1: GASTRO-INTESTINAL SYSTEM

ANTACIDS BNF 1.1.1

Indications: Occasional dyspepsia and/or acid reflux; H_2-receptor antagonists (see p.26) and PPIs (see p.31) are used when continuous gastric acid reduction is indicated.[1]

Pharmacology

Antacids taken by mouth to neutralize gastric acid include:

- magnesium salts
- aluminium hydroxide
- hydrotalcite (aluminium magnesium carbonate hydroxide hydrate)
- calcium carbonate
- sodium bicarbonate.

Magnesium salts *are laxative and can cause diarrhoea;* ***aluminium salts*** *constipate.* Most proprietary antacids contain a mixture of **magnesium salts** and **aluminium salts** so as to have a neutral impact on intestinal transit. With doses of 100–200mL/24h or more, the effect of **magnesium salts** tends to override the constipating effect of **aluminium**.[2]

The sodium content of some antacids and alginate products may be detrimental in patients on salt-restricted diets, e.g. those with hypertension, heart failure or renal impairment. **Magnesium trisilicate mixture BP**, Gaviscon® Liquid, Acidex® liquid, and Peptac® oral suspension all contain 6mmol/10mL; Gaviscon® Advance liquid contains 4.6mmol/10mL. This compares with $<$1mmol/10mL in **co-magaldrox**.

Regular use of **sodium bicarbonate**, an ingredient in many OTC products, may cause sodium loading and metabolic alkalosis. **Calcium carbonate** may cause rebound acid secretion about 2h after each dose, and regular use may cause hypercalcaemia, particularly if taken with **sodium bicarbonate**.

Aluminium hydroxide binds dietary phosphate. It is of benefit in patients with hyperphosphataemia in renal failure. Long-term complications of phosphate depletion and osteomalacia are not an issue in advanced cancer. **Hydrotalcite**, an aluminium-magnesium complex, binds bile

salts and is of specific benefit in patients with bile salt reflux, e.g. after certain forms of gastroduodenal surgery.

In post-radiation oesophagitis and candidosis which is causing painful swallowing, an **aluminium hydroxide-magnesium hydroxide** suspension containing **oxetacaine**, a local anaesthetic, can be helpful; this is unauthorized in the UK. 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.

Other agents which are added to antacid products include alginates (see p.3) and **simeticone** (silica-activated **dimeticone**; see p.4).

Most antacid tablets feel gritty when sucked; some patients dislike this. Some proprietary products contain peppermint oil which masks the chalky taste of the antacid and helps belching by decreasing the tone of the lower oesophageal sphincter. Some are fruit-flavoured, e.g. Tums® (chewable tablet).

Cautions

Risk of hypermagnesaemia if magnesium-containing antacids are used in patients with renal impairment; **calcium carbonate** is preferable.

The administration of antacids should be separated from the administration of e/c tablets because direct contact between e/c tablets and antacids can result in damage to the enteric coating with consequential exposure of the drug to gastric acid, and of the stomach mucosa to the drug.

Antacids tend to delay gastric emptying and thus may modify drug absorption; if possible avoid administration at the same time as other drugs. Antacids should not be administered by enteral feeding tube as they can coagulate with the feed (see Chapter 22, Table 2, p.733).

Drug interactions

Antacids will temporarily increase the pH of the stomach contents, and this may affect drug absorption. These interactions can generally be avoided by separating administration of the antacid and the affected drug by ⩾2h, e.g.:

- *reduced absorption*: some antiretrovirals (**atazanavir**, **delavirdine**, **tipranavir**), **cefpodoxime**, **fexofenadine**, **itraconazole** *capsules* (but not oral solution)
- *increased absorption*: **flurbiprofen**, **ibuprofen**.[3]

With certain drugs, magnesium salts form an insoluble complex in the GI tract, thereby decreasing absorption, e.g.:

- oral bisphosphonates (**alendronic acid**, **ibandronic acid**, **risedronate**): take magnesium salts ⩾30min after the bisphosphonate
- quinolone antibacterials (e.g. **ciprofloxacin**): take the quinolone 2h before or ⩾4h after the magnesium salt
- **tetracycline** antibacterials: separate administration by ⩾2h.[3]

Magnesium hydroxide interacts with **sodium polystyrene sulfonate** resin (used to treat hyperkalaemia) and creates an excess of bicarbonate ions, which can lead to metabolic alkalosis; avoid by giving the resin rectally.[3]

If magnesium salts lead to alkalinization of the urine, the excretion of round-the-clock anti-inflammatory doses of **aspirin** is increased. Occasional doses of **aspirin** are not affected.[3]

Supply

The cheapest single-ingredient products are **magnesium trisilicate mixture BP** and **aluminium hydroxide** capsules; if a combination is required, the cheapest liquid product is Mucogel®. Note: Low Na^+ is defined as $<$1mmol/tablet or 10mL dose.

Aluminium hydroxide
Alucap® (Meda)
Capsules 475mg, 28 days @ 1 t.d.s. & at bedtime = £4.50; *low* Na^+.

Magnesium trisilicate mixture BP (generic)
Oral suspension (**magnesium trisilicate** 250mg, **magnesium carbonate** 250mg and **sodium hydrogen carbonate** 250mg/5mL) 28 days @ 10mL t.d.s. & at bedtime = £5; *peppermint flavour, 6mmol Na^+/10mL.*

Co-magaldrox
Maalox® (Sanofi-Aventis)
Oral suspension (sugar-free) **co-magaldrox** 195/220 (**magnesium hydroxide** 195mg, **aluminium hydroxide** 220mg/5mL), 28 days @ 10mL t.d.s. & at bedtime = £6.50; *low Na^+*.

Mucogel® (Chemidex)
Oral suspension (sugar-free) **co-magaldrox** 195/220 (**magnesium hydroxide** 195mg, **aluminium hydroxide** 220mg/5mL), 28 days @ 10mL t.d.s. & at bedtime = £4; *low Na^+*.

Calcium carbonate is available either on its own as an OTC product e.g. Tums®, or in combination with an **alginate** (see Compound alginate products, p.4).

Hydrotalcite (aluminium-magnesium complex) is available only in combination with **simeticone** (see p.5).

Sodium bicarbonate is present in many OTC products.

With **oxetacaine**
Oral suspension **oxetacaine** 10mg, **aluminium hydroxide** 200mg, **magnesium hydroxide** 100mg/5mL, 28 days @ 10mL t.d.s. a.c. & at bedtime = £117; *low Na^+* (Unauthorized product, available as a special order from Rosemont; see Appendix 1, p.817. *Available as Mucaine® suspension (Wyeth) in some countries.*

Also see Compound alginate products, p.4 and **simeticone**, p.5.

1 NICE (2004) Dyspepsia. Management of dyspepsia in adults in primary care. *Clinical Guideline*. **CG17**. www.nice.org.uk
2 Morrissey J and Barreras R (1974) Antacid therapy. *New England Journal of Medicine*. **290**: 550–554.
3 Baxter K and Preston CL (2014). *Stockley's Drug Interactions (online edition)*. Pharmaceutical Press, London. Available from: www.medicinescomplete.com

Updated (minor change) June 2014

COMPOUND ALGINATE PRODUCTS BNF 1.1.2

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 oesophageal 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® products, Peptac® and Acidex® oral suspensions are sodium alginate products and weak antacids; most of the antacid content adheres to the alginate raft. This neutralizes acid

which seeps into the oesophagus around the raft but does nothing to correct the underlying causes, e.g. lax lower oesophageal sphincter, hyperacidity, delayed gastric emptying, obesity. Indeed, alginate-containing products are no better than **simeticone**-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, Peptac® and Acidex® oral suspensions contain approximately Na^+ 6mmol/10mL. Gaviscon® Advance oral suspension and tablets contain Na^+ 4.6mmol/10mL and 2.3mmol/tablet, respectively. They should not be used in patients on a salt-restricted diet, e.g. those with fluid retention, heart failure or renal impairment.

Do not administer antacid products containing alginates at the same time of day as e/c tablets, or via enteral feeding tubes. Preferably avoid co-administration with other drugs (see Antacids, p.2).

Dose and use
Several products are available but none is recommended.

Supply
Gaviscon® products, Peptac® and Acidex® oral suspensions all contain sodium alginate 250mg, sodium bicarbonate 133.5mg and calcium carbonate 80mg/5mL and are prescribable on the NHS and available OTC (for full details see BNF and SPCs).

Other compound alginate products are also available (see BNF); some have high sugar content.

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.

Updated October 2012

SIMETICONE BNF 1.1.1

Class: Antifoaming agent (antiflatulent).

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

Pharmacology
Simeticone (silica-activated dimeticone or dimethylpolysiloxane) is a mixture of liquid dimeticones with silicon dioxide. It is an antifoaming agent present in several proprietary combination antacids, e.g. Altacite Plus®, Maalox Plus®. It alters the surface tension of bubbles, causing them to coalesce. This facilitates belching, easing flatulence, distension and postprandial gastric discomfort. Simeticone-containing antacids are as effective as alginate-containing products in the treatment of acid reflux.[1] Altacite Plus® or Maalox Plus® should be used in preference to Gaviscon® products or Acidex® and Peptac® oral suspensions because they contain much less sodium and are cheaper.
Onset of action <5min.
Duration of action 1–2h.

Cautions
Although Maalox Plus® contains both **aluminium** and **magnesium**, at higher doses (e.g. >100–200mL/day) the laxative effect of **magnesium** tends to override the constipating effect of **aluminium**.[2]

Do not administer antacid products containing simeticone at the same time of day as e/c tablets, or via enteral feeding tubes. Preferably avoid co-administration with other drugs (see Antacids p.2).

Dose and use

Altacite Plus® is preferred because it contains a higher dose of simeticone than Maalox Plus®.

- 10mL p.r.n. or 10mL q.d.s

Supply

Altacite plus® Peckforton

Oral suspension (sugar-free) simeticone 125mg, **hydrotalcite** 500mg/5mL, 28 days @ 10mL q.d.s. = £7; *low* Na^+.

Maalox Plus® (Sanofi Aventis)

Oral suspension (sugar-free) simeticone 25mg, dried **aluminium hydroxide** 220mg, **magnesium hydroxide** 195mg/5mL, 28days @ 10mL q.d.s. = £9; *low* Na^+.

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

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

Updated April 2013

ANTIMUSCARINICS BNF 1.2, 4.6 & 15.1.3

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

Pharmacology

Chemically, antimuscarinics are classified as tertiary amines or quaternary ammonium compounds. The naturally-occurring belladonna alkaloids, **atropine**, **hyoscyamine** (**l-atropine**) and **hyoscine *hydrobromide***, are tertiary amines, whereas the numerous semisynthetic and synthetic derivatives fall into both categories. Thus, **dicycloverine**, **oxybutynin** and **tolterodine** are tertiary amines, and **glycopyrronium**, **propantheline** and **hyoscine *butylbromide*** are quaternary ammonium compounds. **Hyoscyamine** (**l-atropine**, not UK) is twice as potent as racemic **atropine**.

Numerous other drugs have antimuscarinic effects (Box A). In addition, some drugs generally not considered antimuscarinic have been shown to have detectable antimuscarinic activity by means of a radioreceptor assay, including **codeine**, **digoxin**, **dipyridamole**, **isosorbide**, **nifedipine**, **prednisolone**, **ranitidine**, **theophylline**, **warfarin**.[1] Theoretically, these drugs could exacerbate toxicity, particularly in debilitated elderly patients.

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.551).

At toxic doses, all the tertiary amines, including **hyoscine *hydrobromide***, cause CNS stimulation resulting in mild central vagal excitation, respiratory stimulation, agitation and delirium. However, in contrast to **atropine**, **hyoscine *hydrobromide*** causes CNS depression at typical therapeutic doses.

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.[3] They are also less well absorbed from the GI tract.

Box A Drugs with antimuscarinic effects used in palliative care

- Analgesics
  - pethidine (*not* recommended)
  - nefopam (mostly postoperative)
- Antidepressants
  - TCAs, e.g. amitriptyline, imipramine
  - paroxetine (SSRI)
- Antihistamines, e.g.
  - chlorphenamine
  - cyclizine
  - dimenhydrinate (not UK)
  - promethazine
- Antiparkinsonians, e.g.
  - orphenadrine
  - procyclidine
- Antipsychotics (atypical)
  - clozapine
  - olanzapine
- Antipsychotics (typical)
  - phenothiazines, e.g.
    - chlorpromazine
    - levomepromazine
    - prochlorperazine
- Antisecretory drugs
  - belladonna alkaloids
    - atropine
    - hyoscine
    - hyoscyamine (l-atropine, not UK)[a]
  - glycopyrronium
- Antispasmodics, e.g.
  - dicycloverine
  - mebeverine
  - oxybutynin
  - propantheline
  - tolterodine

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

Box B Peripheral antimuscarinic effects

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

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

Gastro-intestinal
Dry mouth (inhibition of salivation)
Heartburn (relaxation of lower oesophageal sphincter)
Constipation (decreased intestinal motility)

Urinary tract
Hesitancy of micturition
Retention of urine

Skin
Reduced sweating
Flushing

Peripheral antimuscarinic effects are a class characteristic (Box B), 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.'

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] In some patients, a reduction in excess saliva results in improved speech.[5]

In the UK, parenteral antimuscarinics are widely used to reduce death rattle (noisy respiratory secretions) in those close to death (see Quick Prescribing Guide p.11). Although the use of

antimuscarinics for this purpose has been questioned,[6,7] such use is often, although not always, beneficial.[8–10] For example, a prospective clinical survey concluded that antimuscarinics reduce death rattle in 1/2–2/3 of patients.[11]

In relation to death rattle, belladonna alkaloids are generally equally effective,[8,9] although **glycopyrronium** may sometimes be effective when belladonna alkaloids have not been.[12] Although one study reported that **hyoscine *hydrobromide*** acts faster than **glycopyrronium**, there is no detectable difference between the two drugs after 1h.[13]

Antimuscarinics used as antispasmodics and/or antisecretory drugs differ in their pharmacokinetic characteristics (Table 1). In relation to death rattle, availability, fashion, familiarity and cost are probably the main influences in choice of drug.

Table 1 Pharmacokinetic details of antimuscarinic drugs used for death rattle (noisy respiratory secretions)[4]

	Bio-availability	*Plasma halflife*	*Duration of action (antisecretory)*
Atropine	50% PO	2–2.5h[a]	no data
Glycopyrronium	<5% PO	1–1.5h[a]	7h
Hyoscine *butylbromide*	<1% PO[14]	1–5h[14]	<2h[b15]
Hyoscine *hydrobromide*	60–80% SL	1–4h[a]	1–9h

a. after IM injection into deltoid muscle
b. in volunteers; possibly longer in moribund patients.

Cautions

Myasthenia gravis, conditions predisposing to tachycardia (e.g. thyrotoxicosis, heart failure, β 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.

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 m/r tablets, but reduced absorption from others, e.g. **paracetamol** tablets. Dissolution and absorption of SL tablets (e.g. **glyceryl trinitrate**) may be reduced because of decreased saliva production.

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.

Both antimuscarinics and opioids cause constipation (by different mechanisms) and, if used together, will result in an increased need for laxatives, and may even result in paralytic ileus. On the other hand, **morphine** and **hyoscine *butylbromide*** or **glycopyrronium** are sometimes purposely combined in terminally ill patients with inoperable intestinal obstruction in order to prevent colic and to reduce vomiting.

Drug interactions

Because antimuscarinics competitively block the final common (cholinergic) pathway through which prokinetics act,[16] concurrent prescription with **metoclopramide** and **domperidone** should be avoided as far as possible.

Undesirable effects

What is a desired effect becomes an undesirable effect in different circumstances (see Box B). Thus, dry mouth is an almost universal *undesirable* effect of antimuscarinics except when a reduction of oropharyngeal secretions is intended, as in death rattle.

Dose and use

By injection, there is no good evidence to recommend one antimuscarinic in preference to another.[9] However, because **atropine** and **hyoscyamine** (not UK) tend to stimulate the CNS rather than

sedate, concurrent prescription of **midazolam** or **haloperidol** is more likely to be necessary. In the UK where alternatives are available, these two antimuscarinics are *not* recommended.

When given IM, **atropine**, **hyoscine *hydrobromide*** and **glycopyrronium** are all absorbed faster from the deltoid muscle than from the gluteal muscles.[4]

Antispasmodic

Antimuscarinics are used to relieve smooth muscle spasm in the bladder (see **oxybutynin**, p.551) 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 2).

Table 2 Antisecretory and antispasmodic drugs: typical SC doses

Drug	*Stat and p.r.n. doses*	*CSCI dose/24h*
Glycopyrronium	200microgram	600–1,200microgram
Hyoscine *butylbromide*	20mg	20–300mg[a]
Hyoscine *hydrobromide*[b]	400microgram	1,200–2,000microgram

a. death rattle 20–60mg, some centres use up to 120mg; intestinal obstruction 60–300mg.
b. atropine doses are generally the same as hyoscine hydrobromide.

Antisecretory

Drooling (and sialorrhoea)

Seen particularly in patients with ALS/MND, advanced Parkinson's disease and with various disorders of the head and neck. A recent survey of UK neurologists[17] with a special interest in MND/ALS showed that their preferred first-line drugs for sialorrhoea are:

- **hyoscine *hydrobromide***, e.g. 1mg/3 days TD[18]
- **amitriptyline**, e.g. 10–25mg at bedtime
- **atropine**, e.g. 1% ophthalmic solution, 4 drops on the tongue or SL q4h p.r.n.

In relation to the latter, drop size varies with applicator and technique. Thus, the dose varies from 200–500microgram per drop (800microgram–2mg/dose). It is important to titrate the dose upwards until there is an adequate effect; in an RCT, 500microgram q.d.s. was no better than placebo.[19]

Glycopyrronium is the most popular second-line drug, typically PO or SL.[17] It has also been used for drooling in other conditions (see Glycopyrronium, p.12).

In patients in whom antimuscarinics are contra-indicated, ineffective or not tolerated, the parotid ± submandibular glands can be injected with **botulinum toxin**.[17] Injections are generally effective within 2 weeks, and benefit lasts 3–4 months.[20–24] In patients with a relatively long prognosis (years rather than months), radiotherapy and surgery are further options.[17]

Death rattle (noisy respiratory secretions)

In end-stage renal failure, do *not* use **hyoscine *hydrobromide*** for death rattle because of an increased risk of delirium. Instead, use **hyoscine *butylbromide*** (dose unchanged) or **glycopyrronium** (dose halved).

Treatment regimens are all unauthorized and based mainly on local clinical experience. In the UK antimuscarinic drugs for death rattle are generally given SC.[25] See Table 2 and Quick Prescribing Guide, p.11.

In some countries the SL route is preferred, particularly in home care because it circumvents the need for injections, e.g. **glycopyrronium** 100microgram/mL oral solution, 1mL (100microgram) SL q6h p.r.n. (prepared locally from **glycopyrronium** powder, see p.13).

Paraneoplastic pyrexia and sweating

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

Box C Symptomatic drug treatment of paraneoplastic pyrexia and sweating

Prescribe an antipyretic:
- paracetamol 500–1,000mg q.d.s. or p.r.n. (generally less toxic than an NSAID)
- NSAID, e.g. ibuprofen 200–400mg t.d.s. 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)
- hyoscine *hydrobromide* 1mg/3 days TD[25]
- glycopyrronium up to 2mg PO t.d.s.[26]

If an antimuscarinic fails, other options include:
- propranolol 10–20mg b.d.–t.d.s.
- cimetidine 400–800mg b.d.[27]
- olanzapine 5mg b.d.[28]
- thalidomide 100mg at bedtime.[29,30]

Thalidomide is generally seen as the last resort even though the response rate appears to be high.[30] This is because it can cause an irreversible painful peripheral neuropathy; it may also cause drowsiness (see p.543).

Overdose

In the past, **physostigmine** (not UK), 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.[32–34] 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.781). Anti-arrhythmics are not advisable if arrhythmias develop; but hypoxia and acidosis should be corrected.

Supply

See individual monographs: **hyoscine *butylbromide*** (p.15), **hyoscine *hydrobromide*** (p.17), **glycopyrronium** (p.12), **propantheline** (p.19), **oxybutynin** (p.551).

1 Tune l *et al.* (1992) Anticholinergic effects of drugs commonly prescribed for the elderly; potential means of assessing risk of delirium. *American Journal of Psychiatry.* **149**: 1393–1394.
2 Caulfield M and Birdsall N (1998) International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. *Pharmacological Review* **50**: 279–290.
3 Sweetman SC (ed) (2005) Martindale: The Complete Drug Reference. (34e). Pharmaceutical Press, London, p. 475.
4 Ali-Melkkila T *et al.* (1993) Pharmacokinetics and related pharmacodynamics of anticholinergic drugs. *Acta Anaesthesiologica Scandinavica.* **37**: 633–642.
5 Rashid H *et al.* (1997) Management of secretions in esophageal cancer patients with glycopyrrolate. *Annals of Oncology.* **8**: 198–199.
6 Wee B and Hillier R (2012) Interventions for noisy breathing in patients near to death. *Cochrane Database of Systematic Reviews.* **1**: CD005177.
7 Lokker ME *et al.* (2014) Prevalence, impact, and treatment of death rattle: a systematic review. *Journal of Pain and Symptom Management.* **47**: 105–122.
8 Likar R *et al.* (2008) Efficacy of glycopyrronium bromide and scopolamine hydrobromide in patients with death rattle: a randomized controlled study. *Wiener Klinische Wochenschrift.* **120**: 679–683.
9 Wildiers H *et al.* (2009) Atropine, hyoscine butylbromide, or scopolamine are equally effective for the treatment of death rattle in terminal care. *Journal of Pain and Symptom Management.* **38**: 124–133.
10 Hugel H *et al.* (2006) Respiratory tract secretions in the dying patient: a comparison between glycopyrronium and hyoscine hydrobromide. *Journal of Palliative Medicine*. **9**: 279–284.
11 Hughes A *et al.* (2000) Audit of three antimuscarinic drugs for managing retained secretions. *Palliative Medicine*. **14**: 221–222.
12 Mirakhur R and Dundee J (1980) A comparison of the effects of atropine and glycopyrollate on various end organs. *Journal of the Royal Society of Medicine*. **73**: 727–730.
13 Back l *et al.* (2001) A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. *Palliative Medicine*. **15**: 329–336.
14 Boehringer Ingelheim GmbH *Data on file.*
15 Herxheimer A and Haefeli L (1966) Human pharmacology of hyoscine butylbromide. *Lancet.* **ii**: 418–421.

