1: GASTRO-INTESTINAL SYSTEM

ANTACIDS

Indications: Occasional dyspepsia and/or acid reflux; H_2-receptor antagonists (see p.27) and PPIs (see p.30) are used when continuous gastric acid reduction is indicated.[1]

Pharmacology

Antacids generally contain one or more of the following which neutralize gastric acid:
- magnesium salts
- aluminium hydroxide
- sodium bicarbonate
- calcium carbonate.

These are sometimes combined with other ingredients which work in other ways to relieve the symptoms of dyspepsia, e.g.:
- hydrotalcite (aluminium magnesium carbonate hydroxide hydrate)
- peppermint oil
- alginate (see p.3)
- simeticone (silica-activated **dimeticone**, see p.4).

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]

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.

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. It is only available as a special order product in the UK. Give 5–10mL (without fluid) 15min before meals & 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.

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. It is available only in combination with **simeticone** in the UK (see p.4).

Peppermint oil is included in some proprietary products. It can help to mask the chalky taste of the antacid and also help belching, by decreasing the tone of the lower oesophageal sphincter.

Cautions

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

The relatively high sodium content (e.g. 4−6mmol/10mL) of some antacids and alginate products may be detrimental to patients on salt-restricted diets, e.g. those with hypertension, heart failure or renal impairment; low sodium alternatives (e.g. <1mmol/10mL) are preferable (see Supply).

Sodium bicarbonate: risk of sodium loading and metabolic alkalosis; do not use as a single product antacid. **Calcium carbonate:** rebound acid secretion, about 2h after a dose; also hypercalcaemia, particularly when taken with **sodium bicarbonate**.

Drug interactions

Antacids can impact on the absorption of other PO drugs by:

- temporarily increasing the pH of the stomach contents
- delaying gastric emptying
- forming insoluble complexes in the GI tract
- damaging enteric coating.

Selected interactions where additional caution may be necessary are listed in Table 1. Generally, these can be avoided by separating administration of the antacid and the affected drug by ≥2h. This is particularly important for e/c formulations because direct contact with 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 should not be administered by enteral feeding tube as they can cause the feed to coagulate and block the tube (see Chapter 28, Table 2, p.793).

Table 1 Interactions between antacids and other PO drugs[a3]

Drug affected	*Comment*
Bisphosphonates	Avoid antacid for ≥2h before and 30min−2h after the bisphosphonate; see individual SPC
Cefpodoxime	
Dexamethasone[b]	
Fexofenadine	
Gabapentin	Bio-availability reduced ≤20%; of uncertain clinical relevance
Itraconazole	Capsules only
Nitrofurantoin[c]	
Polystyrene sulfonate resin	Creates bicarbonate ions which can lead to metabolic alkalosis; avoid by giving the resin PR
Quinolones	Avoid antacid for ≥4h before and 2h after the quinolone; see individual SPC
Rifampicin	
Tetracyclines	

a. *not* an exhaustive list; limited to drugs most likely to be encountered in palliative care and *excludes* anticancer, HIV and immunosuppressive drugs (seek specialist advice)

b. magnesium trisilicate can reduce dexamethasone absorption by ≤75%

c. magnesium trisilicate can reduce nitrofurantoin absorption by ≤50%.

Large doses of antacids may lead to alkalinzation of the urine and thereby affect the action of other drugs, e.g.:

- **methenamine** action is inhibited at urinary pH >5.5
- the excretion of round-the-clock anti-inflammatory doses of **aspirin** is increased. Occasional doses of **aspirin** are not affected.[3]

Dose and use

Generally, antacids should be taken PO p.r.n. after meals and at bedtime. The dose of liquid formulations is generally 10mL.

Supply

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 = £13; *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 = £7; *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 = £7.50; *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 = £7; *low Na^+*.

With **oxetacaine**
Oral suspension **oxetacaine** 10mg, **aluminium hydroxide** 200mg, **magnesium hydroxide** 100mg/5mL, 28 days @ 10mL t.d.s. a.c. & at bedtime = £138; *low Na^+* (Unauthorized product, available as a special order from Rosemont; see Chapter 24, p.751). *Available as Mucaine® suspension (Wyeth) in some countries*.

Also see Compound alginate products, p.3 and **simeticone**, p.4.

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. *Stockley's Drug Interactions*. London: Pharmaceutical Press www.medicinescomplete.com (accessed April 2015).

Updated May 2015

COMPOUND ALGINATE PRODUCTS

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

Class: Alginate.

Indications: Acid reflux ('heartburn').

Pharmacology

Antacid products containing alginic acid or sodium alginate prevent 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 (p.30) and H_2-receptor antagonists (p.27).

Onset of action <5min.

Duration of action 1–2h.

Cautions

The relatively high sodium content (e.g. 4–6mmol/10mL) of compound alginate products may be detrimental to patients on salt-restricted diets, e.g. those with hypertension, heart failure or renal impairment.

Drug interactions

Co-administration of antacids with e/c formulations, certain other drugs or via enteral feeding tubes should be avoided, also see Antacids p.2.

Dose and use

Several products are available but none is recommended.

Supply

Gaviscon® products, Peptac® and Acidex® oral suspensions (all sugar-free) contain **sodium alginate** 250mg, **sodium bicarbonate** 133.5mg and **calcium carbonate** 80mg/5mL (for full details see BNF).

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

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

Updated May 2015

SIMETICONE

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 some proprietary combination antacids, and more recently available alone. 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] Simeticone is inert and is not absorbed.

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] Risk of hypermagnesaemia with magnesium-containing antacids in renal impairment.

Drug interactions

Co-administration of antacids with e/c formulations, certain other drugs or via enteral feeding tubes should be avoided, also see Antacids p.2.

Dose and use

Simeticone capsules and chewable tablets are now available:

- start with 100–125mg PO q.d.s or p.r.n after meals and at bedtime
- maximum daily dose 800mg/24h.

When the above are not available, or an antacid effect is also required, prescribe an antacid formulation containing simeticone. Altacite Plus® is preferred because it contains a higher dose of simeticone than Maalox Plus®:

- give 10mL PO p.r.n. or 10 mL after meals and at bedtime.

Supply

Wind-eze® (Teva)
Capsules 125mg, 28 days @ 125mg q.d.s. = £15.
Tablets chewable 125mg, 28 days @ 125mg q.d.s. = £10.

WindSetlers® (Thornton & Ross)
Capsules 100mg, 28 days @ 100mg q.d.s. = £14.

With antacids
Altacite Plus® (Peckforton)
Oral suspension (sugar-free) simeticone 125mg, **hydrotalcite** 500mg/5mL, 28 days @ 10mL q.d.s. = £12; *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 = £13; *low* Na^+.

Note. all simeticone and simeticone-antacid products are available OTC.

