parenteral formulations) and **rabeprazole** (available only in PO formulations) cause fewer drug-drug interactions, and are preferable from a purely clinical perspective. For recommended dose regimens, see the manufacturers' Product Monographs.

Omeprazole has been used in the management of acute bleeding from an endoscopically proven peptic ulcer, either PO or IV.[22] **Omeprazole** has been used parenterally in palliative care to treat painful reflux esophagitis in patients too ill or unable to take PO medication. Although not approved for SC administration, it has been used successfully by this route for ⩽4 days.[25]

Supply

Pantoprazole (generic)
Tablets EC 20mg, 40mg, 28 days @ 40mg each morning = $39.
Injection (powder for reconstitution with 0.9% saline and use as an IV injection/infusion) 40mg vial = $11.

Pantoloc® (Altana)
Tablets EC 20mg, 40mg, 28 days @ 40mg each morning = $61.
Injection (powder for reconstitution with 0.9% saline and use as an IV injection/infusion) 40mg vial = $15.

Rabeprazole (generic)
Tablets EC 10mg, 20mg, 28 days @ 20mg each morning = $28.

Pariet® (Janssen-Ortho)
Tablets EC 10mg, 20mg, @ 20mg each morning = $39.

Esomeprazole magnesium trihydrate
Nexium® (AstraZeneca)
Delayed release tablet 20mg, 40mg, 28 days @ 40mg each morning = $63.
Sachet of EC delayed release granules (for dispersal in water) 10mg/sachet, 28 days @ 20mg each morning = $126.

Lansoprazole (generic)
Delayed release capsules 15mg, 30mg, 28 days @ 30mg each morning = $42.

Prevacid® (Tap Pharmaceuticals)
Delayed release capsules enclosing EC granules 15mg, 30mg, 28 days @ 30mg each morning = $60.
Delayed release tablets orodispersible (FasTab®) strawberry flavour 15mg, 30mg, 28 days @ 30mg each morning = $60.

Omeprazole (generic)
Capsules enclosing EC granules 10mg, 20mg, 28 days @ 20mg each morning = $31.

Losec® (AstraZeneca)
Delayed release capsules 10mg, 20mg, 28 days @ 20mg each morning = $33.
Delayed release tablets 10mg, 20mg, 28 days @ 20mg each morning = $66.

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LOPERAMIDE

Class: Antidiarrheal.

Indications: Acute non-specific diarrhea; chronic diarrhea associated with inflammatory bowel disease; reducing volume of discharge for ileostomies, colostomies and other intestinal resections.

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 GI tract.[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] as an antidiarrheal agent. 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 **diphenoxylate/atropine**, e.g. Lomotil®)
- **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 (oral solution); 4–6h (caplets, capsules, tablets).[15,16]
Plasma halflife 11h.[15]
Duration of action up to 3 days.[17]

Cautions

Inhibitors of P-glycoprotein (e.g. **cyclosporine**, **clarithromycin**, **erythromycin**, **intraconazole**, **ketoconazole**, **quinidine**, **ritonavir**, **verapamil**) may allow loperamide to cross the blood-brain barrier and thus potentially manifest central opioid effects.[3] Although available evidence is inconclusive for individual drugs, caution should be exercised when using loperamide with any medication known to inhibit P-gycoprotein. Severe hepatic impairment leads to increased plasma concentrations with a risk of CNS effects.

Undesirable effects

For full list, see manufacturer's Product Monograph.
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.[18]

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)
Tablets 2mg, 28 days @ 2mg q.i.d. = $43; also available OTC.
Oral solution 1mg/5mL, 28 days @ 2mg q.i.d. = $188; also available OTC.

Imodium® (McNeil)
Caplets 2mg, 28 days @ 2mg q.i.d. = $101; also available OTC.
Quick dissolve tablets 2mg, 28 days @ 2mg q.i.d. = $121; also available OTC.
Oral solution 2mg/15mL, 28 days @ 2mg q.i.d. = $102 OTC.

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LAXATIVES

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 fibre are rarely feasible options.[4] Although some strong opioids are less constipating than **morphine** (e.g. **fentanyl**),[5] most patients receiving any opioid regularly will need a laxative concurrently.[1] Thus, as a general rule, all patients prescribed **morphine** (or other opioid) should also be prescribed a laxative (see Guidelines, p.26).

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.27).