16 Schuurkes JAJ *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
17 Hobson EV *et al.* (2013) Management of sialorrhoea in motor neuron disease: A survey of current UK practice. *Amyotrophic Lateral Sclerosis Frontotemporal Degeneration*. **14**: 521–527.
18 Talmi YP *et al.* (1990) Reduction of salivary flow with transdermal scopolamine: a four-year experience. *Otolaryngology Head and Neck Surgery*. **103**: 615–618.
19 De Simone GG *et al.* (2006) Atropine drops for drooling: a randomized controlled trial. *Palliative Medicine*. **20**: 665–671.
20 Ondo WG *et al.* (2004) A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. *Neurology*. **62**: 37–40.
21 Jongerius P *et al.* (2004) Effect of botulinum toxin in the treatment of drooling: a controlled clinical trial. *Pediatrics*. **114**: 620–627.
22 Mancini F *et al.* (2003) Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in parkinsonism. *Movement Disorders*. **18**: 685–688.
23 Lipp A *et al.* (2003) A randomized trial of botulinum toxin A for treatment of drooling. *Neurology*. **61**: 1279–1281.
24 Ellies M *et al.* (2004) Reduction of salivary flow with botulinum toxin: extended report on 33 patients with drooling, salivary fistulas, and sialadenitis. *Laryngoscope*. **114**: 1856–1860.
25 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.
26 Mercadante S (1998) Hyoscine in opioid-induced sweating. *Journal of Pain and Symptom Management*. **15**: 214–215.
27 Klaber M and Catterall M (2000) Treating hyperhidrosis. Anticholinergic drugs were not mentioned. *British Medical Journal*. **321**: 703.
28 Pittelkow M and Loprinzi C (2003) Pruritus and sweating in palliative medicine. In: D Doyle *et al.* (eds) *Oxford Textbook of Palliative Medicine* (3e). Oxford University Press, Oxford, pp. 573–587.
29 Zylicz Z and Krajnik M (2003) Flushing and sweating in an advanced breast cancer patient relieved by olanzapine. *Journal of Pain and Symptom Management*. **25**: 494–495.
30 Deaner P (2000) The use of thalidomide in the management of severe sweating in patients with advanced malignancy: trial report. *Palliative Medicine*. **14**: 429–431.
31 Calder K and Bruera E (2000) Thalidomide for night sweats in patients with advanced cancer. *Palliative Medicine*. **14**: 77–78.
32 Aquilonius SM and Hedstrand U (1978) The use of physostigmine as an antidote in tricyclic anti-depressant intoxication. *Acta Anaesthesiologica Scandinavica*. **22**: 40–45.
33 Caine ED (1979) Anticholinergic toxicity. *New England Journal of Medicine*. **300**: 1278.
34 Newton RW (1975) Physostigmine salicylate in the treatment of tricyclic antidepressant overdosage. *Journal of the American Medical Association*. **231**: 941–943.

Updated April 2014

Quick Prescribing Guide: 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 which arises from one or more sources:

- saliva (most common)
- bronchial mucosa
- respiratory tract infection
- pulmonary oedema
- 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 oedema or gastric reflux
- oropharyngeal suction but, because it can be distressing, generally restrict use to unconscious patients.

Drug treatment

Note: because atropine tends to stimulate rather than sedate, concurrent prescription of midazolam or haloperidol is more likely to be necessary. In the UK, atropine is *not* recommended for death rattle.

Saliva

Because they do not affect existing secretions, an antisecretory drug should be given SC as soon as the rattle begins (see Table).

Antimuscarinic antisecretory drugs for death rattle: typical SC doses

Drug	*Stat and p.r.n. SC dose*	*CSCI dose/24h*
Glycopyrronium	200microgram	600–1,200microgram
Hyoscine *butylbromide*	20mg	20–120mg
Hyoscine *hydrobromide*	400microgram	1,200–2,000microgram

In end-stage renal failure, do *not* use **hyoscine *hydrobromide*** because of an increased risk of delirium. Use **hyoscine *butylbromide*** (dose unchanged) or **glycopyrronium** (dose halved) instead.

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 250–1000mg 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 give b.d.

Pulmonary oedema

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).

Updated April 2014

GLYCOPYRRONIUM BNF 15.1.3

Class: Antimuscarinic (anticholinergic).

Indications: Drying secretions (including surgical premedication, control of upper airway secretions, COPD (Seebri Breezhaler®), †sialorrhoea, †drooling, †death rattle (noisy respiratory secretions), †smooth muscle spasm (e.g. intestine, bladder), †inoperable intestinal obstruction), †paraneoplastic pyrexia and sweating, †hyperhidrosis.[1,2]

Pharmacology

Glycopyrronium is a synthetic ionized quaternary ammonium antimuscarinic which penetrates biological membranes slowly and erratically.[3] In consequence it rarely causes sedation or delirium.[4,5] Absorption PO is poor and the IV to PO potency ratio is about 35:1.[6] Even so, glycopyrronium 200–400microgram PO t.d.s. produces plasma concentrations associated with an antisialogogic effect lasting up to 8h.[7–9] By injection, glycopyrronium is 2–5 times more potent than **hyoscine *hydrobromide*** as an antisecretory drug,[6] and may be effective in some patients who fail to respond to **hyoscine**. However, the efficacy of **hyoscine *hydrobromide***, **hyoscine *butylbromide*** and glycopyrronium as antisialogogues is generally similar, with death rattle reduced in 1/2–2/3 of patients.[10] Further, provided that time is taken to explain the cause of the rattle to the relatives and there is ongoing support, relatives' distress is relieved in >90% of cases.[11]

The optimal parenteral single dose is 200microgram.[12,13] It has fewer cardiac effects because of a reduced affinity for muscarinic-type 2 receptors.[14–16] Although at standard doses glycopyrronium does not change ocular pressures or pupil size, it can precipitate narrow-angle glaucoma. It is excreted by the kidneys and lower doses are effective in patients with renal impairment.[3,17]

Glycopyrronium PO or SL has been used to reduce drooling in MND/ALS,[18] head and neck cancer,[9,19] and oesophageal cancer.[20] It has also been given by nebulizer.[21] It is also used as a bronchodilator (inhaled or nebulized) in asthma and COPD.[22]

Bio-availability <5% PO.
Onset of action 1min IV; 30–40min SC, PO.
Time to peak plasma concentration immediate IV; no data SC, PO.
Plasma halflife 1–1.5h.
Duration of action 7h.

Cautions

Increases the peripheral antimuscarinic toxicity of antihistamines, phenothiazines and TCAs (see Antimuscarinics, Box B, p.6). Use with caution in conditions predisposing to tachycardia (e.g. thyrotoxicosis, heart failure, concurrent β_2 agonists), and bladder outflow obstruction (prostatism). Likely to exacerbate acid reflux. Narrow-angle glaucoma may be precipitated in those at risk, particularly the elderly. Use in hot weather or pyrexia may lead to heatstroke.

Drug interactions

Competitively blocks the prokinetic effect of **metoclopramide** and **domperidone**.[23]

Undesirable effects

Peripheral antimuscarinic effects (see Antimuscarinics, Box B, p.6). The US Product Information lists the following effects, which are not included in the UK SPC:

Very common (>10%): inflammation at the injection site.
Common (<10%, >1%): dysphagia, photosensitivity.

Dose and use

Glycopyrronium is an alternative to **hyoscine *hydrobromide***, **hyoscine *butylbromide*** and **atropine**.[19,20,24] For CSCI, dilute with WFI, 0.9% saline or 5% glucose.

CSCI compatibility with other drugs: There are 2-drug compatibility data for glycopyrronium in WFI with **alfentanil**, **clonazepam**, **diamorphine**, **haloperidol**, **hydromorphone**, **levomepromazine**, **metoclopramide**, **midazolam**, **morphine sulfate** and **oxycodone**.

Glycopyrronium is *incompatible* with **dexamethasone** and **ketorolac**. For more details and 3-drug compatibility data, see Appendix 3 (p.821).

Compatibility charts for mixing drugs in 0.9% saline can be found in the extended appendix section of the on-line PCF on www.palliativedrugs.com

Drooling

Administer as a locally prepared solution PO:
- start with 200microgram PO stat and q8h
- if necessary, increase dose progressively every 2–3 days to 1mg q8h[25]
- occasionally doses of ⩽2mg q8h are needed.

A subsequent reduction in dose may be possible, particularly when initial dose escalation has been rapid. Can be given by enteral feeding tube (also see p.733).[9,20]

Examples of locally prepared formulations for PO use are shown in Box A.[26,27] Unauthorized products (tablets, solutions, suspensions) are available as Specials (see Supply). The tablets will disperse in water, but they are not suitable for administration via an enteral feeding tube.

Box A Examples of locally prepared glycopyrronium formulations for PO use

From glycopyrronium powder

Glycopyrronium concentrated solution 1mg/mL[28]
Dissolve 100mg of glycopyrronium powder (obtainable from AMCo) in 100mL of sterile or distilled water.

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

Dilute the required volume of the concentrate 1 part with 9 parts sterile or distilled water (i.e. for every 1mL of concentrate, add 9mL of water) to give a *glycopyrronium oral solution 100microgram/mL*.

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

Glycopyrronium oral suspension 500microgram/mL[26]
Add 5mL of glycerol to 50mg of glycopyrronium 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 suspension is stable for 90 days at room temperature or in a refrigerator.

From glycopyrronium injection[a]

Glycopyrronium oral suspension 100microgram/mL[27]
Combine 25mL of Ora-Plus® and 25mL of Ora-Sweet®; add to 50mL of preservative-free glycopyrronium injection 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).

In a taste test, this formulation masked the bitter taste of glycopyrronium better than water or syrup-based vehicles, and was preferred by most patients.

a. this is an expensive option, particularly for long-term use (see Supply).

Death rattle (noisy respiratory secretions)
- 200microgram SC stat and p.r.n.[29] *and/or*
- 600–1,200microgram/24h CSCI *or*
- 100microgram SL q6h p.r.n.

Antispasmodic and inoperable intestinal obstruction
- 200microgram SC stat and p.r.n. *and/or*
- 600–1,200microgram/24h CSCI.

Paraneoplastic pyrexia and sweating
- start with 200microgram PO t.d.s.
- if necessary, increase progressively to 2mg PO t.d.s.

Localized hyperhidrosis
- apply topically as a 0.5–4% cream (Box B) or aqueous solution once daily–b.d. avoiding the nose, mouth and particularly the eyes; do not wash treated skin for 3–4h[2,30]
- if severe, or if alternative treatments fail, 1–2mg PO b.d.–t.d.s., titrated to response.[1]

Box B Locally prepared glycopyrronium cream 10mg/mL (1%)

Mix 1g of glycopyrronium powder with propylene glycol to make a paste. Incorporate into a water-washable cream base until smooth, making a total of 100g. Refrigerate after preparation. Stable for 60 days.

Supply
Glycopyrronium bromide (generic)
Oral solution or oral suspension 200microgram/5mL, 1mg/5mL, 2mg/5mL, 2.5mg/5mL and 5mg/5mL, 7 days or 28 days @ 1mg t.d.s. = £146 and £150 respectively (unauthorized, available as a special order, see Appendix 1, p.817). *Note price based on 1mg/5mL oral solution specials tariff in community; prices vary significantly between formulations and quantities ordered.*
Tablets *1mg, 2mg,* 28 days @ 1mg t.d.s. = £27 (unauthorized, available to import as a special order via IDIS, see Appendix 1, p.817).
Injection 200microgram/mL, 1mL amp = £0.50, 3mL amp = £1.50. *Note: using the injection to make an oral solution 7 days @ 1mg t.d.s. = £53 worth of glycopyrronium injection.*

Robinul® (AMCo)
Glycopyrronium bromide
Powder for local preparation of oral solutions and topical formulations (see Box A and Box B), 3g = £266.
Note: *using the powder to make the concentrated oral solution = £9 (but need to buy 3g).*

Seebri Breezhaler® (Novartis)
Dry powder inhalation each 50microgram capsule delivers 44microgram glycopyrronium; for use with Seebri Breezhaler device, 28 days @ 1 puff once daily = £28.

1 Solish N *et al.* (2007) A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian Hyperhidrosis Advisory Committee. *Dermatologic Surgery.* **33**: 908–923.
2 Kim WO *et al.* (2008) Topical glycopyrrolate for patients with facial hyperhidrosis. *British Journal of Dermatology.* **158**: 1094–1097.
3 Mirakhur R and Dundee J (1983) Glycopyrrolate pharmacology and clinical use. *Anaesthesia.* **38**: 1195–1204.
4 Gram D *et al.* (1991) Central anticholinergic syndrome following glycopyrrolate. *Anesthesiology.* **74**: 191–193.
5 Wigard D (1991) Glycopyrrolate and the central anticholinergic syndrome (letter). *Anesthesiology.* **75**: 1125.
6 Mirakhur R and Dundee J (1980) A comparison of the effects of atropine and glycopyrollate on various end organs. *Journal of the Royal Society of Medicine.* **73**: 727–730.
7 Ali-Melkkila T *et al.* (1989) Glycopyrrolate; pharmacokinetics and some pharmacodynamics findings. *Acta Anaesthesiologica Scandinavica.* **33**: 513–517.
8 Blasco P (1996) Glycopyrrolate treatment of chronic drooling. *Archives of Paediatric and Adolescent Medicine.* **150**: 932–935.
9 Olsen A and Sjogren P (1999) Oral glycopyrrolate alleviates drooling in a patient with tongue cancer. *Journal of Pain and Symptom Management.* **18**: 300–302.
10 Hughes A *et al.* (2000) Audit of three antimuscarinic drugs for managing retained secretions. *Palliative Medicine.* **14**: 221–222.
11 Hughes A *et al.* (1997) Management of 'death rattle'. *Palliative Medicine.* **11**: 80–81.

12 Mirakhur R *et al.* (1978) Evaluation of the anticholinergic actions of glycopyrronium bromide. *British Journal of Clinical Pharmacology*. **5**: 77–84.
13 Back I *et al.* (2001) A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. *Palliative Medicine*. **15**: 329–336.
14 Scheinin H *et al.* (1999) Spectral analysis of heart rate variability as a quantitative measure of parasympatholytic effect-integrated pharmacokinetics and pharmacodynamics of three anticholinergic drugs. *Therapeutic Drug Monitoring*. **21**: 141–151.
15 Warren J *et al.* (1997) Effect of autonomic blockade on power spectrum of heart rate variability during exercise. *American Journal of Physiology*. **273**: 495–502.
16 Mirakhur R *et al.* (1978) Atropine and glycopyrronium premedication. A comparison of the effects on cardiac rate and rhythm during induction of anaesthesia. *Anaesthesia*. **33**: 906–912.
17 Ali-Melkkila T *et al.* (1993) Pharmacokinetics and related pharmacodynamics of anticholinergic drugs. *Acta Anaesthesiologica Scandinavica*. **37**: 633–642.
18 Hobson EV *et al.* (2013) Management of sialorrhoea in motor neuron disease: A survey of current UK practice. *Amyotrophic Lateral Sclerosis Frontotemporal Degeneration*. **14**: 521–527.
19 Lucas V and Amass C (1998) Use of enteral glycopyrrolate in the management of drooling. *Palliative Medicine*. **12**: 207.
20 Rashid H *et al.* (1997) Management of secretions in esophageal cancer patients with glycopyrrolate. *Annals of Oncology*. **8**: 198–199.
21 Strutt R *et al.* (2002) Nebulized glycopyrrolate for drooling in a motor neuron patient. *Journal of Pain and Symptom Management*. **23**: 2–3.
22 Hansel TT *et al.* (2005) Glycopyrrolate causes prolonged bronchoprotection and bronchodilatation in patients with asthma. *Chest*. **128**: 1974–1979.
23 Schuurkes JAJ *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
24 Davis M and Furste A (1999) Glycopyrrolate: a useful drug in the palliation of mechanical bowel obstruction. *Journal of Pain and Symptom Management*. **18**: 153–154.
25 Arbouw ME *et al.* (2010) Glycopyrrolate for sialorrhea in Parkinson disease: a randomized, double-blind, crossover trial. *Neurology*. **74**: 1203–1207.
26 Anonymous (2004) Glycopyrrolate 0.5mg/mL oral liquid. *International Journal of Pharmaceutical Compounding*. **8**: 218.
27 Landry C *et al.* (2005) Stability and subjective taste acceptability of four glycopyrrolate solutions for oral administration. *International Journal of Pharmaceutical Compounding*. **9**: 396–398.
28 Amass C (2007) *Personal communication.* Pharmacist, East and North Hertfordshire NHS Trust.
29 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.
30 Kavanagh GM *et al.* (2006) Topical glycopyrrolate should not be overlooked in treatment of focal hyperhidrosis. *British Journal of Dermatology*. **155**: 477–500.
31 Glasnapp A and BJ S (2001) Topical therapy for localized hyperhidrosis. *International Journal of Pharmaceutical Compounding*. **5**: 28–29.

Updated April 2014

HYOSCINE BUTYLBROMIDE BNF 1.2

Class: Antimuscarinic.

Indications: Smooth muscle spasm (e.g. bladder, GI tract), †drying secretions (including †sialorrhoea, †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 *butylbromide* is an antimuscarinic (see p.5) and has both smooth muscle relaxant (antispasmodic) and antisecretory properties. It is a quaternary compound and, unlike **hyoscine *hydrobromide***, it does not cross the blood-brain barrier. Consequently, 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.d.s. PO and **paracetamol** 500mg t.d.s. 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.[5]

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

(noisy respiratory secretions). 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.[6,7] 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.[8] On the other hand, the same dose by CSCI is often effective for 1 day in death rattle. Hyoscine *butylbromide* and **hyoscine *hydrobromide*** act faster than **glycopyrronium** for this indication,[9,10] but the overall efficacy is generally the same[11] with death rattle reduced in 1/2–2/3 of patients. However, provided that time is taken to explain the cause of the rattle to the relatives and there is ongoing support, relatives' distress is relieved in >90% of cases.[12]

Bio-availability <1% PO.[1]
Onset of action <10min SC/IM/IV; 1–2h PO.[13]
Time to peak plasma concentration 15min–2h PO.[1]
Plasma halflife 1–5h.[1]
Duration of action <2h in volunteers[8] but possibly longer in moribund patients.

Cautions

Increases the peripheral antimuscarinic effects of antihistamines, phenothiazines and TCAs (see Antimuscarinics, Box B, p.6). Use with caution in conditions predisposing to tachycardia (e.g. thyrotoxicosis, heart failure, β 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.

Drug interactions

Competitively blocks the prokinetic effect of **metoclopramide** and **domperidone**.[1,14]

Undesirable effects

Peripheral antimuscarinic effects (see Antimuscarinics, Box B, p.6).

Dose and use

For CSCI dilute with WFI, 0.9% saline or 5% glucose.

CSCI compatibility with other drugs: There are 2-drug compatibility data for hyoscine *butylbromide* in WFI with **alfentanil**, **clonazepam**, **dexamethasone**, **diamorphine**, **haloperidol**, **hydromorphone**, **levomepromazine**, **midazolam**, **morphine sulfate**, **octreotide** and **oxycodone**.

Incompatibility may occur with **cyclizine**. For more details and 3-drug compatibility data, see Appendix 3 (p.821).

Compatibility charts for mixing drugs in 0.9% saline can be found in the extended appendix of the on-line PCF on www.palliativedrugs.com

Inoperable intestinal obstruction with colic[15,16]

- start with 20mg SC stat and 60mg/24h CSCI
- if necessary, increase to 120mg/24h
- maximum reported dose 300mg/24h.

Note: the maximum benefit from hyoscine *butylbromide* may be seen only after some 3 days.[6] Some centres add **octreotide** 300–500microgram/24h if hyoscine *butylbromide* 120mg/24h fails to relieve symptoms adequately.[17,18]

For patients with obstructive symptoms without colic, **metoclopramide** (p.242) should be tried before an antimuscarinic drug because the obstruction is often more functional than organic.

Death rattle (noisy respiratory secretions)

- 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[10]

For use of alternative antimuscarinics, see Quick Prescribing Guide, p.11.

Supply

Buscopan® (Boehringer Ingelheim)
Tablets 10mg, 28 days @ 20mg q.d.s. = £12. *Also available OTC as Buscopan®* IBS Relief.
Injection 20mg/mL, 1mL amp = £0.50.

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 Thompson DG and Wingate DL (1981) Oral hyoscine butylbromide does not alter the pattern of small intestinal motor activity. *British Journal of Pharmacology*. **72**: 685–687.
6 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.
7 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.
8 Herxheimer A and Haefeli L (1966) Human pharmacology of hyoscine butylbromide. *Lancet*. **ii**: 418–421.
9 Back I *et al.* (2001) A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. *Palliative Medicine*. **15**: 329–336.
10 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.
11 Hughes A *et al.* (2000) Audit of three antimuscarinic drugs for managing retained secretions. *Palliative Medicine*. **14**: 221–222.
12 Hughes A *et al.* (1997) Management of 'death rattle'. *Palliative Medicine*. **11**: 80–81.
13 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.
14 Schuurkes JAJ *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
15 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.
16 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.
17 Ripamonti C and Mercadante S (2004) How to use octreotide for malignant bowel obstruction. *Journal of Supportive Oncology*. **2**: 357–364.
18 Ripamonti CI *et al.* (2008) Management of malignant bowel obstruction. *European Journal of Cancer*. **44**: 1105–1115.

Updated April 2014

HYOSCINE HYDROBROMIDE BNF 4.6 & 15.1.3

Class: Antimuscarinic.

Indications: Prevention of motion sickness, drying secretions (including surgical premedication, †sialorrhoea, †drooling, †death rattle (noisy respiratory secretions) and †inoperable intestinal obstruction), †paraneoplastic pyrexia and sweating, †smooth muscle spasm (e.g. intestine, bladder).

Contra-indications: Narrow-angle glaucoma (unless moribund), prostatic hyperplasia, pyloric obstruction, paralytic ileus

Pharmacology

Hyoscine *hydrobromide* is a naturally occurring belladonna alkaloid with smooth muscle relaxant (antispasmodic) and antisecretory properties. In many countries it is available as both the *hydrobromide* and *butylbromide* salts. Unlike the latter, hyoscine *hydrobromide* crosses the blood-brain barrier, and repeated administration SC q4h will result in accumulation and may lead to sedation and delirium. On the other hand, a small number of patients are stimulated rather than sedated.