1 Pokorny C *et al.* (1985) Comparison of an antacid/dimethicone mixture and an alginate/antacid mixture in the treatment of oesophagitis. *Gut.* **26**: A574.
2 Morrissey J and Barreras R (1974) Antacid therapy. *New England Journal of Medicine.* **290**: 550–554.

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ANTIMUSCARINICS

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

Contra-indications: Narrow-angle glaucoma (unless moribund), tachycardia (heart rate >100 beats/min); see Cautions and **hyoscine *butylbromide*** (p.16), bowel obstruction (unless part of medical management), paralytic ileus, megacolon, prostatic enlargement with urinary retention, myasthenia gravis (unless moribund).

Note. Contra-indications vary between different antimuscarinic drugs (see individual SPCs). When possible, *PCF* collates and standardizes contra-indications across a class of drugs and the above are applicable for antimuscarinics given parenterally, SL, TD and PO. The exception is PO **hyoscine *butylbromide*** (p.16) where low bio-availability reduces the likelihood of systemic antimuscarinic effects.

Pharmacology

Chemically, antimuscarinics are classified as tertiary amines or quaternary ammonium compounds (Box A).

Box A Chemical classification of antimuscarinics

Tertiary amines

Naturally-occurring (belladonna alkaloids)
Atropine
Hyoscine *hydrobromide*
Hyoscyamine (l-atropine; not UK)[a]

Synthetic/semisynthetic
Dicycloverine
Orphenadrine
Oxybutynin
Tolterodine

Quaternary ammonium compounds

Synthetic/semisynthetic
Glycopyrronium
Hyoscine *butylbromide*
Ipratropium bromide
Propantheline
Tiotropium bromide

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

Numerous other drugs have antimuscarinic effects (Box B). 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**, **loperamide**, **nifedipine**, **prednisolone**, **ranitidine**, **theophylline**, **warfarin**.[1] Thus, potentially, multiple drugs can contribute to the total 'antimuscarinic burden', and thereby exacerbate toxicity, particularly in the frail elderly.[2]

Box B 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. hyoscyamine is twice as potent as racemic atropine.

At least five different types of muscarinic receptors have been identified (M_1–M_5).[3] They are widely distributed, but their expression and functional relevance varies between tissues. Most

antimuscarinic drugs act as non-selective antagonists, e.g. **atropine**, **glycopyrronium**, **hyoscine *hydrobromide***, **hyoscine *butylbromide***. Newer drugs have aimed to be more selective in their actions, e.g. **oxybutynin** and **tolterodine** are *relatively* selective for M_3 receptors, which predominate in the bladder (see p.567). Nonetheless, undesirable effects are unavoidable because M_3 receptors are also important in other tissues of the body, e.g. salivary gland and bowel, resulting in dry mouth and constipation.

Within the heart, M_2 receptors are mostly responsible for conveying parasympathetic effects on pacemaker activity, atrioventricular conduction and force of contraction. Other subtypes are also present (M_1, M_3, M_5) but their functional significance is uncertain. Further, cardiac disease can alter receptor expression, e.g. the density of M_2 decreases and M_3 increases in chronic atrial fibrillation.[3] Within the coronary arteries in mice, M_3 receptors are the most important in mediating acetylcholine-induced vasodilation; it is not known if this is true in humans, although the genes for M_2 and M_3 receptors are expressed.[3] Thus, although the cardiac toxicity of **hyoscine *butylbromide*** has been the recent focus of attention (see p.17), *all* antimuscarinics have this potential. This is particularly so in patients with cardiac disease associated with a detrimental autonomic nervous system imbalance (increased sympathetic and decreased parasympathetic (vagal) activity).[4] Indeed, *increasing* vagal activity appears beneficial in cardiac disease, and there is growing interest in the use of electrical stimulation or drugs to augment vagal function, e.g. in heart failure.[4,5]

Antimuscarinic effects can be divided into central and peripheral (Box C); undesirable central and peripheral effects have been summarized as:

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

Box C Antimuscarinic effects

CNS effects
Drowsiness
Cognitive impairment
Delirium
Restlessness
Agitation

Peripheral 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

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, at typical *therapeutic* doses, **hyoscine *hydrobromide*** (but *not* **atropine**) causes CNS depression.

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 have only peripheral effects (Box C).[6] They are also less well absorbed from the GI tract.

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.[7] In some patients, a reduction in excess saliva results in improved speech.[8]

In the UK, parenteral antimuscarinics are widely used to reduce death rattle (noisy rattling breathing) in those close to death (see QCG: Death rattle (noisy rattling breathing), p.12). Although the use of antimuscarinics for this purpose has been questioned,[9,10] such use is often, although not always, beneficial.[11–13] For example, a prospective clinical survey concluded that antimuscarinics reduce death rattle in 1/2–2/3 of patients.[14]

In relation to death rattle, belladonna alkaloids are generally equally effective,[11,12] and **glycopyrronium** may sometimes be effective when the alkaloids have not been.[15] Although one study reported that **hyoscine *hydrobromide*** acts faster than **glycopyrronium**, there is no detectable difference between the two drugs after 1h.[16] In practice, undesirable effects, availability, fashion, familiarity, and cost are probably the main influences in choice of drug.

Antimuscarinic drugs differ in their pharmacokinetic characteristics (Table 1).

Table 1 Pharmacokinetic details of selected antimuscarinic drugs[7]

	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[17]	1–5h[17]	<2h[b,18]
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

After the sudden death of a patient with cardiac disease given an IV bolus of **hyoscine *butylbromide*** at colonoscopy, the MHRA issued a warning highlighting its cardiac toxicity (see p.17).[19]

Cardiac disease, e.g. myocardial infarction, ischaemia, arrhythmia, heart failure, hypertension; other conditions predisposing to tachycardia, e.g. thyrotoxicosis, β agonists. 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.

Use in renal impairment

In end-stage renal failure, do *not* use **hyoscine *hydrobromide*** for death rattle because of an increased risk of delirium. Use **hyoscine *butylbromide*** (dose unchanged) or **glycopyrronium** instead (lower doses may be sufficient).

Antimuscarinics differ in their potential to cause toxicity when renal function is impaired, see Chapter 17 for general information on the choice of antimuscarinic and use in ESRF.

Drug interactions

Concurrent treatment with ≥2 antimuscarinic drugs (including antihistamines, phenothiazines and TCAs; see Box B) will increase the likelihood of undesirable effects, and (when centrally acting) of central toxicity, i.e. restlessness, agitation, delirium (see Box C). Children, the elderly, and patients with renal or hepatic impairment are more susceptible to the central effects of non-quaternary antimuscarinics.

Because antimuscarinics competitively block the final common (cholinergic) pathway through which prokinetics act,[20] concurrent prescription with **metoclopramide** and **domperidone** should be avoided as far as possible.