There are several classes of laxatives (Box 1.E).[8,9] At doses commonly used, **docusate sodium** acts mainly by lowering surface tension, thus enabling water to percolate into the substance of the feces; at higher doses it will also act as a contact (stimulant) laxative (see p.29).

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] 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. However, in practice, a combination of a peristaltic stimulant and a fecal softener is often prescribed,[11,12] although a recent study found no additional benefit when docusate was added to sennosides.[13]

Box 1.E Classification of commonly used laxatives

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

Lubricants
- Mineral oil

Surface-wetting agents
- Docusate sodium
- Docusate calcium

Osmotic laxatives
- Lactulose syrup
- Magnesium hydroxide suspension (Milk of Magnesia®)
- Magnesium sulfate (Epsom Salts)
- Magnesium citrate (Citro-Mag)

Contact (stimulant) laxatives
- Bisacodyl
- Sennosides

Few RCTs of laxatives have been completed in palliative care patients:
- **sennosides** vs. **lactulose**[14]
- **sennosides** vs. **misrakasneham** (an Ayurvedic herbal remedy)[15]
- **sennosides–lactulose** vs. **magnesium hydroxide–mineral oil**.[16]

There were no significant differences between these treatments.

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Guidelines: Opioid-induced constipation

Most patients taking an opioid need a laxative. Thus, as a general rule, all patients prescribed an opioid should also be prescribed a laxative, with the aim of achieving a regular bowel movement without straining every 1–3 days.

A standardized protocol is likely to enhance management. However, occasionally, rather than automatically changing to sennosides (see below), it may be more appropriate to optimize a patient's existing regimen.

1 Ask about the patient's past and present bowel habit and use of laxatives; record the date of last bowel movement.

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 movements.

4 Encourage fluids generally, and fruit juice and fruit specifically.

5 When an opioid is prescribed, unless contra-indicated (e.g. bowel obstruction), also prescribe sennosides:
- generally start with 17.2mg at bedtime and each morning
- if no response after 24 hours, increase to 25.8mg at bedtime and each morning
- if no response after a further 24 hours, consider adding a third daytime dose
- if necessary, consider increasing to a maximum of 34.4mg t.i.d.

6 During dose titration and subsequently, if ⩾3 days since last bowel movement, give laxative suppositories, e.g. glycerin 2.6g and bisacodyl 10mg, or a micro-enema. If these are ineffective, administer a phosphate enema and possibly repeat the next day.

7 If the maximum dose of sennosides is ineffective:
- halve the dose and add an osmotic laxative, e.g. lactulose 20mL b.i.d. or magnesium hydroxide (Milk of Magnesia®) 15–30mL b.i.d., and titrate as necessary *or*
- prescribe SC methylnaltrexone.

Methylnaltrexone

Because constipation in advanced disease is generally multifactorial in origin, methylnaltrexone ($41 per 12mg vial) is likely to augment rather than replace laxatives.
- marketed as a SC injection for use in patients with 'advanced illness' and opioid-induced constipation despite treatment with laxatives
- 50% of patients given methylnaltrexone have a bowel movement within 4 hours, without loss of analgesia or the development of opioid withdrawal symptoms
- dose recommendations:
  - for patients weighing 38–61kg, start with 8mg on alternate days
  - for patients weighing 62–114kg, start with 12mg on alternate days
  - outside this range, give 150*microgram*/kg on alternate days
  - the interval between administrations can be varied, either extended or reduced, but not more than once daily
- in severe renal impairment (creatinine clearance <30mL/minute) reduce the dose:
  - for patients weighing 38–61kg, reduce to 4mg
  - for patients weighing 62–114kg, reduce to 6mg
  - outside this range, reduce to *75microgram/kg*, rounding up the dose volume to the nearest 0.1mL
- methylnaltrexone is contra-indicated in cases of known or suspected GI obstruction
- common undesirable effects include abdominal pain, diarrhoea, flatulence, and nausea; these generally resolve after a bowel movement.

8 Alternatively, switch completely to an osmotic laxative, e.g. lactulose 20–40mL b.i.d.–t.i.d. or magnesium hydroxide (Milk of Magnesia®) 15–60mL b.i.d.

9 An osmotic laxative (lactulose, magnesium hydroxide) may be preferable in patients with a history of colic with stimulant laxatives (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 GI tract 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 GI tract; 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

1 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.