Despite hyoscine *hydrobromide* having a plasma halflife of several hours, the duration of the antisecretory effect in volunteers after a single dose is only about 2h.[1] On the other hand, particularly after repeated injections in moribund patients, a duration of effect of up to 9h has been observed.[2] Hyoscine *hydrobromide* relieves death rattle in 1/2–2/3 of patients.[3] However, provided that time is taken to explain the cause of the rattle to the relatives and there is ongoing support, relatives' distress is relieved in >90% of cases.[2] Hyoscine *hydrobromide* can also be used in other situations where an antimuscarinic effect is needed.

A TD patch is available as prophylactic treatment for motion sickness:[4]

- it comprises a reservoir containing hyoscine 1.5mg
- the average amount of hyoscine absorbed *over 3 days* is 1mg
- because of an initial priming dose released from the patch, steady-state is reached after about 6h, and maintained for 3 days[5]
- after a single application of two patches, the average elimination half-life is 9.5h[6]
- after patch removal, because hyoscine continues to be absorbed from the skin, the plasma concentration only decreases to about one third over the next 24h
- absorption is best when the patch is applied on hairless skin behind the ear.[4]

The patch has also been used to control opioid-induced nausea.[7,8] Other off-label uses include the management of drooling and sialorrhoea in patients with disorders of the head and neck.[9,10]

Bio-availability 60–80% SL.[11]
Onset of action 3–5min IM, 10–15min SL.
Time to peak effect 20–60min SL/SC; 24h TD.
Plasma halflife 1–4h IM.[11]
Duration of action IM 15min (spasmolytic), 1–9h (antisecretory).[11]

Cautions

Increases the antimuscarinic toxicity of antihistamines, phenothiazines and TCAs (see Antimuscarinics, Box B, p.6). Likely to exacerbate acid reflux. Use in hot weather or pyrexia may lead to heatstroke. Myasthenia gravis, bladder outflow obstruction, and in conditions predisposing to tachycardia (e.g. thyrotoxicosis, heart failure and concurrent use with β agonists).

Drug interactions

Interacts competitively to block prokinetic effect of **metoclopramide** and **domperidone**.[12]

Undesirable effects

Antimuscarinic effects (see p.6), including central antimuscarinic syndrome, i.e. agitated delirium, drowsiness, ataxia.

TD patch: despite the relatively small dose, delirium has been reported;[13] local irritation ± rash occasionally occurs.

Dose and use

TD patches contain metal in the backing, and must be removed before MRI to avoid burns.[14] Wash hands after handling the TD patch (and the application site after removing it) to avoid transferring hyoscine *hydrobromide* into the eyes (may cause mydriasis and exacerbate narrow-angle glaucoma).

Drooling and sialorrhoea

- hyoscine *hydrobromide* TD 1mg/3 days; if necessary, use 2 patches concurrently.

Note: an alternative drug PO with antimuscarinic effects may be preferable in some patients because of convenience or concurrent symptom management, e.g. **amitriptyline** (see p.208).

Death rattle (noisy respiratory secretions)

With death rattle caused by excess secretions pooling in the pharynx, an antisecretory drug is best administered as soon as the rattle becomes evident because the drug cannot dry up the existing secretions:

- 400microgram SC stat
- continue with 1,200microgram/24h CSCI
- if necessary, increase to 2,000microgram/24h CSCI
- repeat 400microgram p.r.n.

For CSCI dilute with WFI, 0.9% saline or 5% glucose.

CSCI compatibility with other drugs: There are 2-drug compatibility data for hyoscine *hydrobromide* in WFI with **clonazepam**, **cyclizine**, **dexamethasone**, **diamorphine**, **haloperidol**, **hydromorphone**, **levomepromazine**, **midazolam**, **morphine sulfate** and **oxycodone**.

For more details and 3-drug compatibility data, see Appendix 3 (p.821).

Compatibility charts for mixing drugs in 0.9% saline can be found in the extended appendix of the on-line PCF on www.palliativedrugs.com

Some centres use **hyoscine *butylbromide*** instead (see p.15).[15] Other options include **glycopyrronium** (see p.12) and **atropine** (see p.5).

Supply

Kwells® Bayer Consumer Care
Tablets chewable 150microgram, 300microgram, 12 tablets = £2; *also available OTC*.

Scopoderm TTS® (Novartis Consumer Health)
TD (post-auricular) patch 1.5mg (releasing 1mg over 3 days), 1 patch = £2.

Hyoscine *hydrobromide* (generic)
Injection 400microgram/mL, 1mL amp = £3; 600microgram/mL, 1mL amp = £3.

1 Herxheimer A and Haefeli L (1966) Human pharmacology of hyoscine butylbromide. *Lancet.* **ii**: 418–421.
2 Hughes A *et al.* (1997) Management of 'death rattle'. *Palliative Medicine.* **11**: 80–81.
3 Hughes A *et al.* (2000) Audit of three antimuscarinic drugs for managing retained secretions. *Palliative Medicine*. **14**: 221–222.
4 Clissold S and Heel R (1985) Transdermal hyoscine (scopolamine). A preliminary review of its pharmacodynamic properties and therapeutic efficacy. *Drugs*. **29**: 189–207.
5 Novartis (2014). *Personal communication*. Medical affairs.
6 Novartis (2013) Scopoderm TTS. *SPC*. www.medicines.org.uk.
7 Ferris FD *et al.* (1991) Transdermal scopolamine use in the control of narcotic-induced nausea. *Journal of Pain and Symptom Management.* **6**: 289–393.
8 Harris SN *et al.* (1991) Nausea prophylaxis using transdermal scopolamine in the setting of patient-controlled analgesia. *Obstetrics and Gynecology.* **78**: 673–677.
9 Gordon C *et al.* (1985) Effect of transdermal scopolamine on salivation. *Journal of Clinical Pharmacology.* **25**: 407–412.
10 Talmi YP *et al.* (1990) Reduction of salivary flow with transdermal scopolamine: a four-year experience. *Otolaryngology Head and Neck Surgery.* **103**: 615–618.
11 Ali-Melkkila T *et al.* (1993) Pharmacokinetics and related pharmacodynamics of anticholinergic drugs. *Acta Anaesthesiologica Scandinavica*. **37**: 633–642.
12 Schuurkes JAJ *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
13 Wilkinson J (1987) Side-effects of transdermal scopolamine. *Journal of Emergency Medicine*. **5**: 389–392.
14 Institute for Safe Medication Practices (2004) Medication Safety Alert. Burns in MRI patients wearing transdermal patches. Available from: www.ismp.org/Newsletters/acutecare/articles/20040408.asp?ptr = y
15 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.

Updated April 2014

PROPANTHELINE BNF 1.2 & 7.4.2

Class: Antimuscarinic.

Indications: Smooth muscle spasm (e.g. bladder, intestine), urinary frequency and incontinence, hyperhidrosis, †gustatory sweating in diabetic neuropathy, †paraneoplastic sweating, †drooling and sialorrhoea.

Contra-indications: Narrow-angle glaucoma (unless moribund), myasthenia gravis (unless moribund), obstructive disease of GI or urinary tract, pyloric stenosis, paralytic ileus, severe ulcerative colitis, toxic megacolon, hiatus hernia associated with reflux oesophagitis, prostatic enlargement.

Pharmacology

Propantheline is a quaternary antimuscarinic (see p.5); it does not cross the blood-brain barrier and thus does *not* cause central effects. It doubles gastric emptying half-time[1] and slows GI transit generally. It has variable effects on drug absorption (see Drug interactions). Propantheline is extensively metabolized in the small intestine before absorption. *If taken with food, the effect of propantheline by mouth is almost abolished.*[2]

Bio-availability < 50% PO (much reduced if taken after food).
Onset of action 30–60min.
Time to peak plasma concentration 2h.
Plasma halflife 2–3h.
Duration of action 4–6h.

Cautions

Elderly. Use with caution in conditions predisposing to tachycardia (e.g. thyrotoxicosis, heart failure, β 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.

Drug interactions

Competitively blocks the prokinetic effect of **metoclopramide** and **domperidone**.[3] May reduce the rate, but not the extent, of absorption of **paracetamol**, thereby delaying the onset of analgesia. May increase the absorption of some formulations of **digoxin** and **nitrofurantoin**.[4]

Increases the peripheral antimuscarinic toxicity of antihistamines, phenothiazines and TCAs (see Antimuscarinics, p.6).

Undesirable effects

Peripheral antimuscarinic effects (See Antimuscarinics, Box B, p.6).

Dose and use

Intestinal colic

- start with 15mg t.d.s. *1h before meals* & 30mg at bedtime
- maximum dose 30mg q.d.s.

Urinary frequency

- same as for colic, but largely replaced by **oxybutynin** (p.551), **amitriptyline** (p.208) or **imipramine**.

Sweating

One of several alternatives to reduce paraneoplastic sweating (for other options, see Antimuscarinics, Box C, p.9):

- 15–30mg b.d.–t.d.s. *on an empty stomach*.

Has also been used for hyperhydrosis associated with spinal cord injury.[5]

Drooling and sialorrhoea

Has been used in MND/ALS.
15mg t.d.s.[6] *on an empty stomach*.

Supply

Pro-Banthine® (Archimedes)
Tablets 15mg, 28 days @ 15mg t.d.s. & 30mg at bedtime = £22.

1 Hurwitz A *et al.* (1977) Prolongation of gastric emptying by oral propantheline. *Clin Pharmacol Ther.* **22**: 206–210.
2 Ekenved G *et al.* (1977) Influence of food on the effect of propantheline and L-hyoscyamine on salivation. *Scand J Gastroenterol.* **12**: 963–966.
3 Schuurkes JAJ *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
4 Baxter K and Preston CL. *Stockley's Drug Interactions*. London: Pharmaceutical Press www.medicinescomplete.com (accessed March 2014).
5 Canaday BR and Stanford RH (1995) Propantheline bromide in the management of hyperhidrosis associated with spinal cord injury. *Ann Pharmacother.* **29**: 489–492.
6 Norris FH *et al.* (1985) Motor neurone disease: towards better care. *British Medical Journal.* **291**: 259–262.

Updated April 2014

ORPHENADRINE BNF 4.9.2

Class: Antimuscarinic antiparkinsonian.

Indications: Parkinson's disease, drug-induced parkinsonism, †sialorrhoea (drooling), †extrapyramidal dystonic reactions.

Contra-indications: Glaucoma (unless moribund), GI obstruction, prostatic hypertrophy, urinary retention, tardive dyskinesia (see Chapter 26, p.781).

Pharmacology

Orphenadrine and other antimuscarinic antiparkinsonian drugs are used primarily in Parkinson's disease.[1] They are less effective than **levodopa** in established Parkinson's disease. However, patients with mild symptoms, particularly tremor, may be treated initially with an antimuscarinic drug (alone or with **selegiline**), and **levodopa** added or substituted if symptoms progress. Antimuscarinics exert their antiparkinsonian effect by correcting the relative central cholinergic excess which occurs in parkinsonism as a result of dopamine deficiency. In most patients their effects are only moderate, reducing tremor and rigidity to some extent but without significant action on bradykinesia. They exert a synergistic effect when used with **levodopa** and are also useful in reducing sialorrhoea.

Antimuscarinics reduce the symptoms of drug-induced parkinsonism (mainly antipsychotics) but there is no justification for giving them prophylactically. *Tardive dyskinesia is not improved by the antimuscarinic drugs, and they may make it worse.* No major differences exist between antimuscarinic antiparkinsonian drugs, but orphenadrine sometimes has a mood-elevating effect. Some people tolerate one antimuscarinic better than another. **Procyclidine** may be given parenterally, and is effective emergency treatment for severe acute drug-induced dystonic reactions (see Chapter 26, p.781).
Bio-availability readily absorbed PO.
Onset of action 30–60min.
Time to peak plasma concentration 2–4h PO.
Plasma halflife 15h single dose but ≤40h with multiple doses.
Duration of action 12–24h.

Cautions

Elderly, hepatic or renal impairment, cardiovascular disease, urinary hesitancy. Avoid abrupt discontinuation. In a psychotic patient receiving a phenothiazine, the addition of orphenadrine to reverse a drug-induced acute dystonia (see Chapter 26, p.781) may precipitate a toxic confusional psychosis because of a summation of antimuscarinic effects.

Undesirable effects

Antimuscarinic effects (see p.6). Nervousness, euphoria, insomnia, confusion, hallucinations occasionally.

Dose and use

Parkinsonism

For treatment of previously unrecognized or untreated symptoms in patients with a prognosis of <6 months:

- start with 50mg b.d.–t.d.s.
- if necessary, increase by 50mg every 2–3 days
- normal dose range 150–300mg daily in divided doses
- maximum recommended daily dose 400mg.

Note: **propranolol**, a non-selective β-adrenergic receptor antagonist (β-blocker), is the treatment of choice for akathisia. Antimuscarinic antiparkinsonian drugs are *contra-indicated* in tardive dyskinesia because they may exacerbate the condition (see Chapter 26, p.781).

Supply

Orphenadrine (generic)
Tablets 50mg, 28 days @ 50mg t.d.s. = £74.
(Note: at BNF prices, this is *more expensive* than branded Disipal® tablets.)
Oral solution 50mg/5mL, 28 days @ 50mg t.d.s. = £20.

Biorphen® (Alliance)
Oral solution (sugar-free) 25mg/5mL, 28 days @ 50mg t.d.s. = £36; *anise flavour.*

Disipal® (Astellas)
Tablets 50mg, 28 days @ 50mg t.d.s. = £3. (Note: at BNF prices, this is *cheaper* than generic tablets.)

1 Katzenschlager R *et al.* (2003) Anticholinergics for symptomatic management of Parkinson's disease. *Cochrane Database of Systematic Reviews*. Cd003735.

Updated April 2014

PROKINETICS BNF 1.2

Pharmacology

Prokinetics accelerate GI transit and include:
- D_2 antagonists, e.g. **domperidone** (p.246), **metoclopramide** (p.242)
- $5HT_4$ agonists, e.g. **metoclopramide**, **prucalopride**
- motilin agonists, e.g. **erythromycin**.

Clinical trials are underway of cholinesterase inhibitors and drugs acting at other receptors, e.g. ghrelin agonists.[1]

Drugs which enhance intestinal transit indirectly are not considered prokinetics (e.g. bulk-forming agents, other laxatives, and drugs such as **misoprostol** which cause diarrhoea by increasing GI secretions). 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.[2]

D_2 antagonists and $5HT_4$ agonists act by triggering a cholinergic system in the wall of the GI tract (Table 1, Figure 1).[3] This action is impeded by opioids. Further, antimuscarinic drugs competitively block cholinergic receptors on the intestinal muscle fibres (and elsewhere).[4] 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, the concurrent administration of prokinetics and antimuscarinic drugs is generally 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.235).

Erythromycin is reported to improve symptoms in about half of patients. A review suggested that, overall, its prokinetic effect was greater than that of **metoclopramide** (Table 1). However, the studies, mainly in diabetic gastroparesis, were small and open to bias.[7] Further, **erythromycin** can cause intestinal colic and diarrhoea. There are concerns about the possible development of bacterial resistance or tolerance to its prokinetic effects, although there are reports of **erythromycin** 250mg b.d. given for more than a year without apparent loss of

efficacy.[8,9] Thus, **erythromycin** is generally used second-line when **metoclopramide** and **domperidone** have been ineffective.

Compared with **erythromycin**, **azithromycin** has a longer half-life and the potential for fewer drug interactions and undesirable effects. However, there are few trials to support its use.[10] Non-antibacterial motilin agonists are also undergoing trials, e.g. **atilmotin** and **mitemcinal**.

Use of prokinetics in palliative care

Prokinetics are used in various situations in palliative care (Box A). D_2 antagonists block the dopaminergic 'brake' on gastric emptying induced by stress, anxiety, and nausea from any cause. In contrast, $5HT_4$ agonists have a direct excitatory effect. However, when used for dysmotility dyspepsia, dual-action **metoclopramide** is no more potent than **domperidone** in standard doses.[11,12]

Doses are given in individual monographs for **metoclopramide** (p.242) and **domperidone** (p.246). For **erythromycin**:

- start with 50–100mg q.d.s PO (use suspension)
- if necessary, increase every few days by 25–50mg to a maximum dose of 250mg q.d.s.[3]

Table 1 Comparison of gastric prokinetic drugs[5]

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

a. all percentages rounded to nearest 5%

b. although acceleration in gastric emptying is a useful indicator of the efficacy of a prokinetic drug, it correlates poorly with symptom relief in gastroparesis.[6]

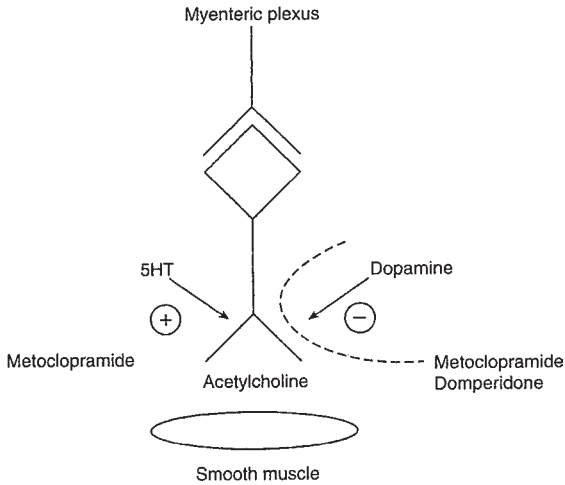

Figure 1 Schematic representation of drug effects on antroduodenal co-ordination via a postganglionic effect on the cholinergic nerves from the myenteric plexus.
⊕ stimulatory effect of 5HT triggered by metoclopramide;
⊖ inhibitory effect of dopamine;
- - - blockade of dopamine inhibition by metoclopramide and domperidone.

Table 2 Drug treatment of hiccup

Class of drug	*Drug*	*Acute relief*	*Maintenance regimen*
Reduce gastric distension ± gastro-oesophageal reflux			
Antiflatulent (carminative)	Peppermint water[a,b]	10mL	10–20mL b.d.
Antiflatulent (defoaming agent)	Simeticone, e.g. in Altacite Plus®	10mL	10mL q.d.s.
Prokinetic	Metoclopramide[b,c]	10mg	10mg t.d.s.–q.d.s.
PPI	Lansoprazole	30mg	30mg each morning
Muscle relaxant (all of these also have central suppressant effects)			
GABA agonist	Baclofen	5mg PO	5–20mg t.d.s., occasionally more[15,16]
Calcium-channel blocker	Nifedipine	10mg PO/SL	10–20mg t.d.s., occasionally more[17,18]
Benzodiazepine	Midazolam	2mg IV, followed by 1–2mg increments every 3–5min	10–60mg/24h by CSCI if patient in last days of life[19]
Central suppression of the hiccup reflex			
Dopamine antagonist	Metoclopramide	As above	As above
	Haloperidol	5–10mg PO or IV if no response	1.5–3mg at bedtime[20,21]
	Chlorpromazine	10–25mg PO or IM; if no response 25–50mg IVI[d]	25–50mg t.d.s.
	Methylphenidate	5mg PO	5–10mg b.d.[22]
GABA agonist	Baclofen	As above	As above
Anti-epileptic	Sodium valproate	200–500mg PO	15mg/kg/24h in divided doses[23]
	Gabapentin	'Burst gabapentin', i.e. 400mg t.d.s. for 3 days, then 400mg once daily for 3 days, then stop; repeat if necessary[d,24]	400mg t.d.s.[e,25,26]

a. facilitates belching by relaxing the lower oesophageal sphincter; an old-fashioned remedy, but can cause gastro-oesophageal reflux
b. peppermint water and metoclopramide should not be used concurrently because of their opposing actions on the gastro-oesophageal sphincter
c. tightens the lower oesophageal sphincter and hastens gastric emptying
d. add to 500mL–1L 0.9% saline and administer over 1h; irritant, do not use SC
e. a smaller dose advisable in elderly frail patients and those with renal impairment, e.g. start with 100mg t.d.s.

Box A Indications for prokinetics in palliative care

Gastro-oesophageal reflux
Hiccup
Delayed gastric emptying
Gastroparesis
  dysmotility dyspepsia
  paraneoplastic autonomic neuropathy
  spinal cord compression
  diabetic autonomic neuropathy
Functional GI obstruction
  drug-induced, e.g. opioids
  cancer of head of pancreas
  linitis plastica (locally diffuse mural infiltration by cancer)

Metoclopramide is also used to relieve hiccup associated with delayed gastric emptying and/or oesophageal reflux (Table 2).[13]

For patients with refractory symptoms, seek advice of a gastroenterologist. In some settings, patients may benefit from **clonidine** (see p.76), intrapyloric **botulinum toxin** or gastric electrical stimulation.[14] Ultimately, some patients may require a venting gastrostomy and/or a feeding jejunostomy.[1]

1 Stevens JE *et al.* (2013) Pathophysiology and pharmacotherapy of gastroparesis: current and future perspectives. *Expert Opinion on Pharmacotherpy.* **14**: 1171–1186.
2 Rayner CK and Horowitz M (2005) New management approaches for gastroparesis. *Nature Clinical Practice Gastroenterology and Hepatology.* **2**: 454–462; quiz 493.
3 Patrick A and Epstein O (2008) Review article: gastroparesis. *Alimentary Pharmacology and Therapeutics.* **27**: 724–740.
4 Schuurkes JAJ *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
5 Sturm A *et al.* (1999) Prokinetics in patients with gastroparesis: a systematic analysis. *Digestion*. **60**: 422–427.
6 Janssen P *et al.* (2013) The relation between symptom improvement and gastric emptying in the treatment of diabetic and idiopathic gastroparesis. *American Journal of Gastroenterology.* **108**: 1382–1391.
7 Maganti K *et al.* (2003) Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *American Journal of Gastroenterology.* **98**: 259–263.
8 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.
9 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.
10 Potter TG and Snider KR (2013) Azithromycin for the treatment of gastroparesis. *Annals of Pharmacotherpy.* **47**: 411–415.
11 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.
12 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.
13 Twycross R *et al.* (2009) *Symptom Management in Advanced Cancer* (4e). palliativedrugs.com, Nottingham, pp. 174–177.
14 Haans JJ and Masclee AA (2007) Review article: The diagnosis and management of gastroparesis. *Alimentary Pharmacology and Therapeutics*. **26 (Suppl 2)**: 37–46.
15 Ramirez FC and Graham DY (1992) Treatment of intractable hiccup with baclofen: results of a double-blind randomized, controlled, crossover study. *American Journal of Gastroenterology.* **87**: 1789–1791.
16 Guelaud C *et al.* (1995) Baclofen therapy for chronic hiccup. *European Respiratory Journal*. **8**: 235–237.
17 Lipps DC *et al.* (1990) Nifedipine for intractable hiccups. *Neurology.* **40**: 531–532.
18 Brigham B and Bolin T (1992) High dose nifedipine and fludrocortisone for intractable hiccups. *Medical Journal of Australia*. **157**: 70.
19 Wilcock A and Twycross R (1996) Case report: midazolam for intractable hiccup. *Journal of Pain and Symptom Management.* **12**: 59–61.
20 Scarnati RA (1979) Intractable hiccup (singultus): report of case. *Journal of the American Osteopathic Association*. **79**: 127–129.
21 Ives TJ *et al.* (1985) Treatment of intractable hiccups with intramuscular haloperidol. *American Journal of Psychiatry.* **142**: 1368–1369.
22 Marechal R *et al.* (2003) Successful treatment of intractable hiccup with methylphenidate in a lung cancer patient. *Supportive Care in Cancer.* **11**: 126–128.
23 Jacobson P *et al.* (1981) Treatment of intractable hiccups with valproic acid. *Neurology.* **31**: 1458–1460.