The increased GI transit time produced by antimuscarinics may allow increased drug absorption from some formulations, e.g. **digoxin** and **nitrofurantoin** tablets and **potassium** 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.

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 bowel obstruction in order to prevent colic and to reduce vomiting.

Undesirable effects

What is a desired effect becomes an undesirable effect in different circumstances (see Box C). 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

In palliative care patients, there is an association between the number of antimuscarinic drugs used and worsening fatigue and quality of life.[2] Thus, when possible, drugs with antimuscarinic effects should be avoided or discontinued.

By injection, there is no good evidence to recommend one antimuscarinic in preference to another.[12] 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, **glycopyrronium**, **hyoscine *butylbromide*** and **hyoscine *hydrobromide*** are used in preference to **atropine**. Generally, *PCF* favours **hyoscine *butylbromide*** based on its lack of central effects and lower cost.

When given IM, **atropine**, **hyoscine *hydrobromide*** and **glycopyrronium** are all absorbed faster from the deltoid muscle than from the gluteal muscles.[7]

Antispasmodic

Antimuscarinics are used to relieve smooth muscle spasm in the bladder (see **oxybutynin**, p.567) and rectum.

Antispasmodic and antisecretory

Antimuscarinics are used to reduce intestinal colic and intestinal secretions, particularly gastric, associated with inoperable organic bowel obstruction in terminally ill patients (Table 2). Also see QCG: Inoperable bowel obstruction, p.242.

Table 2 Antispasmodic and antisecretory drugs: typical SC doses

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

a. atropine doses are generally the same as hyoscine *hydrobromide*.

Antisecretory

Death rattle (noisy rattling breathing)

Treatment regimens are all unauthorized and based mainly on local clinical experience. In the UK antimuscarinic drugs for death rattle are generally given SC/CSCI.[21] See QCG: Death rattle (noisy rattling breathing), p.12.

In some countries the SL route is preferred, particularly in home care because it circumvents the need for injections, e.g. **glycopyrronium**, see p.13).

Drooling (and sialorrhoea)

Seen particularly in patients with ALS/MND, advanced Parkinson's disease and with various disorders of the head and neck. A survey of UK neurologists[22] 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[23]
- **amitriptyline**, e.g. 10–25mg PO 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.[24]

Glycopyrronium is the most popular second-line drug, typically PO or SL.[22] It is recommended for first-line use in patients with cognitive impairment.[25] It has also been used for drooling in other conditions (see Glycopyrronium, p.13).

In patients in whom antimuscarinics are contra-indicated, ineffective or not tolerated, the parotid ± submandibular glands can be injected with **botulinum toxin**.[22] Injections are generally effective within 2 weeks, and benefit lasts 3–4 months.[26–30] In patients with a relatively long prognosis (years rather than months), radiotherapy and surgery are further options.[22]

Paraneoplastic pyrexia and sweating

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

Box D Symptomatic drug treatment of paraneoplastic pyrexia and sweating

Prescribe an antipyretic:

- paracetamol 500–1,000mg PO q.d.s. or p.r.n. (generally less toxic than an NSAID)
- NSAID, e.g. ibuprofen 200–400mg PO 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, e.g.:

- amitriptyline 25–50mg PO at bedtime
- propantheline 15–30mg PO b.d.–t.d.s. on an empty stomach
- hyoscine *hydrobromide* 1mg/3 days TD[31]
- glycopyrronium 200microgram–2mg PO t.d.s.[32]

If an antimuscarinic fails, other PO options include:

- gabapentin, see p.272
- H_2-receptor antagonist, e.g. ranitidine 150mg b.d.[33]
- olanzapine 5mg b.d.[34]
- propranolol 10–20mg b.d.–t.d.s.
- thalidomide 100mg at bedtime.[35,36]

Thalidomide is generally seen as the last resort even though the response rate appears to be high.[36] This is mostly because it can cause an irreversible painful peripheral neuropathy and other undesirable effects (see p.558).

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.[37–39]

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.739).

Anti-arrhythmics are *not* advisable if an arrhythmia develops; but hypoxia and acidosis should be corrected.

1 Tune I *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 Hochman MJ *et al.* (2016) Anticholinergic drug burden in noncancer versus cancer patients near the end of life. *Journal of Pain and Symptom Management*. **52**: 737–743.e733.
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4 He X *et al.* (2015) Novel strategies and underlying protective mechanisms of modulation of vagal activity in cardiovascular diseases. *British Journal of Pharmacology*. **172**: 5489–5500.
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Updated July 2017

Quick Clinical Guide: Death rattle (noisy rattling breathing)

Death rattle occurs in about 50% of dying patients. It is caused by fluid collecting in the upper airway, arising from one or more sources:

- saliva (most common)
- bronchial mucosa (e.g. inflammation/infection)
- pulmonary oedema
- gastric reflux.

Rattling breathing can also occur in patients with a tracheostomy.

Non-drug treatment

- if the patient is unconscious, ease the family's distress by explaining that the rattle is not distressing to the patient
- position the patient semiprone to encourage postural drainage; but upright or semirecumbent if the cause is pulmonary oedema or gastric reflux
- suction of the upper airway but, because it can be distressing, generally restrict use to unconscious patients.

Drug treatment

If the rattle is associated with distressing breathlessness in a semiconscious patient, supplement the recommendations below with an opioid (e.g. morphine) and an anxiolytic sedative (e.g. midazolam).

Saliva

Because they do not affect existing secretions, an antimuscarinic drug should be given SC as soon as the rattle begins (Table). Hyoscine *butylbromide* is widely used because it is the cheapest and is free of CNS effects.

CSCI treatment is generally started at the same time as the first or second SC dose; increase the dose if ≥ 2 p.r.n. doses/day are needed.

Antimuscarinic drugs for death rattle

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

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

Respiratory tract infection

Generally, it is *not* appropriate to prescribe an antibacterial in an imminently dying patient. Rarely, one may be indicated if death rattle is caused by profuse purulent sputum in a semiconscious patient.

Pulmonary oedema

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

Gastric reflux

Consider metoclopramide 20mg SC/IV q3h p.r.n. ± ranitidine 50mg SC/IV b.d.–q.d.s.

Antimuscarinics block the prokinetic effect of metoclopramide; avoid concurrent use if possible.

Updated June 2017

GLYCOPYRRONIUM

Class: Antimuscarinic.

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

Contra-indications: See Antimuscarinics (p.000). For tachycardia (heart rate >100 beats/min), also see Pharmacology and **hyoscine *butylbromide*** (p.17).

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 IV it is about 35 times more potent than PO.[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 parenteral **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]

Parenterally, the optimal single dose of glycopyrronium is 200microgram;[12,13] this appears less likely to increase heart rate and cause tachycardia compared with parenteral doses of other antimuscarinic drugs, e.g. **atropine**, **hyoscine *butylbromide*** (see p.16).[14,15] Nonetheless, comparative patient safety data are lacking and, even in young healthy volunteers, changes in cardiac conduction are seen after 200microgram IV.[14] Thus, particularly in those with cardiovascular disease, it would seem appropriate to consider applying similar contra-indications and cautions as for other antimuscarinics (p.5).