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

Oral measures

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

4 Particularly if taking morphine or another constipating drug, an oral contact (stimulant) laxative should be prescribed, e.g. sennosides 17.2mg b.i.d., bisacodyl tablets 5–10mg b.d. The dose should be carefully titrated to a level which results in normal feces *in the rectum* but without causing an uncontrolled evacuation.

5 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.

6 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.

continued

Rectal measures

7 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 (10–20mg), or a micro-enema deep into the rectum, and wait for 1.5–2 hours
- 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 1 hour 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 5 minutes
  - ▹ if necessary, repeat 3–4 times
  - ▹ check digitally that rectum is fully empty.

8 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.

9 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

Included for general information. Psyllium 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: Colostomy/ileostomy regulation, anal fissure, hemorrhoids, diverticular disease, irritable bowel syndrome, ulcerative colitis.

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

Pharmacology

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, thereby further increasing fecal bulk. 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 bowel obstruction.

Undesirable effects
For full list, see manufacturer's Product Monograph.
Flatulence, abdominal distension, fecal impaction, bowel obstruction.

Dose and use
Psyllium swells in contact with fluid and needs to be swallowed quickly before it absorbs water. Stir the powder briskly in 240mL of water and swallow immediately; carbonated water can be used if preferred. Alternatively, the powder can be mixed with a vehicle such as jam, and followed by 100–200mL of water. Give 3.3–3.4g each morning–t.i.d., preferably after meals; not immediately before bedtime.

Supply
Metamucil Fibre® (Proctor & Gamble)
Wafers 3.4g per 2 wafers, 24 per box = $8; *apple or cinnamon flavour.*
Capsules 525mg, 100 capsules = $20.
Powder Smooth Texture 3.3g per 5.95g of powder, 72 doses = $20; *sugar-free; orange, pink lemonade or berry burst flavour.*

CONTACT (STIMULANT) LAXATIVES

Indications: Prevention and treatment of constipation.

Contra-indications: Large intestinal obstruction.

Pharmacology
Sennosides 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 **sennosides**.

Bisacodyl has a similar laxative effect to **sennosides**.[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]

Few RCTs of laxatives have been completed in palliative care patients:
- **sennosides** vs. **lactulose**[3]
- **sennosides** vs. **misrakasneham** (an Ayurvedic herbal remedy)[4]
- **sennosides** and **lactulose** vs. **magnesium hydroxide** and **mineral oil**.[5]

There were no significant differences between these treatments. However, because they relax the intestinal ring contractions induced by opioids, contact laxatives should be considered the laxatives of choice for patients taking opioids. Compared to **lactulose**, **sennosides**:
- are faster acting
- come in liquid and tablet formulations (the latter may be crushed)
- cause no drug–drug interactions
- are easier to use in fluid-restricted cardiac patients
- may be taken by patients on a galactose-free diet.

Onset of action
Bisacodyl tablets 10–12h; suppositories 20–60min.
Sennosides 6–12h.

Undesirable effects

For full list, see manufacturer's Product Monograph.
Intestinal colic, diarrhea. **Bisacodyl** suppositories may cause local rectal inflammation, and/or fecal discharge.

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 manufacturers' Product Monographs.

Sennosides are widely used as the PO contact laxative of first choice. However, the mode of action of **bisacodyl** (it acts on both small and large intestines) suggests that it may be preferable in some patients. At some centres, the laxative of choice is **sennosides** combined with **docusate sodium**. However, published data suggest that patients generally respond as well to **sennosides** alone.[6]

All palliative care services should have a protocol for the management of opioid-induced constipation (see Guidelines, p.26).[7–10] Likewise, there is need for a protocol for patients with paraplegia and tetraplegia (see Guidelines, p.27).

For many people, the optimum time for taking sennosides is at bedtime, backed up by a second dose in the morning. The onset of action, 6–12h after administration, is then likely to coincide with the natural postprandial increase in intestinal propulsive activity (gastrocolic reflex) which peaks in many people during the hour after a meal, particularly breakfast.[11] However, if a patient experiences laxative-induced colic, a smaller dose should be given more frequently, e.g. t.i.d–q.i.d.

Sennosides

When an opioid is prescribed, unless contra-indicated (e.g. bowel obstruction):
- start with **sennosides** 17.2mg at bedtime and each morning
- if no response after 24h, increase to 25.8mg at bedtime and each morning
- if no response after a further 24h, consider adding a third daytime dose
- if necessary, consider increasing to a maximum of 34.4mg t.i.d.
- if the maximum dose of **sennosides** is ineffective, halve the dose and add an osmotic laxative (see Guidelines, p.26).