24 Moretti R *et al.* (2004) Gabapentin as a drug therapy of intractable hiccup because of vascular lesion: a three-year follow up. *Neurologist*. **10**: 102–106.
25 Schuchmann JA and Browne BA (2007) Persistent hiccups during rehabilitation hospitalization: three case reports and review of the literature. *American Journal of Physical Medicine and Rehabilitation*. **86**: 1013–1018.
26 Tegeler ML and Baumrucker SJ (2008) Gabapentin for intractable hiccups in palliative care. *American Journal of Hospice and Palliative Care*. **25**: 52–54.

Updated March 2014

H_2-RECEPTOR ANTAGONISTS BNF 1.3.1

Class: Gastroprotective drugs.

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

Pharmacology

H_2-receptor antagonists (H_2 antagonists) include **cimetidine**, **famotidine**, **nizatidine** and **ranitidine**. All are equally effective at gastric acid suppression.[1] Other effects include reducing the volume of gastric secretions, and increasing lower oesophageal sphincter pressure.[2,3] **Cimetidine**, alone among H_2 antagonists, can cause serious CYP450-related drug interactions (see Table 1 and Cytochrome P450, p.771). None of the H_2 antagonists, including **cimetidine**, alters the metabolism of **morphine**.[4]

Prophylactic treatment with a standard dose of an H_2 antagonist reduces the incidence of NSAID-related *duodenal* ulcers.[5] Prevention of *gastric* erosions and ulcers is seen only with a double dose.[6,7] 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).[5,8] **Ranitidine** is a good choice in terms of convenience and safety.

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

Cautions

Hepatic impairment, renal impairment.

Drug interactions

CYP450-related drug interactions with **cimetidine** most relevant to palliative care are given in Table 1. **Cimetidine** may also increase levels of **epirubicin**, by an unknown mechanism. There are inconsistent reports of **cimetidine** and **ranitidine** increasing the plasma concentration of **midazolam**.[9]

Because H_2 antagonists increase gastric pH, they can decrease the absorption of some drugs:
- *antifungals*, e.g. **itraconazole** (capsules only), **posaconazole** (but *not* **fluconazole**)
- *antivirals*, e.g. **atazanavir**, **delavirdine** (not UK), **indinavir**, **nelfinavir** and **rilpivirine**
- *protein kinase inhibitors*, e.g. **dasatinib**, **erlotinib**, **gefitinib**, **lapatinib**, **nilotinib**.[9]

This effect varies between drugs and formulations. See the SPC and other sources[9] to determine the risk of treatment failure with concurrent use of an H_2 antagonist. When avoidance is impossible, alternative measures to reduce the interaction include increasing the dose, administering $>$12h after the H_2 antagonist or giving with an acidic drink, e.g. cola.[9]

Conversely, the absorption of **saquinivir** may be *increased* and, because of the risk of QT prolongation, this could be clinically important.[9]

Table 1 Cimetidine CYP450-related interactions most relevant to palliative care[9,10]

Drug group	*Drug plasma levels increased*
Anti-epileptics	Carbamazepine (transient), phenytoin
Benzodiazepines	Alprazolam, diazepam, chlordiazepoxide, flurazepam, nitrazepam, triazolam (midazolam reports inconsistent)
Calcium antagonists	Potentially all, including diltiazem and nifedipine
Coumarin anticoagulants	Warfarin
Local anaesthetics	Lidocaine (IV), procainamide
Opioids	Alfentanil, fentanyl, methadone
SSRIs	All
TCAs	Potentially all
Xanthines	Aminophylline, theophylline
Miscellaneous	Fluorouracil, mefloquine, mirtazapine, moclobemide, quinidine, tacrine, zolmitriptan

Undesirable effects

Cimetidine occasionally causes gynaecomastia.

Possible increased risk of pneumonia (gastric acid suppression leads to bacterial overgrowth in the upper-GI and respiratory tracts); association stronger for PPIs.[11]

Dose and use

Cochrane reviews: PPIs, H_2 antagonists and prokinetics are effective at *relieving symptoms* of non-ulcer dyspepsia and acid reflux, with PPIs having the greatest efficacy.[12,13] PPIs, **misoprostol** and double-dose H_2 antagonists are effective at *preventing* chronic NSAID-related endoscopic peptic ulcers.

Standard doses of H_2 antagonists reduce the risk of duodenal ulcers but not gastric ulcers. **Misoprostol** 400microgram/24h is less effective at preventing gastric ulcers than 800microgram/24h and is still associated with diarrhoea. Of all these treatments, only **misoprostol** 800microgram/24h has been definitely shown to reduce the overall incidence of ulcer *complications* (perforation, haemorrhage or gastric outlet obstruction).[6]

The use of PPIs following peptic ulcer-related upper-GI haemorrhage, significantly reduces rebleeding, need for surgery and rate of ulcer recurrence. In high risk patients (i.e. bleeding or blood vessel visible at endoscopy) PPIs reduce mortality.[14] Ideally, the PPI is commenced following a diagnostic/therapeutic endoscopy, except in circumstances where this is not immediately available.[15] Evidence is insufficient to determine if any differences exist between PPI given IV in high dose or IV/PO in usual doses.[16]

Adding a bedtime dose of an H_2 antagonist to a high dose PPI may improve night-time acid reflux but evidence is lacking.[17]

NICE guidance: PPIs are preferable to H_2 antagonists for the treatment of dyspepsia, gastro-oesophageal reflux disease and peptic ulcers, including NSAID-related peptic ulcers. Although PPIs are more effective in relieving uninvestigated dyspeptic symptoms, offer a trial of H_2 antagonists or a prokinetic if there has been an inadequate response to a PPI.

For patients taking an NSAID and at high risk of peptic ulcer disease, double-dose H_2 antagonists or PPIs significantly reduce endoscopically detected lesions. **Misoprostol** at low dose is less effective and has undesirable effects. When an NSAID-related ulcer is diagnosed, stop the NSAID if possible, treat *H pylori* infection if present (see p.486) and give double-dose H_2 antagonist or PPI. PPIs heal the majority of ulcers.[18]

A PPI should be offered to patients with non-variceal upper-GI haemorrhage when bleeding or stigmata of recent bleeding is confirmed at endoscopy.[19]

If it is necessary to continue with the NSAID, treatments may be less effective. The rate of healing is higher and the risk of recurrence lower with PPIs and **misoprostol** compared with H_2 antagonists.[20]

H_2 antagonists are second-line treatment for gastro-oesophageal reflux disease, non-ulcer dyspepsia and uninvestigated dyspepsia, and are available as an OTC measure for mild dyspepsia.

Cimetidine, **famotidine** and **nizatidine** are significantly more expensive than **ranitidine**; **cimetidine** is also intrinsically more dangerous. Thus, dose recommendations have been limited to **ranitidine**.

The dose and duration of treatment is least with duodenal ulceration and most with reflux oesophagitis and prophylaxis for NSAID-related peptic ulcer, although the dose for ulcer healing can be doubled if the initial response is poor (Table 2). **Ranitidine** is more effective if taken at bedtime rather than with the evening meal.[21]

Table 2 PO treatment regimens for ranitidine

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

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

Parenteral formulations are available for IM and IV use if treatment is considered necessary in a patient with severe nausea and vomiting (see BNF section 1.3.1). Some centres use the SC route (unauthorized), either 50mg SC b.d.–q.d.s. or CSCI 100–200mg/24h without evidence of local inflammation.

Ranitidine has a pH of 6.7–7.3 and is incompatible with **levomepromazine** and **midazolam**. Because there are limited compatibility data with other drugs, it is probably best to administer alone if giving by CSCI (see Chapter 20, p.701).

In renal impairment (creatinine clearance $<$ 50mL/min) the dose of **ranitidine** should be reduced to 150mg at bedtime but increased to 150mg b.d. if an ulcer fails to respond at the lower dose.

Supply

Ranitidine (generic)
Tablets 150mg, 300mg, 28 days @ 150mg b.d. or 300mg at bedtime = £1.50.
Tablets effervescent 150mg, 300mg, 28 days @ 150mg b.d. = £16 or 300mg at bedtime = £15 (*Tablets may contain* Na^+).
Oral solution 75mg/5mL, 28 days @ 150mg b.d. = £37; *may contain alcohol.*
Injection 25mg/mL, 2mL amp = £0.50.

Zantac® (GSK)
Tablets 150mg, 300mg, 28 days @ 150mg b.d. or 300mg at bedtime = £1.50.
Oral solution (sugar-free) 75mg/5mL, 28 days @ 150mg b.d. = £39; *contains 8% alcohol.*
Injection 25mg/mL, 2mL amp = £0.50.

Ranitidine tablets are available as an OTC measure for acid dyspepsia and heartburn.

1 Tougas G and Armstrong D (1997) Efficacy of H_2 receptor antagonists in the treatment of gastroesophageal reflux disease and its symptoms. *Canadian Journal of Gastroenterology.* **11 (Suppl B)**: 51B–54B.
2 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.
3 Iwakiri K *et al.* (2011) The effects of nizatidine on transient lower esophageal sphincter relaxations (TLESRs) and acid reflux in healthy subjects. *Journal of Smooth Muscle Research.* **47**: 157–166.
4 Mojaverian P *et al.* (1982) Cimetidine does not alter morphine disposition in man. *British Journal of Clinical Pharmacology.* **14**: 809–813.
5 Hollander D (1994) Gastrointestinal complications of nonsteroidal anti-inflammatory drugs: prophylactic and therapeutic strategies. *American Journal of Medicine.* **96**: 274–281.
6 Rostom A *et al.* (2002) Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database of Systematic Reviews.* **4**: CD002296.
7 Leontiadis GI *et al.* (2007) Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. *Health Technology Assessment.* **11**: iii–iv, 1–164.
8 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.
9 Baxter K and Preston CL. *Stockley's Drug Interactions*. London: Pharmaceutical Press. www.medicinescomplete.com (accessed October 2012).
10 Sorkin E and Ogawa C (1983) Cimetidine potentiation of narcotic action. *Drug Intelligence and Clinical Pharmacy.* **17**: 60–61.
11 Fohl AL and Regal RE (2011) Proton pump inhibitor-associated pneumonia: Not a breath of fresh air after all? *World Journal of Gastrointestinal Pharmacology and Therapeutics.* **2**: 17–26.
12 Moayyedi P (2006) Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database of Systematic Reviews.* **4**: CD001960.
13 van Pinxteren B *et al.* (2010) Short-term treatment with proton pump inhibitors, H_2- receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database of Systematic Reviews.* **11**: CD002095.
14 Leontiadis G *et al.* (2010) Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database of Systematic Reviews.* **5**: CD002094.
15 Sreedharan A *et al.* (2010) P.Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. *Cochrane Database of Systematic Reviews.* **7**: CD005414.
16 Neumann I *et al.* (2013) Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding. *Cochrane Database of Systematic Reviews.* **6**: CD007999.
17 Wang Y *et al.* (2009) Additional bedtime H_2 receptor antagonist for control of nocturnal gastirc acid breakthrough. *Cochrane Database of Systematic Reviews.* **4**: CD004275.
18 NICE (2004) Dyspepsia. Management of dyspepsia in adults in primary care. *Clinical Guideline* CG17. www.nice.org.uk
19 NICE (2012) Acute upper gastrointestinal bleeding management. *Clinical Guideline* CG141. www.nice.org.uk
20 Frech EJ and Go MF (2009) Treatment and chemoprevention of NSAID-associated gastrointestinal complications. *Therapeutics and Clinical Risk Management.* **5**: 65–73.
21 20 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.

Updated (minor change) April 2014

MISOPROSTOL BNF 1.3.4

Class: Prostaglandin (PG) analogue, gastroprotective drug.

Indications: Healing of gastric and duodenal ulcers, prevention and healing of NSAID-related 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. The protective effects occur at doses lower than those required to inhibit acid secretion.[1] After oral administration, misoprostol is rapidly converted to an active free acid.

Misoprostol helps to both prevent and heal NSAID-related gastroduodenal erosions and ulcers.[2–5] For NSAID-related ulcers, the rate of healing is higher and the risk of recurrence lower with PPIs and misoprostol compared with H_2 antagonists.[6]

PPIs are more effective than misoprostol at healing and preventing the recurrence of duodenal ulcers.[6–8] Misoprostol is as effective as PPIs in preventing relapse of gastric ulcers and, in one RCT when compared with **lansoprazole**, ulcer-free intervals were longer.[9] Overall, the risk of serious GI complications are significantly reduced by misoprostol.[4,5] However, its use is limited by its tendency to cause diarrhoea 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

Diarrhoea (may necessitate stopping treatment), colic, dyspepsia, flatulence, nausea and vomiting, abnormal vaginal bleeding (intermenstrual, menorrhagia, postmenopausal), rashes, dizziness.

Dose and use

Cochrane reviews: PPIs, H_2 antagonists and prokinetics are effective at *relieving symptoms* of non-ulcer dyspepsia and acid reflux, with PPIs having the greatest efficacy.[10,11] PPIs, misoprostol and double-dose H_2 antagonists are effective at *preventing* chronic NSAID-related endoscopic peptic ulcers.

Standard doses of H_2 antagonists reduce the risk of duodenal ulcers but not gastric ulcers. Misoprostol 400microgram/24h is less effective at preventing gastric ulcers than 800microgram/24h, and is still associated with diarrhoea. Of all these treatments, only misoprostol 800microgram/24h has been definitely shown to reduce the overall incidence of ulcer *complications* (perforation, haemorrhage or gastric outlet obstruction).[5]

The use of PPIs following peptic ulcer-related upper-GI haemorrhage, significantly reduces rebleeding, need for surgery and rate of ulcer recurrence. In high risk patients (i.e. bleeding or blood vessel visible at endoscopy) PPIs reduce mortality.[12] Ideally, the PPI is commenced following a diagnostic/therapeutic endoscopy, except in circumstances where this is not immediately available.[13] Evidence is insufficient to determine if any differences exist between PPI given IV in high dose or IV/PO in usual doses.[14]

Adding a bedtime dose of an H_2 antagonist to a high dose PPI may improve night-time acid reflux but evidence is lacking.[15]

NICE guidance: PPIs are preferable to H_2 antagonists for the treatment of dyspepsia, gastro-oesophageal reflux disease and peptic ulcers, including NSAID-related peptic ulcers. Although PPIs are more effective in relieving uninvestigated dyspeptic symptoms, offer a trial of H_2 antagonists or prokinetic if there has been an inadequate response to a PPI.

For patients taking an NSAID and at high risk of peptic ulcer disease, double-dose H_2 antagonists or PPIs significantly reduce endoscopically detected lesions. Misoprostol at low dose is less effective and has undesirable effects. When an NSAID-related ulcer is diagnosed, stop the NSAID if possible, treat H pylori infection if present (see p.486) and give double-dose H_2 antagonist or a PPI. PPIs heal the majority of ulcers.[16]

A PPI should be offered to patients with non-variceal upper-GI haemorrhage when bleeding or stigmata of recent bleeding is confirmed at endoscopy.[17]

If it is necessary to continue with the NSAID, treatments may be less effective. The rate of healing is higher and the risk of recurrence lower with PPIs and misoprostol compared with H_2 antagonists.[6] Misoprostol 800microgram/24h is as effective as PPIs for preventing symptomatic and complicated gastric ulcers, but less effective in preventing duodenal ulcers.[7]

Prophylaxis against NSAID-related ulcers

200microgram b.d.–q.d.s. taken with the NSAID.

NSAID-related ulceration

- 200microgram t.d.s. with meals & at bedtime *or*
- 400microgram b.d. (breakfast and bedtime) for 4–8 weeks.[3]

If it causes diarrhoea, give 200microgram t.d.s. with meals & at bedtime and avoid **magnesium salts**.

Supply

Cytotec® (Pharmacia)
Tablets 200microgram, 28 days @ 200microgram b.d. = £10.

1 Monk JP and Clissold SP (1987) Misoprostol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of peptic ulcer disease. *Drugs*. **33**: 1–30.
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 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.
4 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.
5 Rostom A *et al.* (2002) Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database of Systematic Reviews*. **4**: CD002296.
6 Frech EJ and Go MF (2009) Treatment and chemoprevention of NSAID-associated gastrointestinal complications. *Therapeutics and Clinical Risk Management*. **5**: 65–73.
7 Leontiadis GI *et al.* (2007) Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. *Health Technology Assessment*. **11**: iii-iv, 1–164.
8 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.
9 Graham DY *et al.* (2002) Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. *Archives of Internal Medicine*. **162**: 169–175.
10 Sigterman KE *et al.* (2013) Short-term treatment with proton pump inhibitors, H_2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database of Systematic Reviews*. **5**: CD002095.
11 Moayyedi P (2006) Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database of Systematic Reviews*. **4**: CD001960.
12 Leontiadis G *et al.* (2010) Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database of Systematic Reviews*. **5**: CD002094.
13 Sreedharan A *et al.* (2010) Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. *Cochrane Database of Systematic Reviews*. **7**: CD005415.
14 Neumann I *et al.* (2013) Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding. *Cochrane Database of Systematic Reviews*. **6**: CD007999.
15 Wang Y *et al.* (2009) Additional bedtime H_2 receptor antagonist for control of nocturnal gastirc acid breakthrough. *Cochrane Database of Systematic Reviews*. **4**: CD004275.
16 NICE (2004) Dyspepsia. Management of dyspepsia in adults in primary care. *Clinical Guideline* CG17. www.nice.org.uk
17 NICE (2012) Acute upper gastrointestinal bleeding:management. *Clinical Guideline* CG141. www.nice.org.uk

Updated (minor change) April 2014

PROTON PUMP INHIBITORS — BNF 1.3.5

Class: Gastroprotective drugs.

Indications: Authorized indications vary between products; consult the manufacturers' SPCs for details; they include acid dyspepsia, acid reflux, peptic ulceration, prevention and treatment of NSAID-related ulceration and eradication of *Helicobacter pylori* (with antibacterials).

Pharmacology

Proton pump inhibitors (PPIs) reduce gastric acid output but, unlike H_2 antagonists, they do *not* reduce the volume of gastric secretions. Because they are all rapidly degraded by acid, they are formulated as e/c 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.

PPIs are effective in treating acid-related disorders. They provide symptomatic relief, help prevent and heal peptic ulcers (including those associated NSAIDs), and reduce the risk of recurrent ulceration and rebleeding.[1–3]

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.[4] 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.[5,6] Thus, **omeprazole** 40mg daily is superior to **lansoprazole** 60mg daily and **pantoprazole** 80mg daily in the management of severe gastro-oesophageal reflux disease (oesophagitis and stricture).[7]

Comparative studies with newer PPIs show **esomeprazole** (the S-enantiomer of **omeprazole**) 40mg once daily and **rabeprazole** 20mg once daily cause rapid relief of reflux symptoms and suppress acid for longer periods. However, the endoscopic healing rate of ulcers and reflex oesophagitis is similar to other PPIs.[8–10] **Esomeprazole** and **rabeprazole** may be more effective in patients who have not responded to other PPIs. Whereas **omeprazole**, **lansoprazole** and **pantoprazole** are metabolized mainly via CYP2C19, this is not so with **esomeprazole** and **rabeprazole**. Thus, in CYP2C19 extensive metabolizers, the plasma concentrations of the former three PPIs are reduced, but not **esomeprazole** and **rabeprazole**.[9]

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.[11–13] 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).[14] Pharmacokinetic data are shown in Table 1.

Onset of action <2h.

Duration of action >24h.

Table 1 Pharmacokinetic details of PPIs given PO

	Bio-availability (%)	*Time to peak plasma concentration (h)*	*Plasma halflife (h)*
Esomeprazole	68 (20mg dose) 89 (40mg dose)	1–2	1.3
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[b]

a. increases to 3–6h in cirrhosis

b. increases to 2–3h in hepatic impairment.