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 may be sufficient in patients with severe renal impairment, see Chapter 17, p.695) [3,16]

Glycopyrronium can also be used in other situations where an antimuscarinic effect is needed, e.g. paraneoplastic pyrexia and sweating (see Antimuscarinics, Box D, p.10), hyperhidrosis, sialorrhoea and drooling.

Glycopyrronium PO or SL has been used to reduce drooling in adults with various conditions, e.g. MND/ALS, Parkinson's disease, cancers of the head and neck or oesophagus.[17–19] An oral solution is now authorized for drooling in children and adolescents ≥3 years with chronic neurological disorders. It has also been given by nebulizer.[19] It is also used as a bronchodilator (inhaled or nebulized) in asthma and COPD.[20,21]

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

See Antimuscarinics (p.5); renal impairment (also see Chapter 17, p.695).

Drug interactions

Concurrent treatment with ≥2 antimuscarinic drugs (including antihistamines, phenothiazines and TCAs; see Antimuscarinics, Box B, p.6) will increase the likelihood of undesirable effects (see Antimuscarinics, Box C, p.7).

See Antimuscarinics (p.5).

Undesirable effects

Peripheral antimuscarinic effects (see Antimuscarinics, Box C, p.7). 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**.[18,22,23] For indications where a parenteral antimuscarinic is required, *PCF* generally prefers **hyoscine *butylbromide***; it is unlikely to cause CNS effects and is cheaper than glycopyrronium.

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.863).

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*.

Antispasmodic and inoperable intestinal obstruction

- start with 200microgram SC stat
- continue with 600–1,200microgram/24h CSCI *and/or* 200micorgram SC q2h p.r.n.

Death rattle (noisy rattling breathing)[24]

See QCG: Death rattle (noisy rattling breathing), p.12:

- start with 200microgram SC stat
- continue with 600–1,200microgram/24h CSCI *and/or* 200micorgram SC q1h p.r.n.
- alternatively the SL route can be used; 100microgram SL q6h p.r.n.

Drooling

Administer PO as an oral solution/suspension. Tablets are expensive and only available in higher doses. Various products are available (see Supply), but the only authorized product for drooling is Sialanar® for use in children. When considering an unauthorized product, cost, suitability and availability, particularly in a non-hospital setting, need to be considered (see Chapter 24, p.751).

- 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. Oral solutions/suspensions can be given by enteral feeding tube (also see p.785).[9,18]

Paraneoplastic pyrexia and sweating

- start with 200microgram PO t.d.s.
- if necessary, increase progressively to 2mg PO t.d.s. (also see Antimuscarinics, Box D, p.10)

Localized hyperhidrosis

- apply topically as a 0.5–4% cream or aqueous solution once daily–b.d. avoiding the nose, mouth and particularly the eyes; do not wash treated skin for 3–4h[2,26]
- if severe, or if alternative treatments fail, 1–2mg PO b.d.–t.d.s., titrated to response (see above and Supply for products available).[1]

Supply

Glycopyrronium *bromide* (generic)
Oral solution 1mg/5mL, 28 days @ 1mg t.d.s = £255. *Authorized as add on therapy in treatment of peptic ulcer.*
Tablets 1mg, 2mg, 28 days @ 1mg t.d.s. = £602. *Authorized as add on therapy in treatment of peptic ulcer.*
Injection 200microgram/mL, 1mL or 3mL amp = £1.50.

Sialanar® (Proveca)
Oral solution 320miorgram/mL glycopyrronium base (equivalent to 400micorgram/mL (2mg/5mL) glycopyrronium bromide), 28 days @ 1mg t.d.s = £270. *Authorized for drooling in children and adolescents ≥3 years.*

Unauthorized oral products
Glycopyrronium *bromide*
Oral solution or oral suspension 200microgram/5mL, 500microgram/5mL, 2.5mg/5mL and 5mg/5mL, 28 days @ 1mg t.d.s. = £68; (available as a special order, see Chapter 24, p.751) price based on 5mg/5mL oral solution specials tariff in community; prices vary significantly between formulations and quantities ordered.

For locally prepared formulations, see Box A.

Unauthorized topical products
Glycopyrronium *bromide*
Cream 2% (20mg/mL) in Cetomacrogol cream (Formula A) 30g = £390; (available as a special order, see Chapter 24, p.751).
For a locally prepared cream, see Box B.

Box A Examples of locally prepared glycopyrronium formulations for PO use

From glycopyrronium powder[27]

Glycopyrronium oral solution 100microgram/mL

Dissolve 100mg of glycopyrronium powder (obtainable from AMCo) in 100mL of sterile or distilled water to produce a 1mg/mL concentrate. This is stable for about 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.

Cost: 28 days @ 1mg (10mL) t.d.s. = £11 worth of glycopyrronium powder (but need to buy 3g = £327).

Glycopyrronium oral suspension 500microgram/mL[28]

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.

Cost: 28 days @ 1mg (2mL) t.d.s. = £9 worth of glycopyrronium powder (but need to buy 3g = £327).

From glycopyrronium injection

Glycopyrronium oral suspension 100microgram/mL[29]

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.

Cost: 28 days @ 1mg (10mL) t.d.s. = £210 worth of glycopyrronium injection.

Box B Example of locally prepared glycopyrronium cream 10mg/mL (1%)[30]

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.

Cost: 100g = £109 worth of glycopyrronium *powder* (but need to buy 3g = £327).

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HYOSCINE BUTYLBROMIDE

Class: Antimuscarinic.

Indications: Smooth muscle spasm (e.g. bladder, GI tract), †drying secretions (e.g. †death rattle (noisy rattling breathing), †inoperable bowel obstruction).

Contra-indications: ***Parenteral:*** See Antimuscarinics (p.5). For tachycardia (heart rate >100 beats/min), also see Cautions.

Pharmacology

Hyoscine *butylbromide* is an antimuscarinic (see p.16) and has both smooth muscle relaxant (antispasmodic) and antisecretory properties. It is a quaternary compound and, unlike **hyoscine *hydrobromide*** (p.19), 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 bowel obstruction, and as an antisecretory drug for death rattle (noisy rattling breathing). In bowel obstruction, in comparison with hyoscine *butylbromide* (60–80mg/24h CSCI), **octreotide** (300–800microgram/24h CSCI; p.544) provides more effective and rapid improvements in nausea and vomiting and reduction in NG tube output.[6,7] However, in those patients responding to either drug, after about 3–6 days, overall symptom relief is similar, and NG tube removal is possible with both.[6,7] Further, the presence of colic would favour the use of hyoscine *butylbromide* over **octreotide**. For a suggested management approach, see QCG: Inoperable bowel obstruction (p.242).