During dose titration and subsequently, if ⩾3 days elapse since last bowel movement, rectal measures should be considered. Note: at some centres, 12mg tablets are used in order to reduce the number of tablets to be taken.

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.

Supply

Sennosides (generic)
Tablets total **sennosides**/tablet 8.6mg, 12mg, 28 days @ 2 tablets b.i.d. = $12 and $16 respectively.

Senokot® (Purdue Frederick)
Tablets standardized **sennosides**/tablet 8.6mg, 28 days @ 2 tablets b.i.d. = $17.

Oral syrup standardized **sennosides** 1.7mg/mL, 28 days @ 10mL b.i.d. = $33.

Combination products
Docusate sodium and sennosides (generic)
Tablets **docusate sodium** 50mg, **sennosides** 8.6mg, 28 days @ 2 tablets b.i.d. = $20.

Senokot-S® (Purdue)
***Tablets* docusate sodium** 50mg, **sennosides** 8.6mg, 28 days @ 2 tablets b.i.d. = $30.

Bisacodyl (generic)
Tablets EC 5mg, 28 days @ 10mg at bedtime = $5.
Suppositories 10mg, 28 days @ 10mg once daily = $37.

Dulco-lax® (Boehringer Ingelheim)
Tablets EC 5mg, 28 days @ 10mg at bedtime = $15.
Suppositories 5mg, 10mg, 28 days @ 10mg once daily = $48.

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 Sciences*. **48**: 1206–1212.
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 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.
5 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]
6 Hawley PH and Byeon JJ (2008) A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *Journal of Palliative Medicine*. **11**: 575–581.
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.
11 Guyton A and Hall J (eds) (2006) *Textbook of Medical Physiology* (11e). Elsevier Saunders, Philadelphia.

DOCUSATE SODIUM

Class: Surface-wetting agent (fecal softener).

Indications: Constipation, 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] Although sometimes used together with a contact (stimulant) laxative for the management of opioid-induced constipation, published data indicate that patients generally respond equally well to **sennosides** alone.[9]
Onset of action 12–72h.

Cautions

Docusate enhances the absorption of **mineral oil**, and this combination should be avoided.[10]

Undesirable effects

For full list, see manufacturer's Product Monograph.

Diarrhea, nausea, colic, rashes. Docusate syrup can cause an unpleasant after-taste or burning sensation; this is minimized by drinking plenty of water after taking the syrup.

Dose and use

Docusate is often used alone in 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, 240mg, 28 days @ 100mg b.i.d. or 240mg b.i.d. = $4 and $6 respectively.
Syrup 4mg/1mL, 28 days @100mg b.i.d. = $61.
Oral drops 50mg/5mL, 28 days @ 100mg b.i.d. = $181.

Colace® (Wellspring)
Capsules 100mg, 28 days @ 100mg b.i.d. = $17.
Syrup 4mg/mL, 28 days @100mg b.i.d. = $61.
Oral drops 10mg/mL, 28 days @100mg b.i.d. = $186.

Combination products
With **sennosides** (generic)
Tablets docusate sodium 50mg, **sennosides** 8.6mg, 28 days @ 1 tablet b.i.d. = $10.

Senokot S® (Purdue)
Tablets docusate sodium 50mg, **sennosides** 8.6mg, 28 days @ 1 tablet b.i.d. = $15.

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 R *et al.* (2009) *Symptom Management in Advanced Cancer* (4e). palliativedrugs.com, Nottingham, pp. 108–111.
9 Hawley PH and Byeon JJ (2008) A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *Journal of Palliative Medicine.* **11**: 575–581.
10 Godfrey H (1971) Dangers of dioctyl sodium sulfosuccinate in mixtures. *Journal of the American Medical Association.* **215**: 643.

LACTULOSE

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; 15mL contains 19 calories, but because bio-availability is negligible (about 3%), 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 Product monograph.

Abdominal bloating, discomfort and flatulence, diarrhea, colic.

Dose and use

Lactulose is used particularly in patients who experience 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 (MACROGOL)

Class: Osmotic laxative.

Indications: Constipation, †fecal impaction.