Cautions

The dose should be reduced in severe hepatic impairment (see Dose and use). Ocular damage has been reported, mostly with IV **omeprazole**.[15,16] PPIs possibly cause vasoconstriction by blocking H^+/K^+-ATPase. Because the retinal artery is an end-artery, anterior ischaemic optic neuropathy may result. If the PPI is stopped, visual acuity may improve but some patients have become permanently blind, in some instances after only 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**. Concern about serious cardiac events (infarction, death) with **omeprazole** and **esomeprazole** is now considered to be groundless.[17]

PPIs are an independent risk factor for *Clostridium difficile* infection; and the association is stronger than for other acid-reducing agents. Patients are at risk of recurrent *Clostridium difficile* colitis, up to nearly 5 times more likely.[18–23] Although the spores of *Clostridium difficile* are resistant to gastric acid, reduced acidity allows bacteria to survive. Counts of *Clostridium difficile* organisms, which cannot survive at normal stomach pH, increase when the pH is >5, and go on to infect the bowel. Further, the cells can live up to 6h on moist surfaces, long enough to allow transmission between patients.[24]

The concomitant use of PPIs and antibacterials further increases the risk of *Clostridium difficile* infection.[25]

Drug interactions

Although PPIs are metabolized by CYP450 (see Chapter 25, p.771), clinically important interactions with PPIs are rare.[26,27] 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**, **voriconazole**).[28] No other significant CYP450 drug–drug interactions have been identified with **pantoprazole** or **rabeprazole**.[28,29]

A minor pharmacokinetic interaction between **omeprazole** and **warfarin**, resulting in a less than 15% rise in **R-warfarin** levels (the less active enantiomer) is of limited clinical relevance. However, isolated cases of raised INRs have been reported with all PPIs.[28] It is recommended that, in patients taking **warfarin**, the INR is monitored if **omeprazole** or **esomeprazole** is started or stopped.[30]

The antithrombotic effect of **clopidogrel** (a pro-drug activated by CYP2C19) can be reduced by the concurrent administration of **omeprazole**, **esomeprazole** and **rabeprazole**.[31–33] Although the evidence for the other PPIs is inconsistent,[32–34] it would seem wise to avoid concurrent prescription with any PPI, and use an H_2 antagonist (e.g. **ranitidine**) instead.

Because PPIs increase gastric pH, they can decrease the absorption of some drugs:

- *antifungals*, e.g. **itraconazole** (capsules only), **posaconazole** (but *not* **fluconazole**)
- *antivirals*, e.g. **atazanavir**, **delavirdine** (not UK), **indinavir**, **nelfinavir** and **rilpivirine**
- *protein kinase inhibitors*, e.g. **dasatinib**, **erlotinib**, **gefitinib**, **lapatinib**, **nilotinib**.[28,35]

This effect varies between drugs and formulations. See the SPC and other sources[28] to determine the risk of treatment failure with concurrent use of a PPI. When avoidance is impossible, alternative measures to reduce the interaction include increasing the dose, administering >12h after the PPI or giving with an acidic drink, e.g. cola.[36]

Conversely, the absorption of **saquinivir** may be *increased* and, because of the risk of QT prolongation, this could be clinically important.[28]

The absorption of **digoxin** may also be *increased*; however, this may only be important with high PPI doses in the elderly.[28]

Undesirable effects

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

Severe hypomagnesaemia: rare and generally with prolonged use, i.e. >1 year. Particularly when used concurrently with **digoxin** or a drug which can cause hypomagnesaemia (see p.571), measure serum magnesium before starting PPI and periodically during use (e.g. every 3 months).[37]

Observational studies suggest a modest increase in the risk of hip and vertebral fracture in the elderly with prolonged use of PPIs. Those at risk of osteoporosis should ensure an adequate intake of vitamin D and calcium, using supplements if necessary.[38]

Possible increased risk of pneumonia (gastric acid suppression leads to bacterial overgrowth in the upper-GI and respiratory tracts); association weaker for H_2 antagonists.[39]

Dose and use

Cochrane reviews: PPIs, H_2 antagonists and prokinetics are effective at *relieving symptoms* of non-ulcer dyspepsia and acid reflux, with PPIs having the greatest efficacy.[40,41] PPIs, **misoprostol** and double-dose H_2 antagonists are effective at *preventing* chronic NSAID-related endoscopic peptic ulcers.

Standard doses of H_2 antagonists reduce the risk of duodenal ulcers but not gastric ulcers. **Misoprostol** 400microgram/24h is less effective at preventing gastric ulcers than 800microgram/24h and is still associated with diarrhoea. Of all these treatments, only **misoprostol** 800microgram/24h has been definitely shown to reduce the overall incidence of ulcer *complications* (perforation, haemorrhage or gastric outlet obstruction)[42]

The use of PPIs following peptic ulcer-related upper-GI haemorrhage, significantly reduces rebleeding, need for surgery and rate of ulcer recurrence. In high risk patients (i.e. bleeding or blood vessel visible at endoscopy) PPIs reduce mortality.[43] Ideally, the PPI is commenced following a diagnostic/therapeutic endoscopy, except in circumstances where this is not immediately available.[44] Evidence is insufficient to determine if any differences exist between PPI given IV in high dose or IV/PO in usual doses.[45]

Adding a bedtime dose of an H_2 antagonist to a high dose PPI may improve night-time acid reflux but evidence is lacking.[46]

NICE guidance: PPIs are preferable to H_2 antagonists for the treatment of dyspepsia, gastro-oesophageal reflux disease and peptic ulcers, including NSAID-related peptic ulcers. Although PPIs are more effective in relieving uninvestigated dyspeptic symptoms, offer a trial of an H_2 antagonists or a prokinetic if there has been an inadequate response to a PPI.

For patients taking an NSAID and at high risk of peptic ulcer disease, double-dose H_2 antagonists or PPIs significantly reduce endoscopically detected lesions. **Misoprostol** at low dose is less effective and has undesirable effects. When an NSAID-related ulcer is diagnosed, stop the NSAID if possible, treat *H pylori* infection if present (see p.486) and give double-dose H_2 antagonist or PPI. PPIs heal the majority of ulcers.[47]

A PPI should be offered to patients with non-variceal upper-GI haemorrhage when bleeding or stigmata of recent bleeding is confirmed at endoscopy.[48]

PPIs are used together with antibacterials for the eradication of *Helicobacter pylori* (see p.486).

Lansoprazole

The SPC for **lansoprazole** states that administration should be 1h before breakfast each morning in order to achieve 'optimal acid inhibition'. However, this precaution is unnecessary.[11,14]

- 30mg each morning for 4–8 weeks for treatment of ulcers and reflux oesophagitis
- 15mg each morning for prophylaxis of ulcers and reflux oesophagitis, increase to 30mg daily if necessary
- 30mg b.d. when used with antibacterials to eradicate *Helicobacter pylori* (see p.487).

Omeprazole

- 20mg each morning for both treatment and prevention of ulcer recurrence
- 40mg each morning in reflux oesophagitis if poor response to standard dose
- 20mg b.d. or 40mg each morning when used with antibacterials to eradicate *Helicobacter pylori* (see p.487).

In severe hepatic impairment, the dose should be limited to **lansoprazole** 30mg/day and **omeprazole** 20mg/day.

For patients who cannot safely swallow tablets, **lansoprazole** and **omeprazole** can be given as orodispersible or dispersible tablets. Some capsules containing e/c granules can be opened and the e/c granules swallowed with water or fruit juice, or mixed with apple sauce or yoghurt; check with the specific manufacturer's SPC. *Care must be taken not to crush or chew the e/c granules.*

Specific procedures are available from the manufacturers for administration by enteral feeding tubes (see p.731). For patients with obstructive dysphagia and acid dyspepsia or with severe gastritis and vomiting, the rectal route has also been used.[49]

Omeprazole, when given for non-variceal upper-GI haemorrhage, is administered either PO or IV.[48] **Omeprazole** and **esomeprazole** have been used parenterally in palliative care to treat painful reflux oesophagitis in patients unable to take PO medication.

Although not authorized for SC administration, **omperazole** 40mg for infusion diluted as per IVI (see supply) has been given by CSCI over 3–4h for $\leqslant$4 days.[50,51]

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

Supply

Lansoprazole (generic)
Capsules enclosing e/c granules 15mg, 30mg, 28 days @ 30mg each morning = £2.

Zoton® (Wyeth)
Tablets orodispersible (FasTab®) 15mg, 30mg, 28 days @ 30mg each morning = £6.

Omeprazole (generic)
Capsules enclosing e/c granules 10mg, 20mg, 40mg, 28 days @ 20mg each morning = £2.
Capsules enclosing e/c tablet 10mg, 20mg, 28 days @ 20mg each morning = £2; *do not open capsules*.
Tablets e/c 10mg, 20mg, 40mg, 28 days @ 20mg each morning = £5.
Tablets dispersible (e/c pellets) 10mg, 20mg, 40mg, 28 days @ 20mg each morning = £12.
Injection (as bolus) powder for reconstitution in 10mL of diluent provided. Give as a slow IV injection over 5min. 40mg vial with diluent = £5.
Infusion powder for reconstitution in 5mL of infusion fluid 0.9% saline or 5% glucose. Further dilute to 100mL and give IVI over at least 20–30min. 40mg vial = £5.

Losec® (AstraZeneca)
Capsules enclosing e/c granules 10mg, 20mg, 40mg, 28 days @ 20mg each morning = £12.
Tablets dispersible (multiple-unit pellet system, MUPS®) ***enclosing e/c pellets*** 10mg, 20mg, 40mg, 28 days @ 20mg each morning = £12.
Injection (as bolus) powder for reconstitution in 10mL of diluent provided. Give as a slow IV injection over 5min. 40mg vial with diluent = £5.
Infusion powder for reconstitution in 5mL of infusion fluid 0.9% saline or 5% glucose. Further dilute to 100mL.and give IVI over at least 20–30min. 40mg vial = £5.

Omeprazole e/c tablets are available as an OTC measure for heartburn.

*For details of **esomeprazole**, **pantoprazole** and **rabeprazole**, see BNF; **esomeprazole** and **rabeprazole** are significantly more expensive. Combination products of **omeprazole** with **ketoprofen** and **esomeprazole** with **naproxen** are also available.*

1 Frech EJ and Go MF (2009) Treatment and chemoprevention of NSAID-associated gastrointestinal complications. *Therapeutics and Clinical Risk Management.* **5**: 65–73.
2 Leontiadis GI *et al.* (2007) Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. *Health Technology Assessment.* **11**: iii–iv, 1–164.
3 Leontiadis GI *et al.* (2005) Systematic review and meta-analysis of proton pump inhibitor therapy in peptic ulcer bleeding. *British Medical Journal.* **330**: 568.
4 DTB (1997) Pantoprazole - a third proton pump inhibitor. *Drug and Therapeutics Bulletin.* **35**: 93–94.
5 Dammann H *et al.* (1993) The effects of lansoprazole, 30 or 60mg daily, on intragastric pH and on endocrine function in healthy volunteers. *Alimentary Pharmacology and Therapeutics.* **7**: 191–196.
6 Koop H *et al.* (1996) Intragastric pH and serum gastrin during administration of different doses of pantoprazole in healthy subjects. *European Journal of Gastroenterology and Hepatology.* **8**: 915–918.
7 Jaspersen D *et al.* (1998) A comparison of omeprazole, lansoprazole and pantoprazole in the maintenance treatment of severe reflux oesophagitis. *Alimentary Pharmacology and Therapeutics.* **12**: 49–52.
8 Zheng N (2009) Comparative study of omeprazole, lansoprazole, pantoprazole and esomeprazole for the system relief in patients with reflux oesophagitis. *World Journal of Gastroenterology.* **28**: 900–995.
9 Shi S and Klotz U (2008) Proton pump inhibitors: an update of their clinical use and pharmacokinetics. *European Journal of Clinical Pharmacology.* **64**: 935–951.
10 Pace F *et al.* (2007) A review of rabeprazole in the treatment of acid-related diseases. *Therapeutics and Clinical Risk Management.* **3**: 363–379.
11 Moules I *et al.* (1993) Gastric acid inhibition by the proton pump inhibitor lansoprazole is unaffected by food. *British Journal of Clinical Research.* **4**: 153–161.
12 Delhotal-Landes B *et al.* (1991) The effect of food and antacids on lansoprazole absorption and disposition. *European Journal of Drug Metabolism and Pharmacokinetics.* **3**: 315–320.
13 Andersson T (1990) Bioavailability of omeprazole as enteric coated (EC) granules in conjunction with food on the first and seventh days of treatment. *Drug Investigations.* **2**: 184–188.
14 Brummer RJM and Geerling BJ (1995) Acute and chronic effect of lansoprazole and omeprazole in relation to food intake. *Gut.* **37**: 127.
15 Schonhofer P (1994) Intravenous omeprazole and blindness. *Lancet.* **343**: 665.
16 Schonhofer P *et al.* (1997) Ocular damage associated with proton pump inhibitors. *British Medical Journal.* **314**: 1805.
17 Health Canada (2008). Available from: www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_34-eng.php
18 Kim JW *et al.* (2010) Proton pump inhibitors as a risk factor for recurrence of Clostridium difficile-associated diarrhea. *World Journal of Gastroenterology.* **16**: 3573–3577.
19 Cunningham R and Dial S (2008) Is over-use of proton pump inhibitors fuelling the current epidemic of Clostridium difficile-associated diarrhoea? *Journal of Hospital Infection.* **70**: 1–6.

20 Yearsley KA *et al.* (2006) Proton pump inhibitor therapy is a risk factor for Clostridium difficile-associated diarrhoea. *Alimentary Pharmacology and Therapeutics*. **24**: 613–619.
21 Dial S *et al.* (2005) Use of gastric acid suppressive agents and the risk of community acquired Clostridium difficile-associated diarrhoea. *Journal of the American Medical Association*. **294**: 2984–2995.
22 Cadle RM *et al.* (2007) Association of proton-pump inhibitors with outcomes in Clostridium difficile colitis. *American Journal of Health System Pharmacy*. **64**: 2359–2363.
23 Garey KW *et al.* (2008) Meta-analysis to assess risk factors for recurrent Clostridium difficile infection. *Journal of Hospital Infection*. **70**: 298–304.
24 Jump RL *et al.* (2007) Vegetative Clostridium difficile survives in room air on moist surfaces and in gastric contents with reduced acidity: a potential mechanism to explain the association between proton pump inhibitors and C. difficile-associated diarrhea? *Antimicrobial Agents and Chemotherapy*. **51**: 2883–2887.
25 Kwok CS *et al.* (2012) Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. *American Journal of Gastroenterology*. **107**: 1011–1019.
26 Andersson T (1996) Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. *Clinical Pharmacokinetics*. **31**: 9–28.
27 Tucker G (1994) The interaction of proton pump inhibitors with cytochrome P450. *Alimentary Pharmacology and Therapeutics*. **8**: 33–38.
28 Baxter K and Preston CL *Stockley's Drug Interactions*. London: Pharmaceutical Press www.medicinescomplete.com (accessed October 2012).
29 Steinijans W (1996) Lack of pantoprazole drug interactions in man: an updated review. *International Journal of Clinical Pharmacology and Therapeutics*. **34**: S31–S50.
30 MHRA (2009) Public assessment report. Warfarin: changes to product safety information December 2009. Available from: www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con065506.pdf
31 Kreutz RP *et al.* (2010) Impact of proton pump inhibitors on the effectiveness of clopidogrel after coronary stent placement: the clopidogrel Medco outcomes study. *Pharmacotherapy*. **30**:787–796.
32 Ho M *et al.* (2009) Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *Journal of the American Medical Association*. **301**: 937–944.
33 Juurlink DN *et al.* (2009) A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *Canadian Medical Association Journal*. **180**: 713–718.
34 MHRA (2010) Clopidogrel and proton pump inhibitors: interaction - updated advice. *Drug Safety Update* **3**. www.mhra.gov.uk/safetyinformation
35 European Agency for the Evaluation of Medicinal Products (2004) Important new pharmacokinetic data demostrating that REYATAZ (atazanavir sulphate) combined with NORVIR (ritonavir) and omeprazole should not be co-administered. In: *EMEA public statement*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/08/WC500095461.pdf
36 Baxter K (2012) Stockley's Drug Interactions (online edition). Pharmaceutical Press, London. Available from: www.medicinescomplete.com
37 MHRA (2012) Proton pump inhibitors in long term use: reports of hypomagnesaemia. *Drug Safety Update* **5**. www.mhra.gov.uk/safetyinformation
38 MHRA (2012) Proton pump inhibitors in long-term use: recent epidemiological evidence of increased risk of bone fracture. *Drug Safety Update* **5**. www.mhra.gov.uk/safetyinformation
39 Fohl AL and Regal RE (2011) Proton pump inhibitor-associated pneumonia: Not a breath of fresh air after all? *World Journal of Gastrointestinal Pharmacology and Therapeutics*. **2**: 17–26.
40 Moayyedi P (2006) Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database of Systematic Reviews*. **4**: CD001960.
41 Sigterman KE *et al.* (2013) Short-term treatment with proton pump inhibitors, H_2- receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database of Systematic Reviews*. **5**: CD002095.
42 Rostom A *et al.* (2002) Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database of Systematic Reviews*. **4**: CD002296.
43 Leontiadis G *et al.* (2010) Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database of Systematic Reviews*. **5**: CD002094.
44 Sreedharan A *et al.* (2010) P.Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. *Cochrane Database of Systematic Reviews*. **7**: CD005414. DOI.
45 Neumann I *et al.*(2013) Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding. *Cochrane Database of Systematic Reviews*. **6**: CD007999.
46 Wang Y *et al.* (2009) Additional bedtime H_2 receptor antagonist for control of nocturnal gastirc acid breakthrough. *Cochrane Database of Systematic Reviews*. **4**: CD004275.
47 NICE (2004) Dyspepsia. Management of dyspepsia in adults in primary care. *Clinical Guideline* CG17. www.nice.org.uk
48 NICE (2012) Acute upper gastrointestinal bleeding management. *Clinical Guideline* CG141. www.nice.org.uk
49 Zylicz Z and van Sorge A (1998) Rectal omeprazole in the treatment of reflux pain in esophageal cancer. *Journal of Pain and Symptom Management*. **15**: 144–145.
50 Desmidts T and Constans T (2009) Subcutaneous infusion of esomeprazole in elderly patients in palliative care: A report of two cases. *Journal of the American Geriatrics Society*. **57**: 1724–1725.
51 Agar M *et al.* (2004) The use of subcutaneous omeprazole in the treatment of dyspepsia in palliative care patients. *Journal of Pain and Symptom Management*. **28**: 529–531.

Updated (minor change) April 2014

LOPERAMIDE BNF 1.4.2

Class: Antimotility drug.

Indications: Acute and chronic diarrhoea, †ileostomy (to improve faecal consistency).[1]

Contra-indications: Colitis (ulcerative, infective, or antibiotic-associated); acute dysentery; conditions where inhibition of peristalsis should be avoided because of a risk of ileus, megacolon or toxic megacolon.

Pharmacology

Loperamide is a potent μ-opioid receptor agonist (μ agonist).[2] Although well absorbed from the GI tract, loperamide is almost completely extracted and metabolized by cytochrome P450 in the liver (particularly CYP3A4) where it is conjugated, and the conjugates excreted in the bile. Because of this extensive first-pass metabolism, little loperamide reaches the systemic circulation.

The antidiarrhoeal action of loperamide results from direct absorption into the gut wall. Like **morphine** and other μ agonists, loperamide increases intestinal transit time by decreasing propulsive activity and increasing non-propulsive activity via its effect on the myenteric plexus in the longitudinal muscle layer.[3,4] Loperamide also increases anal sphincter tone and improves night-time continence in patients with ileo-anal pouches.[5]

Loperamide also modifies the intestinal transport of water and electrolytes by stimulating absorption,[6] and by an anti-secretory action mediated by calmodulin antagonism, a property not shared by other opioids.[7–9]

Paradoxically, loperamide reduces the sodium-dependent uptake of glucose and other nutrients from the small bowel.[10] The development of tolerance to the GI effects of loperamide has been demonstrated in animal studies.[11] However, loperamide has been successfully used in patients with chronic diarrhoea for several years without evidence of tolerance.[12]

Loperamide is a substrate for P-glycoprotein, the efflux membrane transporter in the blood-brain barrier, and, although highly lipophilic,[4] loperamide is actively excluded from the CNS.[13,14] Consequently, unlike **morphine** which has both central and peripheral constipating effects, loperamide generally acts only peripherally[2] (but see Drug interactions and Undesirable effects).

Loperamide has an effect on peripheral μ-opioid receptors activated by inflammation, and has been investigated as a possible *topical analgesic* for painful ulcers of the skin or mouth.[15,16] There are preliminary reports of the successful use of orodispersible tablets (Imodium® Instants) 2mg q3–2h p.r.n. as an adjuvant analgesic for oral pain from mucositis or cancer.[17] (Note: Imodium® *oral solution* contains alcohol and should *not* be used.) However, oral **morphine** solution (without alcohol) may be a better option, particularly long-term.

Unlike other drugs used for diarrhoea, e.g. **diphenoxylate** (in **co-phenotrope**) and **codeine**, loperamide has no analgesic effect in therapeutic and supratherapeutic doses. The lack of CNS effects is one reason why loperamide is a popular first-line choice for the control of diarrhoea, including when secondary to surgery, radiotherapy or chemotherapy.[18,19]

However, **octreotide** (see p.530) is recommended first-line for chemotherapy or radiotherapy-induced diarrhoea when severe (i.e. an increase of ⩾7 stools/24h over baseline, hospital admission and IV fluids required for >24h), and second-line for less severe diarrhoea which does not respond to loperamide 16–24mg/24h.[18–20]

As an antidiarrhoeal, loperamide is about 3 times more potent mg for mg than **diphenoxylate** and 50 times more potent than **codeine**.[21] It is longer acting and, if used regularly, generally needs to be given only b.d. However, its maximum therapeutic impact may not manifest for 16–24h; this has implications for initial dosing.[14] The following regimens are approximately equivalent:

- loperamide 2mg b.d.
- **diphenoxylate** 2.5mg q.d.s. (in **co-phenotrope**)
- **codeine phosphate** 60mg q.d.s.

Loperamide is available in a range of formulations. Orodispersible tablets (Imodium® Instants), which melt on the tongue, are bio-equivalent to the capsules and are preferred by some patients. A combination product with **simeticone** provides more rapid relief of diarrhoea and abdominal discomfort from bloating in acute non-specific diarrhoea than either loperamide or **simeticone** alone.[22,23] One suggested explanation is that the surfactant effect of **simeticone** enhances the

contact of loperamide with the gut mucosa. However, both these formulations are relatively expensive (see Supply).
Bio-availability ~0.3%.
Onset of action about 1h; maximum effect 16–24h.[24]
Time to peak plasma concentration 2.5h (oral solution); 5h (capsules).[25]
Plasma halflife 11h.[25]
Duration of action up to 3 days.[12]

Cautions

In severe diarrhoea, ensure adequate fluid and electrolyte replacement is given with loperamide, e.g. by using oral rehydration salts or, if necessary, IV fluids. Patients with AIDS are at risk of toxic megacolon if loperamide is used in viral or bacterial colitis.