In healthy volunteers, 20mg SC 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** (p.13) 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 5–10h.
Duration of action <2h in volunteers[8] but possibly longer in moribund patients.

Cautions

The MHRA has issued a warning highlighting the risk of serious undesirable effects with hyoscine *butylbromide* injection in patients with underlying cardiac disease.[14] This followed the death of a patient in 2016 from cardiac arrest after IV hyoscine *butylbromide* during colonoscopy, and the Coroner's recommendation to the MHRA to clarify the cautions in the SPC emphasizing that 'additional caution should be exercised when administering IV hyoscine *butylbromide* to patients with ischaemic heart disease.'

In its own review, the MHRA identified reports of 8 deaths over 16 years associated with the use of IV/IM hyoscine *butylbromide*, and published the following advice:

- hyoscine *butylbromide* injection can cause serious undesirable effects including tachycardia, hypotension and anaphylaxis
- these undesirable effects can result in a fatal outcome in patients with underlying cardiac disease, e.g. heart failure, coronary heart disease, cardiac arrhythmia, hypertension
- hyoscine *butylbromide* injection should be used with caution in patients with cardiac disease
- monitor these patients, and ensure that resuscitation equipment, and personnel who are trained how to use this equipment, are readily available
- hyoscine *butylbromide* injection is contra-indicated in patients with tachycardia.

SPCs have been changed to reflect this advice.

However, full data are not available, and it is difficult to interpret the specific relevance of the reports to use in a palliative care setting, where the SC/CSCI route of administration is more likely than IV/IM.

Nonetheless, in healthy volunteers, an increase in heart rate of ~15 bpm is evident 5min after hyoscine *butylbromide* 20mg SC which lasts about 1h. On the other hand, no effect on heart rate was observed with doses <0.4mg/min CIVI.[8] This equates to <575mg/24h, well above typical doses given CSCI in palliative care.

PCF advises clinicians to remind themselves of the longstanding cautions relating to the use of any antimuscarinic, particularly in patients with cardiovascular disease, and to continue to balance the potential for benefit and harm for each patient individually.

See Antimuscarinics (p.8). PO **hyoscine *butylbromide*** has a low bio-availability reducing the likelihood of systemic antimuscarinic effects.

Drug interactions

Concurrent treatment with ≥2 antimuscarinic drugs (including antihistamines, phenothiazines and TCAs; see Antimuscarinics, Box B, p.6) will increase the likelihood of undesirable effects (see Antimuscarinics, Box C, p.7).

See Antimuscarinics (p.8).

Undesirable effects

Common (<10%,>1%): peripheral antimuscarinic effects (see Antimuscarinics, Box C, p. 7).
Unknown: hypotension (IV), anaphylactic shock (see Cautions).

Dose and use

Hyoscine *butylbromide* is generally used SC/CSCI in palliative care because of poor PO bio-availability ± unsuitability of the PO route. 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.863).

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

- start with 20mg SC stat and 60mg/24h CSCI and 20mg SC q1h p.r.n.
- if necessary, increase to 120mg/24h
- maximum reported dose 300mg/24h.

Note. The maximum benefit from hyoscine *butylbromide* may be seen only after about 3 days.[6,7] Some centres add **octreotide** 500microgram/24h CSCI if hyoscine *butylbromide* 120mg/24h fails to relieve symptoms adequately, see QCG: Inoperable bowel obstruction (p.242).[15,16]

For patients with obstructive symptoms without colic, **metoclopramide** (see p.244) should be tried before an antimuscarinic drug because the obstruction is often more functional than organic. See QCG: Inoperable bowel obstruction (p.242).

Death rattle (noisy rattling breathing)

See QCG: Death rattle (noisy rattling breathing), p.12:

- start with 20mg SC stat
- continue with 20–60mg/24h CSCI, and/or 20mg SC q1h p.r.n.
- some centres use higher doses, namely 60–120mg/24h CSCI.[10]

Bladder spasm

Use only when more specific bladder antispasmodics (see p.567) are inappropriate, e.g. PO route unavailable.

- start with 20mg SC stat
- continue with 60–120mg/24h CSCI, and/or 20mg SC q1h p.r.n.

Supply

Buscopan® (Boehringer Ingelheim)
Tablets 10mg, 28 days @ 20mg q.d.s. = £12. *Also available OTC as Buscopan® IBS Relief and Buscopan® Cramps*.
Injection 20mg/mL, 1mL amp = £0.25.

1 Boehringer Ingelheim GmbH *Data on file*.
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HYOSCINE HYDROBROMIDE

Class: Antimuscarinic.

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

Contra-indications: See Antimuscarinics (p.5). For tachycardia (heart rate >100 beats/min), also see **hyoscine *butylbromide*** (p.17).

Pharmacology

Hyoscine *hydrobromide* is a naturally occurring belladonna alkaloid with smooth muscle relaxant (antispasmodic) and antisecretory properties. Unlike **hyoscine *butylbromide***, 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 (also see p.5). For this reason, *PCF* generally prefers **hyoscine *butylbromide***; it is also cheaper.

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, e.g. sialorrhoea, drooling, paraneoplastic pyrexia and sweating (see p.10) and smooth muscle spasm (e.g. intestine, bladder).

Hyoscine *hydrobromide* has anti-emetic properties (see p.235). However, generally, it is only used as prophylactic treatment for motion sickness PO or by TD patch.[4] The TD patch:

- 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 and also oesophageal spasm.[7-9] Other off-label uses include the management of drooling and sialorrhoea in children and adults with various conditions, including disorders of the head and neck.[10-12]

Bio–availability 60–80% SL.[13]
Onset of action 3–5min IM, 10–15min SL.
Time to peak effect 20–60min SL/SC; 24h TD.
Plasma halflife 1–4h IM.[13]
Duration of action IM 15min (spasmolytic), 1–9h (antisecretory).[13]

Cautions

See Antimuscarinics (p.5); renal impairment (see Dose and use and also Chapter 17, p.695).

Drug interactions

Concurrent treatment with ≥2 antimuscarinic drugs (including antihistamines, phenothiazines and TCAs; see Antimuscarinics, Box B, p.6) will increase the likelihood of undesirable effects, and (when centrally acting) of central toxicity, i.e. restlessness, agitation, delirium (see Antimuscarinics, Box C, p.7). Children, the elderly, and patients with renal or hepatic impairment are more susceptible to the central effects of antimuscarinics.

See Antimuscarinics (p.5).

Undesirable effects

Antimuscarinic effects (see Box C, p.7), including central antimuscarinic syndrome, i.e. agitated delirium, drowsiness, ataxia.

TD patch: despite the relatively small dose, delirium has been reported;[14] local irritation ± rash occasionally occurs.