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

Pharmacology

Polyethylene glycol acts by virtue of an osmotic action in the intestines, thereby producing an increase in fecal volume which induces a laxative effect. Polyethylene glycol is unchanged in the GI tract, virtually unabsorbed and has no known pharmacological activity. Any absorbed polyethylene glycol is excreted via the urine.

At some centres in Germany, 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 3,350 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 Product Monograph.
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 17g dose is taken in 250mL of water.

Constipation
- start with 17g once daily
- if necessary, increase progressively to 17g t.i.d. (this is three times the manufacturer's dose recommendation).

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

Fecal impaction
- 8 doses (8 x 17g) on day 1, to be taken in <6h
- patients with cardiovascular impairment should restrict intake to not more than 2 doses/h
- repeat on days 2 and 3 p.r.n.

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

Supply
Lax-A-Day® (Pharmascience)
Oral powder polyethylene glycol 3,350 510g bottle, (30 doses) = $37.

RestoraLAX® (Schering-Plough)
Oral powder polyethylene glycol 3,350 17g/sachet, 28 days @ 1sachet once daily = $50; 510g bottle (30 doses) = $32.

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

Class: Osmotic laxative.

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

Pharmacology
Magnesium 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 daily.[3] Also see **Magnesium**, p.429.

Magnesium hydroxide mixture BP contains about 8% of hydrated magnesium oxide. Magnesium sulfate is more potent and tends to produce a large volume of liquid feces. 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 result.

An RCT of magnesium hydroxide and **mineral oil** 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 USP
For opioid-induced constipation (see p.26), as an alternative to **lactulose** when an osmotic laxative is indicated:
- if the maximum dose of **sennosides** is ineffective, halve the dose and add magnesium hydroxide 15–30mL b.i.d., and titrate as necessary
- alternatively, switch completely to magnesium hydroxide 15–60mL b.i.d.

Magnesium hydroxide (or **lactulose**) may be preferable in patients with a history of colic with contact (stimulant) laxatives (see p.32).

Magnesium sulfate
A typical dose is 4–10g of crystals once daily *before breakfast*; dissolve in warm water and take with extra fluid.

Supply
Selected products only; all are available OTC.
Magnesium hydroxide
Magnesium Hydroxide Mixture USP
Oral suspension hydrated magnesium oxide 415mg (7.1mmol elemental magnesium)/5mL, 500mL bottle = $8, *do not store in a cold place*.

Phillips Milk of Magnesia® (Bayer)
Tablets 311mg, Bottle of 100 = $9.
Oral suspension 400mg/5mL, 769mL bottle = $13; cherry, mint, original flavours.

Magnesium sulfate
Oral solution magnesium sulfate (Epsom Salts) 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

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.27).

In the UK, 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.29). 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.

Osmotic micro-enemas contain mainly **sodium citrate** and **sodium lauryl sulfoacetate** with several excipients, including **glycerin** and sorbitol. **Sodium lauryl sulfoacetate** is a wetting agent (similar to **docusate sodium**), whereas **sodium citrate** draws fluid into the intestine by osmosis, an action enhanced by sorbitol, and displaces bound water from the feces. Osmotic standard enemas contain phosphates, which 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 oral **polyethylene glycols** (see p.33).[4,5]

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

Suppositories (must be placed in contact with rectal mucosa)
Glycerin 2.6g, 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
Lubricant enema (130mL) contains mineral oil; this is generally instilled and left overnight before giving a stimulant laxative suppository or an osmotic enema.

Osmotic micro-enemas (5mL) contain sodium citrate, sodium lauryl sulfoacetate, glycerin, and sorbitol.

Osmotic standard enemas (65–130mL), contain phosphates.

Supply

Suppositories
Glycerin
***Suppositories* glycerin** 2.34g, in adult suppository of 2.6g, 28 days @ 2.6g once daily = $7.

Bisacodyl (generic)
Suppositories 10mg, 28 days @ 10mg once daily = $37.

Dulco-lax® (Boehringer Ingelheim)
Suppositories 5mg, 10mg, 28 days @ 10mg once daily = $48.

Enemas
Fecal softener enema
Fleet® Ready-to-use Mineral Oil enema (Johnson & Johnson-Merck), **mineral oil** 100%, 130mL, 1 enema = $11.