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.[26]

Severe hepatic impairment can increase plasma concentrations of loperamide and the risk of undesirable effects, including depression of consciousness.[27] Depression of consciousness may also occur in children, particularly <2 years, who receive excessive doses[28,29] or after an unintentional overdose.[30] If **naloxone** is considered necessary, repeated doses may be needed because loperamide has a longer duration of action than **naloxone** (see p.455).

Imodium® *oral solution* contains Na^+ 4.85mg/5mL, which should be taken into account for patients on a sodium-controlled diet.

Drug interactions

CYP3A4 inhibitors (e.g. **erythromycin**, **fluconazole**, **quinidine** (not UK), **ritonavir**) can increase plasma concentrations of loperamide (see Chapter 25, Table 8, p.775).[27]

Inhibitors of P-glycoprotein (e.g. **ciclosporin**, **clarithromycin**, **erythromycin**, **itraconazole**, **quinidine** (not UK), **ritonavir**, **verapamil**) could potentially allow more loperamide to cross the blood-brain barrier and cause central opioid effects. Although one study in healthy volunteers of **quinidine** (not UK) with loperamide found a blunted respiratory response to CO_2 (indicating respiratory depression),[14] others have failed to demonstrate significant CNS effects.[31]

However, with typical doses of loperamide, it is unlikely that these interactions are clinically relevant.[31]

Undesirable effects

Common (<10%, >1%): headache, dizziness, nausea, flatulence, constipation.
Uncommon (<1%, >0.1%): drowsiness, dry mouth, dyspepsia, vomiting, abdominal pain or discomfort, rash.
Rare (<0.1%, >0.01%): fatigue, depression of consciousness, unco-ordination, hypertonia, abdominal distension, ileus, faecal impaction, megacolon, urinary retention, angioedema, pruritus, urticaria, bullous skin eruptions.

Dose and use

Ensure that the diarrhoea is not secondary to faecal impaction.

Acute diarrhoea

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

Chemotherapy- or radiotherapy-induced diarrhoea

- if mild–moderate, give 4mg stat and 2mg after each loose bowel action
- if not responding to doses of 24mg/24h, switch to **octreotide** (see p.530)
- if severe, use **octreotide** first-line (see p.530).

Chronic diarrhoea

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

Supply

Loperamide (generic)
Capsules 2mg, 28 days @ 2mg q.d.s. = £4.
Tablets 2mg, 28 days @2mg q.d.s. = £8.

Imodium® (Janssen)
Oral solution (sugar-free) 1mg/5mL, 28 days @ 2mg q.d.s. = £13; *contains alcohol*; also contains Na^+ 4.85mg/5mL.

With **simeticone**
Imodium® Plus (McNeil)
Caplets (capsule-shaped tablets) containing loperamide 2mg, **simeticone** 125mg, 28 days @ 1 q.d.s. = £33 (based on 12-caplet pack); also available OTC: 12 caplets = £7.
Note: the following NHS brands can be bought OTC but are expensive: Imodium® Instant Melts, Imodium® Soft Capsules, Imodium® Plus Comfort tablets.

1 UK Medicines Information (2013) Can high dose loperamide be used to reduce stoma output? *Medicines Q & A*. **185.3**: www.evidence.nhs.uk
2 Shannon H and Lutz E (2002) Comparison of the peripheral and central effects of the opioid agonists loperamide and morphine in the formalin test in rats. *Neuropharmacology*. **42**: 253–261.
3 Van Nueten JM *et al.* (1979) Distribution of loperamide in the intestinal wall. *Biochemical Pharmacology*. **28**: 1433–1434.
4 Ooms L *et al.* (1984) Mechanisms of action of loperamide. *Scandinavian Journal of Gastroenterology*. **19 (Suppl 96)**: 145–155.
5 Hallgren T *et al.* (1994) Loperamide improves anal sphincter function and continence after restorative proctocolectomy. *Digestive Diseases and Sciences*. **39**: 2612–2618.
6 Dashwood MR *et al.* (1990) Autoradiographic demonstration of [3H] loperamide binding to opioid receptors in rat and human small intestine. *Progress in Clinical and Biological Research*. **328**: 165–169.
7 Merritt J *et al.* (1982) Loperamide and calmodulin. *Lancet*. **1**: 283.
8 Zavecz J *et al.* (1982) Relationship between anti-diarrheal activity and binding to calmodulin. *European Journal of Pharmacology*. **78**: 375–377.
9 Daly J and Harper J (2000) Loperamide: novel effects on capacitative calcium influx. *Celluar and Molecular Life Sciences*. **57**: 149–157.
10 Klaren P *et al.* (2000) Effect of loperamide on Na+/D-glucose cotransporter activity in mouse small intestine. *Journal of Pharmacy and Pharmacology*. **52**: 679–686.
11 Tan-No K *et al.* (2003) Development of tolerance to the inhibitory effect of loperamide on gastrointestinal transit in mice. *European Journal of Pharmaceutical Sciences*. **20**: 357–363.
12 Heel R *et al.* (1978) Loperamide: A review of its pharmacological properties and therapeutic efficacy in diarrhoea. *Drugs*. **15**: 33–52.
13 Heykants J *et al.* (1974) Loperamide (R 18553), a novel type of antidiarrheal agent. Part 5: The pharmacokinetics of loperamide in rats and man. *Arzneimittel-Forschung*. **24**: 1649–1653.
14 Sadeque A *et al.* (2000) Increased drug delivery to the brain by P-glycoprotein inhibition. *Clinical Pharmacology and Therapeutics*. **68**: 231–237.
15 Nozaki-Taguchi N *et al.* (2008) Potential utility of peripherally applied loperamide in oral chronic graft-versus-host disease related pain. *Japan Journal of Clinical Oncology*. **38**: 857–860.
16 Nozaki-Taguchi N and Yaksh TL (1999) Characterization of the antihyperalgesic action of a novel peripheral mu-opioid receptor agonist–loperamide. *Anesthesiology*. **90**: 225–234.
17 Regnard C (2011) *Personal communication. St Oswald's Hospice, Newcastle.*
18 Maroun JA *et al.* (2007) Prevention and management of chemotherapy-induced diarrhea in patients with colorectal cancer: a consensus statement by the Canadian Working Group on Chemotherapy-Induced Diarrhea. *Current Oncology*. **14**: 13–20.
19 Benson AB *et al.* (2004) Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea *Journal of Clinical Oncology*. **22**: 2918–2926.
20 Bhattacharya S (2009) Octreotide in chemotherapy induced diarrhoea in colorectal cancer: a review article. *Acta Gastroenterologica Belgica*. **72**: 289–295.
21 Schuermans V *et al.* (1974) Loperamide (R18553), a novel type of antidiarrhoeal agent. Part 6: clinical pharmacology. Placebo-controlled comparison of the constipating activity and safety of loperamide, diphenoxylate and codeine in normal volunteers. *Arzneimittel-Forschung Drug Research*. **24**: 1653–1657.
22 Kaplan MA *et al.* (1999) Loperamide-simethicone vs loperamide alone, simethicone alone, and placebo in the treatment of acute diarrhea with gas-related abdominal discomfort. A randomized controlled trial. *Archives of Family Medicine*. **8**: 243–248.
23 Hanauer SB *et al.* (2007) Randomized, double-blind, placebo-controlled clinical trial of loperamide plus simethicone versus loperamide alone and simethicone alone in the treatment of acute diarrhea with gas-related abdominal discomfort. *Current Medical Research Opinion*. **23**: 1033–1043.

24 Dreverman JWM and van der Poel AJ (1995) Loperamide oxide in acute diarrhoea: a double-blind placebo-controlled trial. *Alimentary Pharmacology and Therapeutics*. **9**: 441–446.
25 Killinger J *et al.* (1979) Human pharmacokinetics and comparative bioavailability of loperamide hydrochloride. *Journal of Clinical Pharmacology*. **19**: 211–218.
26 Eronen M *et al.* (2003) Lethal gastroenteritis associated with clozapine and loperamide. *American Journal of Psychiatry*. **160**: 2242–2243.
27 Baker DE (2007) Loperamide: a pharmacological review. *Reviews in Gastroenterological Disorders*. **7 (Suppl 3)**: S11–18.
28 Friedli G and Haenggeli CA (1980) Loperamide overdose managed by naloxone. *Lancet*. **ii**: 1413.
29 Minton N and Smith P (1987) Loperamide toxicity in a child after a single dose. *British Medical Journal*. **294**: 1383.
30 Litovitz T *et al.* (1997) Surveillance of loperamide ingestions: an analysis of 216 poison center reports. *Journal of Toxicology and Clinical Toxicology*. **35**: 11–19.
31 Vandenbossche J *et al.* (2010) Loperamide and P-glycoprotein inhibition: assessment of the clinical relevance. *Journal of Pharmacy and Pharmacology*. **62**: 401–412.

Updated May 2014

LAXATIVES BNF 1.6

There is limited RCT evidence about laxative use in palliative care patients.[1,2] Consequently, guidelines for the management of constipation in palliative care are based largely on consensus best practice and expert opinion.[2–5]

Constipation is common in advanced cancer,[1,6] and is generally caused by multiple factors, e.g. poor diet, weakness, the underlying disease, drugs (particularly opioids). It can be defined as the passage of small hard faeces infrequently and with difficulty,[5] and is characterized by:

- *slow GI transit:* prolonged transit time allows more absorption of water from the faeces by the GI tract, manifesting as decreased frequency of bowel movements and small hard faeces[7,8]
- *disordered rectal evacuation:* the need to strain when defaecating.[7]

The aims of drug management of constipation are:

- to restore the amount of water in the faeces by:
  - reducing bowel transit time
  - increasing faecal water
  - increasing the ability of the faeces to retain water.
- to improve rectal evacuation by improving faecal consistency and promoting peristalsis.

There are two broad classes of laxatives: those acting predominantly as *faecal softeners* and those acting predominantly as *bowel stimulants* (Table 1).

Faecal softeners also increase faecal mass, and can thereby stimulate peristalsis. Further, **lactulose** (an osmotic laxative) is converted by colonic fermentation to organic acids which act as contact stimulants in the large bowel (see p.52).[9] Conversely, stimulant laxatives reduce water absorption from the faeces and thus have a softening action (see p.48).

Table 1 Classification of commonly used laxatives

Class of laxative	*General mode of action*	*Common laxatives*
Faecal softeners		
Surface-wetting agents	Act as a detergent, lowering surface tension, thereby allowing water and fats to penetrate hard, dry faeces	Docusate sodium Poloxamer 188 (in co-danthramer)
Osmotic laxatives	Water is retained in the gut lumen with a subsequent increase in faecal volume	Lactulose syrup Magnesium hydroxide suspension (Phillips' Milk of Magnesia®); sometimes combined with liquid paraffin (a lubricant), e.g. Mil-Par® Magnesium sulfate (Epsom Salts) Macrogols (e.g. Movicol®)

continued

Table 1 Continued

Class of laxative	*General mode of action*	*Common laxatives*
Stimulant laxatives	Act via direct contact with the submucosal and myenteric plexus, resulting in rhythmic muscle contractions and improved intestinal motility. Also increase water secretion into the bowel lumen	
	Acting on small and large bowel	Bisacodyl Dantron
	Acting on large bowel	Senna Sodium picosulfate
Lubricants	Coat the surface of the stool to make it more slippery and easier to pass	Liquid paraffin[a] Arachis oil
Bulk-forming agents (fibre)	Increases faecal bulk through water-binding and increasing bacterial cell mass. This causes intestinal distension and thereby stimulates peristalsis; only a limited role in palliative care	Ispaghula (psyllium) husk (e.g. Fybogel®, Regulan®) Methylcellulose (e.g. Celevac®) Sterculia (e.g. Normacol®)

a. limited role in palliative care due to potentially serious undesirable effects.

At doses commonly used, **docusate sodium** (⩽400mg/24h) acts mainly by lowering surface tension (enabling water and fats to penetrate into the substance of the faeces) but at higher doses it also acts as a stimulant laxative (see p.51).

To date, RCTs of laxatives in palliative care patients have failed to show clinically meaningful differences (Table 2). Two Cochrane reviews on the management of constipation in palliative care patients have concluded that there is inadequate experimental evidence to guide the optimal treatment of constipation with laxatives.[1,2]

Given the limited RCT evidence, the following should be noted:

- an appreciation of the pathophysiology of constipation (particularly opioid-induced),[5,16] and of how different laxatives work, and their cost will guide laxative choice
- generally, all laxatives given in sufficient quantities are capable of normalizing bowel function in constipated patients[17,18]
- compliance with laxative therapy may be limited in individual patients by palatability, undesirable effects (e.g. colic, flatulence), volume required, and polypharmacy. Patient preference and drug tolerability should be taken into account
- the concurrent prescription of several different laxatives should be avoided
- laxative doses should be titrated every 1–2 days according to response up to the maximum recommended or tolerable dose before changing to an alternative
- different laxatives from the same class may have slightly different effects/modes or action. Thus, of the stimulant laxatives, **senna** and **sodium picosulfate** act mainly in the large bowel, whereas **bisacodyl** and **dantron** act on both large and small bowel
- immobile patients with faecal incontinence are at risk of perineal skin irritation from **dantron**-containing laxatives
- anal seepage with associated irritation can be problematic with **liquid paraffin**. Absorption of **liquid paraffin** can also cause granulomatous reaction formation. Absorption is enhanced by concomitant use of **docusate sodium**
- traditionally a combination of a bowel stimulant with a faecal softener has been recommended in palliative care patients.[5,19] However, the results of the RCT which compared **senna** alone with **senna** and **docusate** in hospice patients (see Table 1)[14] and comparable results from a non-randomized non-blinded sequential cohort study in cancer inpatients[20] suggest that it is reasonable to prescribe a stimulant laxative alone, at least initially[15]

- if an adequate result is not achieved after 3–4 days using a stimulant laxative alone despite dose titration, consider adding a faecal softener
- if colic occurs, a softener should be added
- if faecal leakage occurs, the dose of the faecal softener will need to be reduced.[3,5]

Table 2 RCTs of laxatives in palliative care patients

Interventions	*Sample size*	*Outcome*
Senna and lactulose vs. co-danthramer (dantron and poloxamer)[10]	N = 51	Participants on high-dose strong opioids; those receiving senna and lactulose had more bowel evacuations compared with those receiving co-danthramer, but there was no difference in patient preference
Senna and lactulose vs. magnesium hydroxide and liquid paraffin (unpublished data)[11]	N = 118	No significant difference in efficacy outcomes between interventions
Senna vs. lactulose[12]	N = 75	No significant difference in efficacy outcomes between interventions
Senna vs. misrakasneham (Ayurvedic herbal remedy)[13]	N = 36	No significant difference in efficacy outcomes between interventions
Senna vs. senna and docusate[14]	N = 74	No significant difference between the groups, suggesting no benefit in routinely adding docusate. However, a high proportion of patients in each group required rescue rectal interventions (74% and 69%), suggesting neither treatment was very effective. Although the dose of senna could be titrated to response, the dose of docusate was fixed, and thus may not always have been optimal[15]

Rectal interventions *(also see Rectal products for constipation, p.57)*

About one third of patients also need rectal measures[21,22] either because of failed oral treatment or electively, e.g. in bedbound frail elderly patients, patients with paralysis (see p.46).

Rectal products available for the management of constipation include suppositories and enemas. As far as possible, rectal interventions should be avoided in patients who are neutropenic or thrombocytopenic because of the risk, respectively, of infection or bleeding.

Opioid-induced constipation

Opioids are a major contributory factor for constipation in palliative care patients, reducing quality of life, and sometimes resulting in opioid discontinuation.[23–25] Opioids cause constipation by increasing ring contractions, decreasing propulsive intestinal activity, and by enhancing the resorption of fluid and electrolytes.[26,27] Tolerance does not develop to these effects.[28] Although some strong opioids are possibly less constipating than **morphine** (e.g. **buprenorphine**, **fentanyl**, **methadone**), most patients receiving any opioid regularly will need a laxative concurrently.[1,29] Thus, as a general rule, all patients prescribed **morphine** (or other opioid) should also be prescribed a laxative (see p.44).

Methylnaltrexone, a peripherally-acting opioid antagonist, represents an additional approach to the management of opioid-induced constipation (see p.44 and p.456). A recent Cochrane review concluded that there is some evidence that, compared with placebo, **methylnaltrexone** is effective in patients taking opioids who have not had a good response with conventional laxatives.[2]

1 Miles CL *et al.* (2006) Laxatives for the management of constipation in palliative care patients. *Cochrane Database of Systematic Reviews*. **4**: CD003448.

2 Candy B *et al.* (2011) Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Cochrane Database of Systematic Reviews*. **19**: CD003448.

3 NICE (2013) Palliative cancer care - constipation. Clinical Knowledge Summaries http://cks.nice.org.uk
4 Librach SL *et al.* (2010) Consensus recommendations for the management of constipation in patients with advanced, progressive illness. *Journal of Pain and Symptom Management.* **40**: 761–773.
5 Larkin PJ *et al.* (2008) The management of constipation in palliative care: clinical practice recommendations. *Palliative Medicine.* **22**: 796–807.
6 Droney J *et al.* (2008) Constipation in cancer patients on morphine. *Supportive Care in Cancer.* **16**: 453–459.
7 Soligo M *et al.* (2006) Patterns of constipation in urogynecology: clinical importance and pathophysiologic insights. *American Journal of Obstetrics and Gynecology.* **195**: 50–55.
8 Lewis SJ and Heaton KW (1997) Stool form scale as a useful guide to intestinal transit time. *Scandinavian Journal of Gastroenterology.* **32**: 920–924.
9 Jouet P *et al.* (2008) Effects of therapeutic doses of lactulose vs. polyethylene glycol on isotopic colonic transit. *Alimentary Pharmacology and Therapeutics.* **27**: 988–993.
10 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.
11 Tarumi Y *et al.* (2013) Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. *Journal of Pain and Symptom Management.* **45**: 2–13.
12 Sykes N (1991) A clinical comparison of lactulose and senna with magnesium hydroxide and liquid paraffin emulsion in a palliative care population. [cited in Candy B et al. (2011) Laxatives or methylprednisolone for the management of constipation in palliative care patients. *Cochrane Database of Systematic Reviews*. CD003448.]
13 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.
14 Sykes N (2013) Emerging evidence on docusate: commentary on Tarumi et al. *Journal of Pain and Symptom Management.* **45**: 1.
15 Clemens KE and Klaschik E (2008) Management of constipation in palliative care patients. *Current Opinion in Supportive and Palliative Care.* **2**: 22–27.
16 Fallon M and Hanks G (1999) Morphine, constipation and performace status in advanced cancer patients. *Palliative Medicine.* **13**: 159–160.
17 Sykes NP (1996) A volunteer model for the comparison of laxatives in opioid-related constipation. *Journal of Pain and Symptom Management.* **11**: 363–369.
18 Portenoy RK (1987) Constipation in the cancer patient: causes and management. *Medical Clinics of North America*. **71**: 303–311.
19 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.
20 Sykes N (1991) A clinical comparison of laxatives in a hospice. *Palliative Medicine.* **5**: 307–314.
21 Twycross RG and Lack SA (1986) *Control of Alimentary Symptoms in Far Advanced Cancer.* Churchill Livingstone, Edinburgh, pp. 173–174.
22 Twycross RG and Harcourt JMV (1991) The use of laxatives at a palliative care centre. *Palliative Medicine.* **5**: 27–33.
23 Sykes N (1998) The relationship between opioid use and laxative use in terminally ill cancer patients. *Palliative Medicine.* **12**: 375–382.
24 Bell T *et al.* (2009) Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. *Journal of Opioid Management.* **5**: 137–144.
25 Candrilli SD *et al.* (2009) Impact of constipation on opioid use patterns, health care resource utilization, and costs in cancer patients on opioid therapy. *Journal of Pain and Palliative Care Pharmacotherapy.* **23**: 231–241.
26 Beubler E (1983) Opiates and intestinal transport: in vivo studies. In: LA Turnberg (ed) *Intestinal secretion.* Smith Kline and French, Hertfordshire, pp. 53–55.
27 Kurz A and Sessler DI (2003) Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs.* **63**: 649–671.
28 Ross GR *et al.* (2008) Morphine tolerance in the mouse ileum and colon. *Journal of Pharmacology and Experimental Therapeutics.* **327**: 561–572.
29 Radbruch L *et al.* (2000) Constipation and the use of laxatives: a comparison between transdermal fentanyl and oral morphine. *Palliative Medicine.* **14**: 111–119.

Updated June 2014

Quick Prescribing Guide: Opioid-induced constipation

Generally, all patients prescribed an opioid should also be prescribed a stimulant laxative, with the aim of achieving a regular bowel movement, without straining, every 1–3 days. A standardized protocol aids management.

Sometimes, rather than automatically changing to the local standard laxative, it may be more appropriate to optimize a patient's existing regimen.

These guidelines can also be followed in patients who are not on opioids, although smaller doses may well suffice.

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

2 Palpate for faecal 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 diarrhoea suggestive of faecal impaction with overflow.

3 For inpatients, keep a daily record of bowel actions.

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

5 When an opioid is prescribed, prescribe senna (see below) or dantron-containing stimulant laxative (see overleaf), and titrate the dose according to response.

6 During dose titration and subsequently, if ⩾3 days since last bowel action, give suppositories, e.g. bisacodyl 10mg and glycerol 4g, or a micro-enema. If these are ineffective, administer a phosphate enema and possibly repeat the next day.

7 If the maximum dose of the stimulant laxative is ineffective, halve the dose and add an osmotic laxative, then titrate as necessary, e.g.
- macrogols (e.g. Movicol®) 1 sachet each morning *or*
- lactulose 15mL once daily–b.d.

8 In a patient receiving opioids, if adequately titrated conventional laxatives fail to produce the desired response, consider SC methylnaltrexone (see below).

9 If the stimulant laxative causes bowel colic, divide the total daily dose into smaller more frequent doses or change to a faecal softener (see above), and titrate as necessary.

10 As initial treatment, a faecal softener is preferable in patients with a history of colic with stimulant laxatives.

Dose schedule for senna
• if *not* constipated: ▹ generally start with 15mg at bedtime ▹ if no response after 24–48h, increase to 15mg at bedtime and each morning • if already constipated ▹ generally start with 15mg at bedtime and each morning ▹ if no response after 24–48h, increase to 22.5mg at bedtime and each morning • if no response after a further 24–48h, consider adding a third daytime dose • if necessary, consider increasing to a maximum of 30mg t.d.s.