Dose and use

Death rattle (noisy rattling breathing)

See QCG: Death rattle (noisy rattling breathing), p.12:

- start with 400microgram SC stat
- continue with 1,200microgram/24h CSCI, and/or 400microgram SC q1h p.r.n.
- if necessary, increase to 1,600microgram/24h CSCI
- avoid in patients with end-stage renal failure because of an increased risk of delirium.

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.863).

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*.

Note. *PCF* favours **hyoscine *butylbromide*** (see p.16); it is cheaper and is free of CNS effects. Other options include **glycopyrronium** (see p.13) and **atropine** (see p.5).

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.210).

TD patches contain metal and must be removed before MRI to avoid burns (see p.831). 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).

Supply

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

Scopoderm® (GlaxoSmithKline Consumer Health)
TD (post-auricular) patch 1.5mg (releasing 1mg over 3 days), 1 patch = £2.50.

Hyoscine *hydrobromide* (generic)
Injection 400microgram/mL, 1mL amp = £4.75; 600microgram/mL, 1mL amp = £5.50.

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PROPANTHELINE

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: See Antimuscarinics (p.5). In addition, hiatus hernia associated with reflux oesophagitis, severe ulcerative colitis.

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 half-emptying 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
See Antimuscarinics (p.5).

Drug interactions
Concurrent treatment with ≥2 antimuscarinic drugs (including antihistamines, phenothiazines and TCAs; see Antimuscarinics, Box B, p.6) will increase the likelihood of undesirable effects (see Antimuscarinics, Box C, p.7).

See Antimuscarinics (p.5).

Undesirable effects
Peripheral antimuscarinic effects (see Antimuscarinics, Box C, p.7).

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** (see p.567), **amitriptyline** (see p.210) or **imipramine**.

Sweating
One of several alternatives to reduce paraneoplastic sweating (for other options, see Antimuscarinics, Box D, p.10):
- give 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:
- give 15mg t.d.s.[6] *on an empty stomach*.

However, other options are generally preferred, see p.10.

Supply
Pro-Banthine® (Kyowa Kirin)
Tablets 15mg, 28 days @ 15mg t.d.s. & 30mg at bedtime = £26.

1 Hurwitz A *et al.* (1977) Prolongation of gastric emptying by oral propantheline. *Clin Pharmacol Ther*. **22**: 206–210.
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ORPHENADRINE

Class: Antimuscarinic antiparkinsonian.

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

Contra-indications: See Antimuscarinics (p.5) and Tardive dyskinesia (p.739).

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 21, p.739).

Orphenadrine is almost completely metabolized in the liver, producing numerous metabolites which are excreted in the urine.

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

See Antimuscarinics (p.5). Avoid abrupt discontinuation.

Drug interactions

Concurrent treatment with ≥2 antimuscarinic drugs (including antihistamines, phenothiazines and TCAs; see Antimuscarinics, Box B, p.6) will increase the likelihood of undesirable effects, and (when centrally acting) of central toxicity, i.e. restlessness, agitation, delirium (see Antimuscarinics, Box C, p.7). Children, the elderly, and patients with renal or hepatic impairment are more susceptible to the central effects of antimuscarinics.

See Antimuscarinics (p.5).

Undesirable effects

Antimuscarinic effects (see p.5). 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 PO 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.

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 21, p.739).

Supply

Orphenadrine (generic)
Tablets 50mg, 28 days @ 50mg t.d.s. = £67.
Oral solution (sugar-free) 50mg/5mL, 28 days @ 50mg t.d.s. = £100.

1 Katzenschlager R *et al.* (2003) Anticholinergics for symptomatic management of Parkinson's disease. *Cochrane Database of Systematic Reviews*. CD003735. www.thecochranelibrary.com

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PROKINETICS

Pharmacology

Prokinetics accelerate GI transit and include:

- D_2 antagonists, e.g. **domperidone** (p.247), **metoclopramide** (p.244)
- $5HT_4$ 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).

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]

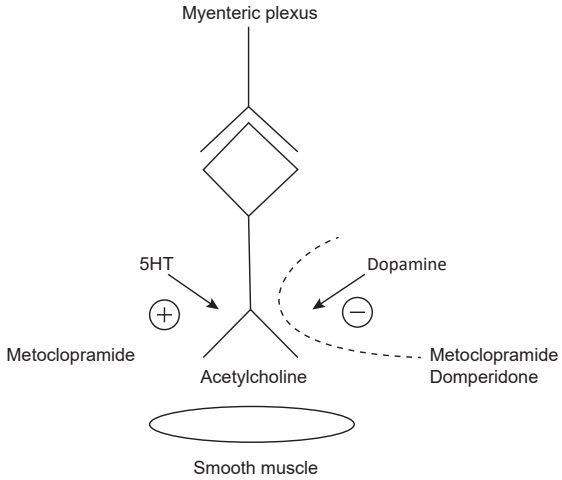

Figure 1 Schematic representation of drug effects on antroduodenal co-ordination via a postganglionic effect on the cholinergic nerves from the myenteric plexus.
⊕ stimulatory effect of 5HT triggered by metoclopramide;
⊖ inhibitory effect of dopamine;
– – – blockade of dopamine inhibition by metoclopramide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

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 halflife 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]

Box A Indications for prokinetics in palliative care

- Gastro-oesophageal reflux
- Delayed gastric emptying
- Hiccup
- 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)

Table 2 Drug treatment of hiccup (PO unless stated otherwise)

Class of drug	*Drug*	*Acute relief*	*Maintenance regimen*
Reduce gastric distension ± gastro-oesophageal reflux			
Antiflatulent (carminative)	Peppermint water[a,b]	10mL	Probably best used p.r.n. only
Antiflatulent (defoaming agent)	Simeticone	See p.4	See p.4
Prokinetic	Metoclopramide[b,c]	10mg	10mg t.d.s.[15]
PPI	Lansoprazole	30mg	30mg each morning
Central suppression of the hiccup reflex			
First-line options			
GABA agonist	Baclofen	5mg	5–20mg t.d.s., occasionally more[16,17]
Anti-epileptic	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,18]	400mg t.d.s.[19,20]
Second-line options			
Dopamine antagonist	Metoclopramide	As above	As above
Third-line options			
L-type calcium-channel blocker	Nifedipine	10mg PO/SL	10–20mg t.d.s., occasionally more[21,22]
Anti-epileptic	Valproate	200–500mg	15mg/kg/24h in divided doses[23]
Dopamine antagonist	Haloperidol	1.5−3mg b.d.–t.d.s. (≤5mg t.d.s if severe)	500microgram–1mg t.d.s. (≤3mg t.d.s. if severe)
Benzodiazepine	Midazolam	2mg IV, followed by 1–2mg increments every 3–5min	10–60mg/24h by CSCI if patient in last days of life[24]

a. facilitates belching by relaxing the lower oesophageal sphincter; an old-fashioned remedy, can result in 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. a smaller dose advisable in elderly frail patients and those with renal impairment, e.g. start with 100mg t.d.s.