Osmotic micro-enemas
These all contain **sodium citrate**, **sodium lauryl sulfoacetate**, **glycerin** and sorbitol and are supplied in 5ml single-dose disposable packs with nozzle:

Microlax Micro Enema® (McNeil Consumer Healthcare), **sodium citrate** 90mg, **sodium lauryl sulfoacetate** 9mg, sorbitol 625mg/mL single dose with nozzle, 5mL = $2.

Osmotic standard enema
Fleet® Ready-to-use enema (Johnson & Johnson-Merck), **monobasic sodium phosphate** 20.8g, **dibasic sodium phosphate** 7.8g in 130mL, 1 enema = $8.

Fleet® Ready-to-use Pediatric enema (Johnson & Johnson-Merck), **monobasic sodium phosphate** 10.4g, **dibasic sodium phosphate** 3.9g in 65 ml, 1 enema = $8.

Enemol® (Pendopharm), **monobasic sodium phosphate** 20.8g, **dibasic sodium phosphate** 7.8g in 130mL, 1 enema = $5.

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

Because hemorrhoids can be more troublesome if associated with the evacuation of hard feces, constipation must be corrected (see Laxatives, p.24).

Peri-anal pruritus, soreness and excoriation are best treated by the application of a bland ointment or cream. Suppositories are often not effective because they are inserted into the rectum, bypassing the anal canal where the medication is needed.

Soothing products containing mild astringents (e.g. **bismuth subgallate**, **zinc sulfate**, **hamamelis/witch hazel**) often provide symptomatic relief in hemorrhoids. Some products also contain vasoconstrictors and/or antiseptics.

Lidocaine ointment is used mainly to relieve pain associated with an anal fissure but will also relieve pruritus ani. Local anesthetic ointments are absorbed through the anal mucosa and, if applied excessively, could theoretically produce a systemic effect. They should be used for only a few days because all 'caines' can cause contact dermatitis.

Corticosteroids may be helpful if local inflammation is exacerbating discomfort. Infection (e.g. *Herpes simplex*) must first be excluded; and treatment limited to 7–10 days. Pain associated with spasm of the internal anal sphincter may be helped by topical **nitroglycerin** ointment (see p.53).

Dose and use

Topical products should be applied:
- t.i.d.–q.i.d. for the first 24h
- then b.i.d. and after defecation for 5–7 days or longer if necessary
- then daily for 3–5 days after symptoms have cleared.

Local anesthetic-containing products to ease painful defecation can also be applied b.i.d., p.r.n. (including before defecation if possible).

Supply

Various OTC products are available, and are not included here. The following list is highly selective.

Astringent
Anusol® (McNeil Consumer Healthcare)
***Ointment* zinc sulphate** 0.5%, 30g = $8.

Local anesthetic
Lidocaine (generic)
Ointment 5%, 35g = $9

Xylocaine® (Astra Zeneca)
***Ointment* lidocaine** 5%, 35g = $10.

Local anesthetic plus astringent
Anusol Plus® (McNeil Consumer Healthcare)
***Ointment* pramoxine** 1%, **zinc sulfate** 0.5%, 30g = $10.

Corticosteroid plus astringent
Generic
***Ointment* hydrocortisone** 0.5%, **zinc sulfate** 0.5%, 30g = $13.
Anusol HC ® (McNeil Consumer Healthcare)
***Ointment* hydrocortisone** 0.5%, **zinc sulfate** 0.5%, 30g = $24.

Corticosteroid plus local anesthetic and astringent
Anugesic®HC (McNeil Consumer Health)
***Ointment* hydrocortisone** 0.5%, **pramoxine** 1%, **zinc sulfate** 0.5%, 30g = $28.

PANCREATIN

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 a H_2-receptor antagonist, e.g. **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
- do not mix the capsule contents with alkaline foods or drinks, e.g. dairy products, because this degrades the EC coating
- take immediately after mixing because the EC coating starts to dissolve if left to stand.

Undesirable effects

For full list, see manufacturer's Product Monograph.

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 10,000 units and Creon 25® contains 25,000 units.

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® 25, 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®, lipase 5,000 units, amylase 16,600 units, protease 18,750 units, 28 days @ 2 t.i.d. = $31.

Capsules enclosing EC granules Creon 10®, lipase 10,000 units, amylase 33,200 units, protease 37,500 units, 28 days @ 2 t.i.d. = $49.

Capsules enclosing EC granules Creon 25®, lipase 25,000 units, amylase 74,000 units, protease 62,500 units, 28 days @ 2 t.i.d. = $153.