Dose schedule for dantron-containing laxatives[a,b]

	Co-danthramer strong capsules	*Co-danthramer strong suspension*	*Co-danthrusate capsules*	*Co-danthrusate suspension*
Dantron content	37.5mg/capsule	75mg/5mL	50mg/capsule	50mg/5mL
Start with:				
• prophylactic	1 at bedtime	2.5mL at bedtime	1 at bedtime	5mL at bedtime
• if constipated	2 at bedtime	5mL at bedtime	2 at bedtime	10mL at bedtime
If necessary, adjust every 2–3 days up to:				
	3 t.d.s.	10mL b.d. *or* 20mL at bedtime	3 b.d.	15mL b.d.
Total daily dose	337.5mg	300mg	300mg	300mg

a. because dantron has been linked with liver and bowel tumours in rodents, dantron-containing laxatives are licensed for use only in the 'terminally ill'

b. in patients with urinary or faecal incontinence, dantron-containing laxatives are best avoided because of the risk of a contact skin burn in the perineum and surrounding areas.

Methylnaltrexone

Methylnaltrexone is relatively expensive (£21 per 12mg vial) and should be considered only when the optimum use of laxatives is ineffective. Because constipation in advanced disease is generally multifactorial in origin, methylnaltrexone 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
- about 1/3–1/2 of patients given methylnaltrexone have a bowel movement within 4h, 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 150microgram/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/min) reduce the dose:
  - for patients weighing 62–114kg, reduce to 8mg
  - 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 bowel obstruction. It should be used with caution in patients with conditions which may predispose to perforation. Common undesirable effects include abdominal pain/colic, diarrhoea, flatulence, and nausea; these generally resolve after a bowel movement; postural hypotension can also occur.

Updated June 2014

Quick Prescribing Guide: 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 faeces:
- every day in long-term paraplegia/tetraplegia, e.g. post-traumatic
- every 1–3 days in advanced cancer.

2 Secondary: to prevent both incontinence (faeces too soft, over-treatment with laxatives) and an anal fissure (faeces 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 stimulant laxative should be prescribed, e.g. senna 15mg b.d., bisacodyl tablets 5–10mg b.d. The dose should be carefully titrated to a level which results in normal faeces *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. ispaghula.

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

Rectal measures

7 Initially, if impacted with faeces, empty the rectum digitally. Then, develop a daily routine:
- as soon as convenient after waking up in the morning, insert 2 glycerol suppositories, or 1–2 bisacodyl suppositories (10–20mg), or an osmotic 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 faeces
- the patient should be encouraged to have a hot drink after about 1h in the hope that it will stimulate a gastro-colonic reflex
- if there is a strong sacral reflex, some faeces will be expelled as a result of the above two measures
- to ensure complete evacuation of the rectum and sigmoid colon, digitally stimulate the rectum:
- insert gloved and lubricated finger (either soap or gel)
  - ▹ rotate finger 3–4 times
  - ▹ withdraw and wait 5min
  - ▹ if necessary, repeat 3–4 times
  - ▹ check digitally that rectum is fully empty.

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 defaecate 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.

Updated June 2014

ISPAGHULA (PSYLLIUM) HUSK BNF 1.6.1

Ispaghula husk is *not recommended* for patients taking constipating drugs, and in those with decreasing dietary intake and activity. However, it can be helpful in regulating the consistency of faeces (making them more formed) in a patient with a colostomy/distal ileostomy.

Class: Bulk-forming laxative.

Indications: Colostomy/ileostomy regulation, anal fissure, haemorrhoids, diverticular disease, irritable bowel syndrome, ulcerative colitis.

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

Pharmacology

Ispaghula (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 faecal bulk. Like other bulk-forming laxatives, ispaghula stimulates peristalsis by increasing faecal mass. Its water-binding capacity also helps to make loose faeces 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

Flatulence, abdominal distension, faecal impaction, bowel obstruction.

Dose and use

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

Supply

Fybogel® (Reckitt Benckiser)

Oral powder 3.5g/sachet, 28 days @ 1 sachet b.d. = £4; *low Na^+; sugar- and gluten-free; plain, lemon or orange flavour.*

Regulan® (Procter & Gamble)
Oral powder 3.4g/sachet, 28 days @ 1 sachet b.d. = £4.50; *sugar- and gluten-free; orange or lemon-lime flavour.*

This is not a complete list; see BNF for more information.

Updated June 2014

STIMULANT LAXATIVES BNF 1.6.2

Indications: Prevention and treatment of constipation.

Contra-indications: Severe dehydration, acute inflammatory bowel disease, large bowel obstruction.

Pharmacology

Stimulant laxatives vary in terms of onset times, sites of action, and undesirable effects, depending on where in the GI tract the parent drug is converted to its active metabolite. Stimulant laxatives act 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.

Senna (sennosides) is a naturally-occurring plant-derived anthranoid. It is an inactive glycoside which passes unabsorbed and unchanged through the small intestine and is hydrolyzed by *bacterial glycosidases* in the large intestine to yield active compounds.[1] Thus, **senna** has no effect on the small intestine but becomes active in the large intestine. Differences in bacterial flora may be partly responsible for differences in individual responses.

Dantron, a synthetic anthranoid, is not a glycoside and has a direct action on the small intestine as well as the large intestine.[2] Whereas systemic absorption of **senna** or its metabolites is small, **dantron** is absorbed to some extent from the small intestine with subsequent significant urinary excretion.

Phenolics such as **bisacodyl** and **sodium picosulfate** are also pro-drugs. They are hydrolyzed to the same active metabolite but the mode of hydrolysis differs.[1] **Bisacodyl** 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.[3] **Bisacodyl** is often given by suppository. The laxative effect is the result of local direct contact with the rectal mucosa after dissolution of the suppository, and after activation by hydrolysis. Thus the minimum time for response is generally >20min.[4] In contrast, **sodium picosulfate** is hydrolyzed by *colonic bacteria* and its action is thus confined to the large intestine. Its activity is potentially more uncertain because it depends on bacterial flora.

Phenolphthalein is another stimulant laxative, and is present in some proprietary laxatives. **Phenolphthalein** exists in two forms: white and yellow. The yellow form contains several impurities produced during manufacture. These impurities enhance the laxative effect of **phenolphthalein** so that the comparable dose of the yellow form is only two thirds that of the pure white form. The active constituent of **phenolphthalein** is released in two stages: by metabolism in the liver and subsequently in the colon, and it probably undergoes enterohepatic circulation.[5] Some people respond to small doses. However, it can cause a drug rash (see Undesirable effects) and is generally not considered a first-line laxative.

To date, RCTs of stimulant laxatives in palliative care patients have failed to show clinically meaningful differences (see Laxatives, Table 2, p.42). A small non-blinded dose-ranging study in palliative care patients with opioid-induced constipation, showed that **sodium picosulfate** alone yielded a satisfactory result in 15/20 patients (normal stool consistency, no need for enemas, suppositories or manual evacuation, and no noteworthy undesirable effects).[12]

Traditionally a combination of a bowel stimulant with a stool softener has been recommended in palliative care patients.[13,14] However, the results of the RCT which compared **senna** alone with

senna and **docusate** in hospice patients (see Laxatives, Table 2, p.42)[10] and comparable results from a non-randomized non-blinded sequential cohort study in cancer inpatients suggest that it is reasonable to prescribe a stimulant laxative alone, at least initially.[11] In countries where combined products are not available, this also reduces the patient's tablet load.[15]

If a stimulant laxative is used alone but an adequate result is not achieved despite dose titration within a week, consider adding a faecal softener. If faecal leakage occurs, the dose of the faecal softener will need to be reduced.[13,16]

Onset of action

Bisacodyl tablets 6–12h;[4] suppositories 20–60min.
Dantron 6–12h.
Senna 8–12h.
Sodium picosulfate 6–24h (median 12h).[12]

Cautions

Because very high doses in rodents revealed a carcinogenic risk,[17–19] UK marketing authorizations for laxatives containing **dantron** are limited to constipation in terminally ill patients.

Undesirable effects

Intestinal colic, diarrhoea. **Bisacodyl** suppositories may cause local rectal inflammation. **Dantron** discolours urine, typically red but sometimes green or bluish. It may also stain the peri-anal skin. Prolonged contact with skin (e.g. in urinary or faecally incontinent patients) may cause a **dantron** burn (a red erythematous rash with a definite edge); if ignored, this may cause painful excoriation.

Phenolphthalein occasionally causes a drug rash or photosensitivity. Rarely, it causes encephalitis which can be fatal.

Dose and use

The doses recommended here for opioid-induced constipation are often higher than those featured in the BNF and SPCs. For frail patients not receiving opioids or other constipating drugs, the PO starting doses of a stimulant laxative will generally be lower.

Because round-the-clock opioids constipate, b.d. or t.d.s. laxatives may well be necessary, rather than the traditional once daily dose (at bedtime or each morning). Requirements do not correlate closely with the opioid dose; individual titration is necessary.

All palliative care services should have a protocol for the management of opioid-induced constipation (see Quick Prescribing Guide, p.44).[20–23] Likewise, there is need for a protocol for patients with paraplegia and tetraplegia (see Quick Prescribing Guide, p.46).

Bisacodyl

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

Dantron

Variable, according to preparation, individual need and patient acceptance (see Quick Prescribing Guide, p.44).

Senna

- if *not* constipated:
  - generally start with 15mg at bedtime
  - if no response after 24–48h, increase to 15mg at bedtime and each morning
- if already constipated:
  - generally start with 15mg at bedtime and each morning
  - if no response after 24–48h, increase to 22.5mg at bedtime and each morning
- if no response after a further 24–48h, consider adding a third daytime dose
- if necessary, consider increasing to a maximum of 30mg t.d.s.

Sodium picosulfate

- start with 5–10mg (5–10mL of oral solution) at bedtime; 10mg if taking regular opioids
- if necessary, increase daily by 5mg until a satisfactory result is achieved
- median satisfactory dose = 15mg at bedtime
- typical maximum dose = 30mg.[12]

Consider a lower dose b.d. in the frail elderly.

Supply

Bisacodyl (generic)
***Tablets* e/c** 5mg, 28 days @ 10mg at bedtime = £2.
Suppositories 10mg, 28 days @ 10mg once daily = £8.

Dantron
Co-danthramer (**dantron** and **poloxamer 188**) (generic)

Co-danthramer suspension 5mL = 1 **co-danthramer** capsule.
Co-danthramer suspension 15mL = 5mL *strong* **co-danthramer** suspension.
Strong **co-danthramer** suspension 5mL = 2 *strong* **co-danthramer** capsules.

***Capsules* co-danthramer** 25/200 (**dantron** 25mg, **poloxamer 188** 200mg), 28 days @ 2 at bedtime = £12.
***Strong capsules* co-danthramer** 37.5/500 (**dantron** 37.5mg, **poloxamer 188** 500mg), 28 days @ 2 at bedtime = £15.
***Oral suspension* co-danthramer** 25/200 in 5mL (**dantron** 25mg, **poloxamer 188** 200mg/5mL), 28 days @ 10mL at bedtime = £96.
***Strong oral suspension* co-danthramer** 75/1000 in 5mL (**dantron** 75mg, **poloxamer 188** 1g/5mL), 28 days @ 5mL at bedtime = £117.

Co-danthrusate (**dantron** and **docusate sodium**) (generic)
***Capsules* co-danthrusate** 50/60 (**dantron** 50mg, **docusate sodium** 60mg), 28 days @ 2 at bedtime = £29.
***Oral suspension* co-danthrusate** 50/60 in 5mL (**dantron** 50mg, **docusate sodium** 60mg/5mL), 28 days @ 10mL at bedtime = £126.

Senna (generic)
Tablets total **sennosides**/tablet 7.5mg, 28 days @ 15mg at bedtime = £10.

Senokot® (Reckitt Benckiser)
Tablets total **sennosides**/tablet 7.5mg (~~NHS~~).
Oral solution (sugar-free) total **sennosides** 7.5mg/5mL, 28 days @ 10mL at bedtime = £1.50.

Sodium picosulfate (generic)
Oral solution (elixir) 5mg/5mL, 28 days @ 10mL at bedtime = £5; *contains alcohol.*

Note: **sodium picosulfate** oral solution 5mg/5mL is available as Dulcolax® Pico liquid. The proprietary name Dulcolax® (~~NHS~~) is also used for **bisacodyl** tablets and suppositories.

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 Lennard-Jones J (1994) Clinical aspects of laxatives, enemas and suppositories. In: M Kamm and J Lennard-Jones (eds) *Constipation*. Wrightson Biomedical Publishing, Petersfield, pp. 327–341.
3 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.
4 Flig E *et al.* (2000) Is bisacodyl absorbed at all from suppositories in man? *International Journal of Pharmaceutics*. **196**: 11–20.
5 Godding EW (1975) Constipation and allied disorders: 3. Therapeutic agents-chemical laxatives (section 2). *Pharmaceutical Journal*. **215**: 60–62.
6 Sykes N (1991) A clinical comparison of laxatives in a hospice. *Palliative Medicine*. **5**: 307–314.
7 Sykes N (1991) A clinical comparison of lactulose and senna with magnesium hydroxide and liquid paraffin emulsion in a palliative care population. [cited in Candy B et al. (2011) Laxatives or methylprednisolone for the management of constipation in palliative care patients. *Cochrane Database of Systematic Reviews*. CD003448.]
8 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.

9 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.
10 Tarumi Y *et al.* (2013) Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. *Journal of Pain and Symptom Management*. **45**: 2–13.
11 Sykes N (2013) Emerging evidence on docusate: commentary on Tarumi et al. *Journal of Pain and Symptom Management*. **45**: 1.
12 Twycross RG *et al.* (2006) Sodium picosulfate in opioid-induced constipation: results of an open-label, prospective, dose-ranging study. *Palliative Medicine*. **20**: 419–423.
13 Larkin PJ *et al.* (2008) The management of constipation in palliative care: clinical practice recommendations. *Palliative Medicine*. **22**: 796–807.
14 Portenoy RK (1987) Constipation in the cancer patient: causes and management. *Medical Clinics of North America*. **71**: 303–311.
15 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.
16 NICE (2013) Palliative cancer care - constipation. Clinical Knowledge Summaries. http://cks.nice.org.uk
17 Mori H *et al.* (1985) Induction of intestinal tumours in rats by chrysazin. *British Journal of Cancer.* **52**: 781–783.
18 Mori H *et al.* (1986) Carcinogenicity of chrysazin in large intestine and liver of mice. *Japanese Journal of Cancer Research (Gann)*. **77**: 871–876.
19 CSM (Committee on Safety of Medicines and Medicines Control Agency) (2000) Danthron restricted to constipation in the terminally ill. *Current Problems in Pharmacovigilance*. **26 (May)**: 4.
20 Levy MH (1996) Pharmacologic treatment of cancer pain. *New England Journal of Medicine*. **335**: 1124–1132.
21 Pappagallo M (2001) Incidence, prevalence, and management of opioid bowel dysfunction. *American Journal of Surgery*. **182 (Suppl 5A)**: 11s–18s.
22 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.
23 Herndon CM *et al.* (2002) Management of opioid-induced gastrointestinal effects in patients receiving palliative care. *Pharmacotherapy*. **22**: 240–250.

Updated June 2014

DOCUSATE SODIUM — BNF 1.6.2

Class: Surface-wetting agent (faecal softener).

Indications: Constipation, haemorrhoids, anal fissure, bowel preparation before abdominal radiography, †partial bowel obstruction.

Pharmacology

Although sometimes classified as a stimulant laxative, docusate sodium is principally an emulsifying and wetting agent and has a relatively weak effect on GI transit. Other wetting agents include **poloxamer 188** (in **co-danthramer**). Docusate lowers surface tension, thereby allowing water and fats to penetrate hard, dry faeces. 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 defaecation 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 faecal weight.[7]

In palliative care, docusate is generally *not* recommended as the sole laxative except in patients with partial bowel obstruction. The routine combination of docusate (or alternative surface-wetting agent) and a stimulant laxative has been criticized because of a lack of published data supporting such a regimen.[8] A non-randomized non-blinded sequential cohort study in cancer inpatients failed to show any benefit when docusate was added to **senna**.[9] A more recent 10-day blinded RCT in hospice patients of docusate and **senna** vs **senna** alone likewise showed no significant difference.[10] However, a high proportion of patients in each group required rescue rectal interventions (around 70%), suggesting neither treatment was fully effective. The dose of **senna** could be titrated to response but the dose of docusate was fixed (200mg b.d.), and this may not have been optimal for some patients.[11] On the other hand, it is a high dose in terms of typical UK practice with stimulant-softener laxative combination regimens (e.g. **co-danthrusate**) for opioid-induced constipation.

Onset of action 1–2 days.

Cautions

Docusate enhances the absorption of **liquid paraffin**;[12] combined preparations of these substances are prohibited in some countries.

Undesirable effects
Diarrhoea, nausea, abdominal cramp, rashes. Docusate oral solution may cause a bitter aftertaste or burning sensation, minimized by drinking plenty of water after taking the solution.

Dose and use
At many centres, docusate is used in combination with a stimulant laxative, e.g. **senna**, **bisacodyl** or **dantron** (in **co-danthrusate**) (see Quick Prescribing Guide, p.44). Docusate is often used alone for patients with persistent partial bowel obstruction. Dose varies according to individual need:
- generally start with 100mg b.d.
- if necessary, increase to 200mg b.d.–t.d.s.; *the latter is higher than the BNF maximum dose of 500mg/day.*

Docusate can also be used as an enema (see Rectal products for constipation, p.57).

Supply
Dioctyl® (UCB Pharma)
Capsules 100mg, 28 days @ 100mg b.d. = £4 (based on 100-capsule pack).

Docusol® (Typharm)
Oral solution (sugar-free) 50mg/5mL, 28 days @ 10mL b.d. = £10.

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 Hurdon V *et al.* (2000) How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. *Journal of Pain and Symptom Management.* **19**: 130–136.
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 Tarumi Y *et al.* (2013) Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. *Journal of Pain and Symptom Management.* **45**: 2–13.
11 Sykes N (2013) Emerging evidence on docusate: commentary on Tarumi et al. *Journal of Pain and Symptom Management.* **45**: 1.
12 Godfrey H (1971) Dangers of dioctyl sodium sulfosuccinate in mixtures. *Journal of the American Medical Association.* **215**: 643.

Updated June 2014

LACTULOSE BNF 1.6.4

Class: Osmotic laxative.

Indications: Constipation, hepatic encephalopathy.

Contra-indications: Intestinal obstruction, galactosaemia.

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 by colonic bacteria to organic acids which act as contact stimulants in the large bowel.

The low pH discourages the proliferation of ammonia-producing organisms and thus reduces the absorption of ammonium ions and other nitrogenous compounds; hence its use in hepatic encephalopathy.[2]

Lactulose has been shown to be more effective than increasing dietary fibre.[3] It also increases colonic bacterial flora, i.e. is prebiotic (whereas **macrogols** are not).[4] Lactulose does not affect the management of diabetes mellitus; 15mL of Duphalac® (~~NHS~~) contains 14 calories. However, because bio-availability is negligible, the number of calories absorbed is negligible. (Note: other generic products may differ.)

In a small RCT in palliative care patients receiving high-dose strong opioids, those given a combination of lactulose and **senna** had more bowel evacuations compared with those given **co-danthramer**, but there was no difference in patient preference.[5] In healthy volunteers, lactulose alone was effective in opioid-induced constipation, but the volumes required (mean 55mL b.d.) is likely to preclude widespread use.[6]

A Cochrane review of lactulose and **macrogols** for chronic constipation concluded that **macrogols** are better than lactulose in terms of bowel movements per week, faecal consistency, relief of abdominal pain, and the need for additional products.[7] This review included 10 trials, with a total of nearly 900 patients, aged 3 months to 70 years. However, the volume per dose of **macrogols** is 5–10 times greater than lactulose (see p.54), which will be unacceptable to many patients. Lactulose is also cheaper.

Bio-availability negligible.
Onset of action up to 48h.

Cautions

Lactose intolerance.

Undesirable effects

Abdominal bloating, flatulence (generally only in the first few days of treatment), nausea (may be reduced if diluted with water or fruit juice, or taken with meals), intestinal colic.

Dose and use

Lactulose can be used in patients who experience intestinal colic with stimulant laxatives, or who fail to respond to stimulant laxatives alone:

- start with 15mL b.d. and adjust according to need
- in hepatic encephalopathy, start with 30–50mL t.d.s. and adjust the dose to produce 2–3 soft evacuations per day.

Supply

Lactulose (generic)
Oral solution 10g/15mL, 28 days @ 15mL b.d. = £5.

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 Quah HM *et al.* (2006) Prospective randomized crossover trial comparing fibre with lactulose in the treatment of idiopathic chronic constipation. *Techniques in Coloproctology*. **10**: 111–114.
4 Bouhnik Y *et al.* (2004) Prospective, randomized, parallel-group trial to evaluate the effects of lactulose and polyethylene glycol-4000 on colonic flora in chronic idiopathic constipation. *Alimentary Pharmacology and Therapeutics*. **19**: 889–899.
5 Sykes N (1991) A clinical comparison of laxatives in a hospice. *Palliative Medicine*. **5**: 307–314.
6 Sykes NP (1996) A volunteer model for the comparison of laxatives in opioid-related constipation. *Journal of Pain and Symptom Management*. **11**: 363–369.
7 Lee-Robichaud H *et al.* (2011) Lactulose versus polyethylene glycol for chronic constipation. *Cochrane Database of Systematic Reviews*. **7**: CD007570.

Updated June 2014

MACROGOLS (POLYETHYLENE GLYCOLS) BNF 1.6.4

Class: Osmotic laxative.

Indications: Constipation, faecal impaction (macrogol 3350 sachets).

Contra-Indications: Severe inflammatory bowel conditions, bowel obstruction, paralytic ileus.

Pharmacology

Macrogol 3350 and 4000 are available in the UK (the numbers refer to their respective molecular weights). They act by virtue of an osmotic action in the intestines. Due to the large molecular structure of the macrogol, water is not transported across the bowel wall out of the lumen and hence the volume of the macrogol solution is retained within the lumen to soften the stool directly and stimulate peristalsis indirectly (by producing an increase in faecal volume).