Doses are given in individual monographs for **metoclopramide** (p.244) and **domperidone** (p.247). For **erythromycin**:

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

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 from a gastroenterologist. In some settings, patients may benefit from **clonidine** (p.77), intrapyloric **botulinum toxin** or gastric electrical stimulation.[14] Ultimately, some patients may require a venting gastrostomy and/or a feeding jejunostomy.[1]

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Updated August 2017

H_2-RECEPTOR ANTAGONISTS

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**), †reduction of gastric secretions in bowel obstruction, †paraneoplastic sweating.

Pharmacology

H_2-receptor antagonists (H_2 antagonists) include **cimetidine**, **famotidine**, **nizatidine** and **ranitidine**. All are equally effective at gastric acid suppression.[1] However, because of their greater acid suppression and/or tolerability, PPIs (p.30) are generally preferred over H_2 antagonists and **misoprostol**, which is now rarely used.[2]

Other effects include increasing lower oesophageal sphincter pressure and reducing the volume of gastric secretions.[3,4] H_2 antagonists are more effective than PPIs in reducing the volume of gastric secretions which has led some to recommend the use of **ranitidine** in patients with bowel obstruction.[4,5] Further, injection formulations of **ranitidine** (unlike PPIs) can be mixed with other drugs, making administration by CSCI more convenient (see Dose and use).

Anecdotally, H_2 antagonists are of benefit in paraneoplastic sweating.[6,7] The mechanism is unknown. An early therapeutic trial of **ranitidine** is reasonable on the basis that it is likely to be better tolerated than the other drugs used this setting (see Box D, Antimuscarinics, p.10).

Cimetidine, alone among H_2 antagonists, can cause serious CYP450-related drug interactions (see Table 1 and Chapter 19, Table 8, p.725). **Ranitidine** is a good choice in terms of cost and lack of drug interactions.

***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 (dose reduction required, see SPCs).

Gastric acid suppression is associated with an increased risk of *Clostridium difficile* infection (p.496); H_2 antagonists have a lower risk than PPIs (p.30).[8]

Drug interactions

H_2 antagonists increase gastric pH and this reduces the absorption of some drugs and formulations. Clinically important examples include **itraconazole** (capsules only), **posaconazole**, antivirals and protein kinase inhibitors (seek specialist advice); see respective SPCs for full details. Rarely, absorption is increased, e.g. **saquinivir**.[9]

Cimetidine is the only H_2 antagonist that affects the CYP450 enzyme system. It is classified as a weak inhibitor of multiple CYP enzymes involved in drug metabolism (CYP1A2, CYP2D6, CYP2C19, CYP3A4/5). Thus, caution is required with concurrent use of drugs which are metabolised by these enzymes (see Chapter 19, Table 8, p.725). Table 1 lists interactions where close monitoring ± dose adjustment are required.

Table 1 Clinically important CYP450-related interactions with cimetidine[a,9,10]

Drug group	*Drug effect ↑ by cimetidine*[b]
Anticoagulants	Warfarin and other coumarins
Anti-epileptics	Carbamazepine (transient), phenytoin
Benzodiazepines	Alprazolam, diazepam, chlordiazepoxide, flurazepam, midazolam[c], nitrazepam, triazolam (not UK)
Calcium antagonists	Potentially all, including diltiazem and nifedipine
Local anaesthetics	Flecainide, lidocaine (IV), procainamide
Opioids	Alfentanil, fentanyl, methadone
SSRIs	All
TCAs	Potentially all
Xanthines	Aminophylline, theophylline
Miscellaneous	Erythromycin, mirtazapine, moclobemide, quinine, quinidine (not UK), zaleplon, zolmitriptan

a. *not* an exhaustive list; limited to drugs most likely to be encountered in palliative care and *excludes* anticancer, antiviral, HIV and immunosuppressive drugs (seek specialist advice)
b. either specifically reported or likely based on pharmacokinetic studies
c. midazolam reports inconsistent.

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 (p.30).[11]

Dose and use

NICE guidance: in the treatment of uninvestigated dyspepsia or proven gastro-oesophageal reflux disease, H_2 antagonists are a second-line option after PPIs (p.30). In all other acid-related disorders, where efficacy may be similar, PPIs remain generally preferable to H_2 antagonists.[2]

Dose recommendations are limited to **ranitidine** because of its low cost and lack of drug interactions. **Ranitidine** is more effective if taken at bedtime rather than with the evening meal.[12]

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.

Uninvestigated dyspepsia or reflux-like symptoms

- **ranitidine** 150mg PO b.d. or 300mg at bedtime for 6 weeks.

Proven gastro-oesophageal reflux disease

- **ranitidine** 150mg PO b.d. or 300mg at bedtime for 8–12 weeks.

Proven severe oesophagitis

- **ranitidine** 150mg PO q.d.s. or 300mg b.d. for up to 12 weeks.

Peptic ulcer (including NSAID-related)

- stop the NSAID; if continuation is necessary, use long-term gastric protection after ulcer healing (see below)
- test for *H pylori*:
  - ▷ if negative, use **ranitidine** 150mg PO b.d. or 300mg at bedtime for 4–8 weeks (8 weeks if continuing an NSAID)
  - ▷ if positive, and the ulcer is NSAID-related, use **ranitidine** 150mg PO b.d. or 300mg at bedtime for 8 weeks, followed by eradication therapy (see BNF) *or*
  - ▷ if positive, and the ulcer is *not* NSAID-related, use eradication therapy first and then review (see BNF)
- if symptoms recur, use the lowest effective dose either as long-term maintenance or, when symptoms infrequent, p.r.n.

Gastric protection in patients taking an NSAID at high risk of peptic ulcer disease

- **ranitidine** 300mg PO b.d. *and*
- consider use of a COX-2 selective NSAID (continue gastric protection;[2] also see p.325).

Bowel obstruction

See parenteral administration.

Paraneoplastic sweating

- **ranitidine** 150mg PO b.d.; benefit is generally seen within 2–3 days.[7]

Parenteral administration

If the PO route is unavailable, **ranitidine** 50mg can be administered IM/IV t.d.s–q.d.s. Although unauthorized, some centres use the SC route:

- **ranitidine** 50mg SC b.d.–q.d.s. *or*
- **ranitidine** 150–200mg/24h CSCI, using WFI or 0.9% saline as diluent.

CSCI compatibility with other drugs: limited clinical experience suggests that **ranitidine** is compatible with **diamorphine**, **fentanyl**, **haloperidol, hydromorphone**, **hyoscine butylbromide**, **methadone**, **metoclopramide, morphine sulfate**, **octreotide** and **oxycodone**.