Macrogols are unchanged in the GI tract, virtually unabsorbed and have no known pharmacological activity. Any absorbed macrogols are excreted via the urine; no reduction is required in renal impairment. Macrogols reduce colonic bacterial flora, whereas the use of **lactulose** causes an increase.[1]

Most studies have used isotonic solutions. Adding more water to make a hypotonic (dilute) solution of macrogols is as effective as an isotonic solution in treating constipation but causes hyponatraemia.[2] There are no data on the effect on appetite of the volume of fluid needed with macrogols.

There are no studies in chronic constipation comparing macrogols with stimulant laxatives. However, when clearing the colon before colonoscopy, macrogols are inferior to stimulant laxatives.[3,4]

In an RCT in opioid-induced constipation, macrogols were found to be no better than **lactulose**.[5] On the other hand, a Cochrane review of macrogols and **lactulose** for chronic constipation in adults and in children concluded that macrogols are better than **lactulose** in terms of bowel movements per week, faecal consistency, relief of abdominal pain (children only), and the need for additional products.[6] An earlier systematic review also favoured macrogols.[7] However, the volume per dose of macrogols is 5–10 times greater than **lactulose** (see p.52); this will be unacceptable to many seriously ill patients.

In a second systematic review limited to chronic constipation in children, macrogols were found to be little better than other treatments.[8] Further, in childhood faecal impaction, they are no better than enemas, and cause more faecal incontinence.[9] Children also find macrogols less palatable than **lactulose**.[10] Macrogols are also more expensive.

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

Cautions

Macrogol 3350: stop treatment if symptoms of fluid and electrolyte shift occur (see Undesirable effects).

Macrogol 3350 *concentrated oral liquid* contains both benzyl alcohol and ethanol. Because the dose required for faecal impaction would exceed the maximum acceptable daily intake of benzyl alcohol, this formulation is not authorized for faecal impaction, and the manufacturer's maximum recommended dose for constipation is 25mL (diluted with 100mL of water) t.d.s.

Undesirable effects

Uncommon (<1%, >0.1%): abdominal bloating, discomfort, borborygmi, hyponatraemia (when used as a hypotonic solution), nausea.

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

Frequency unknown: hyper- or hypokalaemia (macrogol 3350 with electrolytes).

Dose and use

Macrogols are generally supplied as powder in sachets. A concentrated oral liquid is also available, but is not authorized for faecal impaction (see Cautions). All formulations need to be dissolved or diluted in water. For adults:

- macrogol 3350 (with electrolytes), dissolve one sachet in half a glass of water (about 125mL) or dilute 25mL of the concentrated oral liquid with 100mL water (total volume 125mL)
- macrogol 4000 (without electrolytes), dissolve in a glass of water (about 250mL). Half-strength macrogol 3350 sachets (with electrolytes) are available for fine-tuning the dose. Paediatric sachets are also available for children aged ⩽12 years (see *BNF for Children*).

Constipation

The solution is generally used immediately after reconstitution or dilution. However, reconstituted macrogol 3350 sachets can be kept (covered) for up to 6h in a refrigerator, and the diluted oral liquid concentrate can be kept (covered) for 24h at room temperature:

- start with 1 sachet or 125mL of *diluted* oral liquid concentrate daily
- if necessary, increase to:
  - 1 sachet or 125mL of *diluted* oral liquid concentrate b.d.–t.d.s. (macrogol 3350)
  - 2 sachets each morning. or 1 sachet b.d. (macrogol 4000).

Faecal impaction

Macrogol 3350:

- start with 8 sachets on day 1, each dissolved in 125mL of water, and taken in $<$6h (total 1L)
- *patients with cardiovascular impairment should restrict intake to 2 sachets/h, i.e. 250mL/h*
- if necessary, repeat on days 2 and 3; most patients do not need the full dose on the second day.

For convenience, all 8 sachets can be made up together in 1L of water and kept in a refrigerator for a maximum of 6h, after which any remaining solution should be discarded.

Supply

Macrogol 3350 (generic)

Oral powder macrogol 3350 13.125g, sodium bicarbonate 178.5mg, sodium chloride 350.7mg, potassium chloride 46.6mg/sachet, 28 days @ 1 sachet once daily = £6; *orange flavour (Laxido®) or lemon flavour (Molaxole®).*

Movicol® (Norgine)

Oral powder macrogol 3350 13.125g, sodium bicarbonate 178.5mg, sodium chloride 350.7mg, potassium chloride 46.6mg/sachet, 28 days @ 1 sachet once daily = £6; *lime-lemon flavour. Also available in plain (sugar-free) and chocolate flavour.*

Concentrated oral liquid macrogol 3350 13.125g, sodium bicarbonate 178.5mg, sodium chloride 350.7mg, potassium chloride 46.6mg/25mL, 28 days @ 25mL (diluted with 100mL water) once daily = £6; *orange flavour, contains alcohol.*

Movicol-Half® (Norgine)

Oral powder (sugar-free) macrogol 3350 6.563g, sodium bicarbonate 89.3mg, sodium chloride 175.4mg, potassium chloride 23.3mg/sachet, 28 days @ 1 sachet once daily = £4; *lime-lemon flavour.*

Macrogol 4000 Dulcobalance® (Boehringer Ingelheim)

Oral powder (sugar-free) macrogol 4000 10g/sachet, 28 days @ 1 sachet once daily = £8; *orange-grapefruit flavour. Available OTC.*

1 Bouhnik Y *et al.* (2004) Prospective, randomized, parallel-group trial to evaluate the effects of lactulose and polyethylene glycol-4000 on colonic flora in chronic idiopathic constipation. *Alimentary Pharmacology and Therapeutics.* **19**: 889–899.

2 Seinela L *et al.* (2009) Comparison of polyethylene glycol with and without electrolytes in the treatment of constipation in elderly institutionalized patients: a randomized, double-blind, parallel-group study. *Drugs and Aging*. **26**: 703–713.

3 Radaelli F *et al.* (2005) High-dose senna compared with conventional PEG-ES lavage as bowel preparation for elective colonoscopy: a prospective, randomized, investigator-blinded trial. *American Journal of Gastroenterology.* **100**: 2674–2680.

4 Valverde A *et al.* (1999) Senna vs polyethylene glycol for mechanical preparation the evening before elective colonic or rectal resection: a multicenter controlled trial. French Association for Surgical Research. *Archives of Surgery.* **134**: 514–519.

5 Freedman MD *et al.* (1997) Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: a double-blinded placebo-controlled trial. *Journal of Clinical Pharmacology.* **37**: 904–907.

6 Lee-Robichaud H *et al.* (2010) Lactulose versus polyethylene glycol for chronic constipation. *Cochrane Database of Systematic Reviews.* **7**: CD007570.

7 Ramkumar D and Rao SS (2005) Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. *American Journal of Gastroenterology.* **100**: 936–971.
8 Pijpers MA *et al.* (2009) Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. *Archives of Disease in Childhood.* **94**: 117–131.
9 Bekkali NL *et al.* (2009) Rectal fecal impaction treatment in childhood constipation: enemas versus high doses oral PEG. *Pediatrics.* **124**: e1108–1115.
10 Voskuijl W *et al.* (2004) PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. *Gut.* **53**: 1590–1594.

Updated June 2014

MAGNESIUM SALTS BNF 1.6.4

Class: Osmotic laxative.

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

Contra-indications: Severe renal impairment.

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.

Magnesium salts are generally not used first line in palliative care patients as they may be unpredictably effective. Magnesium sulfate is more potent than magnesium hydroxide and tends to produce a large volume of liquid faeces. In patients with idiopathic constipation, magnesium salts often lead to a sense of distension and the sudden passage of offensive liquid faeces which is socially inconvenient; it is difficult to adjust the dose to produce a normal soft result. However, when used as an osmotic laxative in conjunction with a stimulant laxative in opioid-induced constipation, this is not generally a problem.

An RCT of magnesium hydroxide and **liquid paraffin** vs. **senna** and **lactulose** failed to differentiate between the two combination treatments.[3]

Cautions

Risk of hypermagnesaemia in patients with renal impairment.

Drug interactions

Oral magnesium salts act as antacids and the resulting increase in gastric pH may affect the absorption of several drugs if taken concurrently (see p.2).

Dose and use

Magnesium hydroxide mixture BP

For opioid-induced constipation (see Quick Prescribing Guide, p.44), as an alternative to **lactulose** when an osmotic laxative is indicated:

- if the maximum dose of a stimulant laxative (e.g. **dantron**, **senna**) is ineffective, halve the dose and add magnesium hydroxide 15–30mL b.d., and titrate as necessary
- alternatively, switch completely to magnesium hydroxide 15–60mL b.d.

Magnesium hydroxide (or **lactulose**) may be preferable in patients with a history of colic with stimulant laxatives (see p.48).

Magnesium sulfate

A typical dose is 5–10g of crystals (one or two 5mL spoonfuls) once daily *before breakfast*; dissolve in about 250mL of warm water.

Supply

All the preparations below are available OTC.

Magnesium Hydroxide Mixture BP

Oral suspension hydrated magnesium oxide 415mg (7.1mmol elemental magnesium)/5mL, available OTC as Phillips' Milk of Magnesia®; *do not store in a cold place*.

Magnesium sulfate

Oral powder (Epsom Salts), also Original Andrew's Salts® (magnesium sulfate, citric acid, sodium bicarbonate).

Oral solution magnesium sulfate (Epsom Salts) 5g/10mL, locally prepared.

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 Sykes N (1991) A clinical comparison of lactulose and senna with magnesium hydroxide and liquid paraffin emulsion in a palliative care population. [cited in Candy B et al. (2011) Laxatives or methylprednisolone for the management of constipation in palliative care patients. *Cochrane Database of Systematic Reviews*. CD003448.]

Updated June 2014

RECTAL PRODUCTS FOR CONSTIPATION — BNF 1.6.2–1.6.4

Indications: Constipation and faecal impaction if oral laxatives are ineffective or not feasible.

Pharmacology

The evidence base for laxative suppositories and enemas in palliative care is generally limited to clinical experience and retrospective studies. Survey data indicate that about one third of palliative care patients receiving opioids require rectal measures (laxative suppositories, enemas and/or digital evacuation) either regularly and electively, or intermittently and p.r.n., generally in addition to laxatives PO (Table 1).[1] However, the need for enemas and digital evacuation has decreased since the introduction of **macrogols** (see p.54).[2,3]

Table 1 Rectal measures for the relief of constipation or faecal impaction[a]

Rectal laxative	*Predominant mode of action*	*Time to effect*[b]
Suppositories[c] *(place in contact with rectal mucosa)*		
Bisacodyl 10mg	Stimulates propulsive activity after hydrolysis by enteric enzymes[4]	20–45min
Glycerol 4g	Hygroscopic; softens and lubricates	15–30min
Enemas *(warm to room temperature before use)*		
Osmotic micro-enema (5mL volume)	Faecal softener and osmotic effect (see text below)	15min
Osmotic standard phosphate enema (118–128mL volume)	Osmotic effect	2–5min
Docusate sodium micro-enema	Faecal softener (surface-wetting agent), some direct stimulant action	5–20min
Arachis (peanut) oil retention enema (130mL volume)	Faecal softener	Overnight retention enema

a. PR digital examination will indicate what is the most appropriate intervention
b. as stated in SPC
c. suppositories should be administered only if there are faeces in the rectum.

There is evidence supporting the use of **bisacodyl** suppositories in postoperative ileus[5] and in pre-colonoscopy preparations,[6] and of **docusate sodium** enemas in spinal injury patients.[7] In practice, for soft faeces, a **bisacodyl** suppository is given on its own; and, for hard faeces, **glycerol** alone or **glycerol** plus **bisacodyl**.

The laxative effect of **bisacodyl** is the result of local direct contact with the rectal mucosa after dissolution of the suppository and after activation by enteric enzymes (see p.48). The minimum time for response is thus generally >20min, and may be up to 3h.[8] Defaecation a few minutes after the insertion of a **bisacodyl** suppository is the result of anorectal stimulation. **Bisacodyl** suppositories occasionally cause faecal leakage, even after a successful evacuation.

Osmotic *micro-enemas* contain sodium citrate and **sodium lauryl sulfoacetate** with several excipients, including **glycerol** and **sorbitol**. **Sodium lauryl sulfoacetate** is a faecal softener (surface-wetting agent) similar to docusate sodium (see p.51), whereas **sodium citrate** draws fluid into the intestine by osmosis, an action enhanced by **sorbitol**.

Osmotic standard enemas contain phosphates. These should be used with caution in elderly patients because of a risk of serious electrolyte disturbances. Fatalities have been reported.[9]

When treating a hard faecal impaction, a **docusate sodium** micro-enema will help to soften the faecal mass. This should be instilled into the rectum and retained overnight before giving a stimulant suppository (**bisacodyl**) or an osmotic enema (Table 1).

An **arachis (peanut) oil** retention enema is sometimes used in patients with a hard faecal impaction: instil and leave overnight before giving a stimulant laxative suppository or an osmotic enema. *Do not use in patients with peanut allergy.*

Digital evacuation is the ultimate approach to faecal impaction but is a distressing procedure and may need sedation. Distress can be reduced by explaining the procedure, using plenty of lubrication, and encouraging the patient to respond to any urge to defaecate.

Supply

Suppositories

Glycerol BP

Glycerol 700mg, gelatin 140mg/1g, adult suppositories 4g, 28 days @ 4g once daily = £7; available OTC.

Bisacodyl (generic) 10mg, 28 days @ 10mg once daily = £8.Dulcolax® (Boehringer Ingelheim) 10mg, 28 days @ 10mg once daily = £4.50 (~~NHS~~); available OTC.

Micro-enemas

Faecal softener, Norgala® (Norgine), **docusate sodium** 120mg in 10g single-use disposable pack, 1 enema = £0.50.

Osmotic, **sodium citrate**, **sodium lauryl sulphoacetate**, **glycerol** and **sorbitol**, supplied in 5mL single-dose disposable packs with nozzle:
Micolette® (Pinewood), Micralax® (RPH), Relaxit® (Crawford), 5mL = £0.50.

Standard enemas

Phosphate enema BP Formula B (generic), **sodium acid phosphate** 12.8g, **sodium phosphate** 10.24g in 128mL, 1 enema with standard tube = £3, 1 enema with long rectal tube = £10.

Fleet® Ready-to-use enema (De Witt), **sodium acid phosphate** 21.4g, **sodium phosphate** 9.4g in 118mL, 1 enema with standard tube = £0.50.

Oil retention enema

Arachis Oil retention enema (generic), **arachis (peanut) oil** in 130mL single-dose disposable pack, 130mL = £8; *do not use in patients with peanut allergy.*

1 Twycross RG and Harcourt JMV (1991) The use of laxatives at a palliative care centre. *Palliative Medicine*. **5**: 27–33.
2 Goldman M (1993) Hazards of phosphate enemas. *Gastroenterology Today*. **3**: 16–17.
3 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.
4 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.

5 Wiriyakosol S *et al.* (2007) Randomized controlled trial of bisacodyl suppository versus placebo for postoperative ileus after elective colectomy for colon cancer. *Asian Journal of Surgery.* **30**: 167–172.
6 Rapier R and Houston C (2006) A prospective study to assess the efficacy and patient tolerance of three bowel preparations for colonoscopy. *Gastroenterology Nursing.* **29**: 305–308.
7 Amir I *et al.* (1998) Bowel care for individuals with spinal cord injury: comparison of four approaches. *Journal of Spinal Cord Medicine.* **21**: 21–24.
8 Flig E *et al.* (2000) Is bisacodyl absorbed at all from suppositories in man? *International Journal of Pharmaceutics.* **196**: 11–20.
9 Ori Y *et al.* (2012) Fatalities and severe metabolic disorders associated with the use of sodium phosphate enemas: a single center's experience. *Archives of Internal Medicine.* **172**: 263–265.

Updated (minor change) April 2014

PRODUCTS FOR HAEMORRHOIDS BNF 1.7 & 15.2

Because haemorrhoids can be more troublesome if associated with the evacuation of hard faeces, constipation must be corrected (see Laxatives, p.40).

Peri-anal pruritus, soreness and excoriation are generally 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.

For haemorrhoids, products containing mild astringents (e.g. **bismuth subgallate**, **zinc oxide**, **hamamelis** (**witch hazel**)) often provide symptomatic relief. Some products, not featured here, 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. Alternative local anaesthetics include **pramocaine** (**pramoxine**) and **cinchocaine** (**dibucaine**). Painful spasm of the internal anal sphincter is often eased by topical glyceryl trinitrate ointment (off-label use, p.79).

Local anaesthetic ointments are absorbed through the anal mucosa but, given the amount of ointment likely to be used, there is no realistic risk of systemic toxicity.[1] However, local anaesthetic ointments 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 (bacterial, viral, e.g. *Herpes simplex* or fungal, e.g. candidosis) must first be excluded, and treatment generally limited to 7–10 days because prolonged use with excessive amounts can lead to atrophy of the anal skin. However, this is unlikely with low concentration hydrocortisone.

Dose and use

Topical products should be applied:

- t.d.s.–q.d.s. for the first 24h
- then b.d. and after defaecation for 5–7 days, or longer if necessary
- then daily for 3–5 days after symptoms have cleared.

Products containing a local anaesthetic (to ease painful defaecation) are best applied 15–20min before defaecation, and p.r.n.

Supply

The following list is highly selective. Other OTC products are also available.

Astringent

Anusol® (McNeil)
Ointment **zinc oxide, bismuth subgallate, Peru balsam, bismuth oxide** 25g. (Available OTC).

Local anaesthetic

Lidocaine (generic)
Ointment 5%, 15g = £6.

Corticosteroid plus astringent

Anusol HC® (McNeil)
Ointment **hydrocortisone acetate** 0.25%, **zinc oxide**, **benzyl benzoate**, **bismuth oxide**, **bismuth subgallate**, **Peru balsam** 30g = £3. (Also available OTC as Anusol Plus HC ointment).

Corticosteroid plus local anaesthetic
Scheriproct® (Bayer)
***Ointment* cinchocaine hydrochloride** 0.5%, **prednisolone hexanoate** 0.19%, 30g = £3.

Corticosteroid plus local anaesthetic and astringent
Xyloproct® (Astra Zeneca)
Ointment (water miscible) **aluminium acetate** 3.5%, **hydrocortisone acetate** 0.275%, **lidocaine** 5%, **zinc oxide**, 20g (with applicator) = £4.

1 Brosh-Nissimov T *et al.* (2004) Central nervous system toxicity following topical skin application of lidocaine. *European Journal of Clinical Pharmacology.* **60**: 683–684.

Updated December 2013

PANCREATIN BNF 1.9.4

Class: Enzyme supplement.

Indications: †Symptomatic steatorrhoea caused by biliary and/or pancreatic obstruction.

Pharmacology

Steatorrhoea (the presence of undigested faecal fat) typically results in pale, bulky, offensive, frothy and greasy faeces which flush away with difficulty, associated with abdominal distension, increased flatus, weight loss, 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).

Reducing gastric acid by concurrently prescribing a PPI leads to greater efficacy.[1] With gastro-resistant (e/c) granules, acid reduction is generally unnecessary provided the granules are swallowed whole without chewing.[2] However, in patients who are not adequately controlled on high-dose gastro-resistant pancreatin (e.g. ⩾120,000 units of lipase/24h), concurrent prescription of a PPI generally leads to improvement.[3,4]

On the other hand, mixing e/c granules with alkaline foods or drinks, or crushing or chewing them before swallowing, destroys the gastro-resistant coating. This causes release of the enzymes in the mouth, possible stomatitis, and reduced efficacy.

Cautions

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

Undesirable effects

Very common (>10%): abdominal pain.
Common (<10%, >1%): nausea and vomiting, constipation or diarrhoea.

Dose and use

There are several different pancreatin products, of which Creon® is a good choice. Capsule strength denotes lipase unit content, e.g. Creon® 10,000 contains 10,000 units. The dose is adjusted upwards according to faecal size, consistency, and frequency:

- generally start with Creon® 10,000 1–2 capsules with each meal
- if a smaller dose is required, use Creon® Micro; this contains 5,000 units of lipase in 100mg of granules
- if necessary, change to a higher strength capsule.

The granules in the capsules are gastro-resistant (e/c). The capsules may be swallowed whole, or the contents sprinkled onto slightly acidic fluid or soft food, e.g. fruit juice or apple sauce, and *swallowed without chewing:*

- 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 gastro-resistant coating
- take immediately after mixing because the gastro-resistant coating dissolves if left to stand.

Extra capsules may be needed if snacks are taken between meals. If the pancreatin continues to be ineffective, prescribe a PPI or H_2-receptor antagonist concurrently, and review.

Supply

Creon® (Abbott Healthcare) A standardized product obtained from pigs; *there is no non-porcine alternative*.

Capsules enclosing gastro-resistant granules Creon® 10,000, lipase 10,000 units, amylase 8,000 units, protease 600 units, 28 days @ 2 t.d.s. = £22.

Creon® 25,000, lipase 25,000 units, amylase 18,000 units, protease 1,000 units, 28 days @ 2 t.d.s. = £47.

Creon® 40,000, lipase 40,000 units, amylase 25,000 units, protease 1,600 units, 28 days @ 2 t.d.s. = £95.

If smaller doses are required:

Gastro-resistant granules Creon® Micro, lipase 5,000 units, amylase 3,600 units, protease 200 units in 100mg, (measuring scoop provided), 28 days @ 200mg t.d.s. = £26.

1 Vecht J *et al.* (2006) Efficacy of lower than standard doses of pancreatic enzyme supplementation therapy during acid inhibition in patients with pancreatic exocrine insufficiency. *Journal of Clinical Gastroenterology.* **40**: 721–725.

2 Stead RJ *et al.* (1988) Treatment of steatorrhoea in cystic fibrosis: a comparison of enteric-coated microspheres of pancreatin versus non-enteric-coated pancreatin and adjuvant cimetidine. *Alimentary Pharmacology and Therapeutics.* **2**: 471–482.

3 Proesmans M and De Boeck K (2003) Omeprazole, a proton pump inhibitor, improves residual steatorrhoea in cystic fibrosis patients treated with high dose pancreatic enzymes. *European Journal of Pediatrics.* **162**: 760–763.

4 Dominguez-Munoz JE *et al.* (2006) Optimising the therapy of exocrine pancreatic insufficiency by the association of a proton pump inhibitor to enteric coated pancreatic extracts. *Gut.* **55**: 1056–1057.

Updated January 2014