There are mixed reports of *incompatibility* with **levomepromazine** and **midazolam**. Successful combinations at lower concentrations are reported; to minimize the risk of precipitation, **ranitidine** should always be the last drug added to an already diluted combination of drugs.

For more information, see the www.palliativedrugs.com SDSD; we encourage members to submit more combinations containing **ranitidine**.

Supply

Ranitidine (generic)
Tablets 150mg, 300mg, 28 days @ 150mg b.d. or 300mg at bedtime = £1.75.
Tablets effervescent 150mg, 300mg, 28 days @ 150mg b.d. or 300mg at bedtime = £29; *may contain Na^+*.
Oral solution 75mg/5mL, 28 days @ 150mg b.d. or 300mg at bedtime = £15; *may contain alcohol. Sugar-free versions available.*
Injection 25mg/mL, 2mL amp = £0.50.

Zantac® (GSK)
Tablets 150mg, 300mg, 28 days @ 150mg b.d. or 300mg at bedtime = £1.25.
Oral solution (sugar-free) 75mg/5mL, 28 days @ 150mg b.d. or 300mg at bedtime = £39; *contains 8% alcohol.*
Injection 25mg/mL, 2mL amp = £0.50.

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

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Updated (minor change) August 2016

PROTON PUMP INHIBITORS

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 *H. pylori* (with antibacterials), †prevention of degradation of pancreatin supplements (see Pancreatin, p.58).

Pharmacology

Proton pump inhibitors (PPIs) include **esomeprazole** (the *S*-enantiomer of **omeprazole**), **lansoprazole**, **omeprazole**, **pantoprazole** and **rabeprazole**. Following absorption they are selectively taken up by gastric parietal cells and converted into active metabolites which irreversibly inhibit the proton pump (H^+/K^+-ATPase), thereby blocking gastric acid secretion.

PPIs provide symptomatic relief of acid dyspepsia and acid reflux, help prevent and heal peptic ulcers (including those associated with NSAIDs), and reduce the risk of recurrent ulceration and rebleeding.[1–3] Because of their greater acid suppression and/or tolerability, PPIs are generally preferred over H_2 antagonists (p.27) and **misoprostol**, which is now rarely used.[4] However, H_2 antagonists are more effective than PPIs in reducing the volume of gastric secretions, which may be an advantage in some situations, e.g. bowel obstruction (see p.27).

There is relatively little comparative data to guide the choice of one PPI over another on the basis of efficacy and thus factors such as patient preference, risk of drug interaction, cost, and local guidelines will determine choice.[4]

Because PPIs are rapidly degraded by acid, they are formulated as e/c granules or tablets. These dissolve in the duodenum where the drug is rapidly absorbed. The bio-availability of **lansoprazole** is reduced by food and the manufacturer recommends that it should be given ≥30min before food. However, the reduced bio-availability appears not to reduce efficacy.[5–7]

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.

Elimination is predominantly by metabolism in the liver to inactive derivatives excreted mostly in the urine. Most PPIs are metabolized via CYP2C19 and to a variable extent CYP3A4; the exception is **rabeprazole** which mostly undergoes non-enzymatic metabolism. CYP2C19 is subject to genetic polymorphism (see Chapter 19, p.719) with higher levels of activity associated with lower plasma concentrations of **omeprazole**, **lansoprazole** and **pantoprazole**, and higher rates of treatment failure, e.g. in *H pylori* eradication.[8,9]

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).

PPIs are an independent risk factor for *Clostridium difficile* infection (see p.496); and the association is stronger than for other acid-reducing agents.[10] Patients are at risk of recurrent *Clostridium difficile* colitis, up to nearly 5 times more likely.[11–16] 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 spores can live up to 6h on moist surfaces, long enough to allow transmission between patients.[17] The concomitant use of PPIs and antibacterials further increases the risk of *Clostridium difficile* infection.[18]

Drug interactions

PPIs increase gastric pH and this can affect the absorption of some drugs and formulations; generally, absorption is reduced, e.g. **itraconazole** (capsules only), **posaconazole**, antivirals and protein kinase inhibitors (seek specialist advice). However, rarely it can be increased, e.g. **digoxin** (high dose PPIs in the elderly) and **saquinivir;**[9] see respective SPCs for full details.

Esomeprazole and **omeprazole** are weak−moderate inhibitors of CYP2C19 (see Chapter 19, p.717). Important interactions include:

- inhibition of the metabolism of **citalopram** and **escitalopram**, increasing the risk of QT interval prolongation (see SSRIs, p.212 and Chapter 20, p.731); the maximum daily dose should be reduced (see SPC)[19]
- a reduction in the antithrombotic effect of **clopidogrel** (a pro-drug activated by CYP2C19); avoid concurrent use with any PPI, use an H_2 antagonist instead[20]
- inhibition of the metabolism of **diazepam**
- inhibition of the metabolism of **warfarin**; isolated reports of raised INR with all PPIs.[9]

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. The measurement of serum magnesium before starting a PPI and periodically thereafter has been suggested for patients using a PPI long-term.[21] However, a routine annual measurement in every patient appears unnecessary and should be reserved for older patients, particularly those taking **digoxin** or drugs which can cause hypomagnesaemia, e.g. diuretics (see p.588).[22]

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.[23]

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.[24]

Ocular damage has been reported, mostly with IV **omeprazole**.[25,26] 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**.

Dose and use

Dose recommendations are limited to **lansoprazole** and **omeprazole** (**esomeprazole** and **rabeprazole** are more expensive) and are mostly based on NICE guidance (see Table 2), which can differ from the SPC and BNF.[4]

The SPC for **lansoprazole** states that administration should be ≥30min before food in order to achieve 'optimal acid inhibition'. However, this precaution is unnecessary (see Pharmacology).

Table 2 NICE dose recommendations[4]

	Low-dose	*Standard dose*	*Double-dose*[a]
Lansoprazole	15mg once daily	30mg once daily	30mg b.d.
Omeprazole	10mg once daily	20mg once daily	40mg once daily

a. in severe hepatic impairment, do not exceed the standard dose.

Uninvestigated dyspepsia or reflux-like symptoms

- use standard dose PPI for 4 weeks; consider testing for *H pylori* in patients with dyspepsia
- subsequently, use the lowest effective dose either as long-term maintenance or, when symptoms infrequent, p.r.n.
- if there is an inadequate response to a PPI, switch to an H_2 antagonist.

Proven gastro-oesophageal reflux disease

- use standard dose PPI for 4–8 weeks
- subsequently, use the lowest effective dose either as long-term maintenance or, when symptoms infrequent, p.r.n.
- if there is an inadequate response to a PPI, switch to an H_2 antagonist.

Proven severe oesophagitis

- use **lansoprazole** 30mg PO or **omeprazole** 40mg once daily for 8 weeks
- if inadequate, increase the dose to b.d. or switch to an alternate PPI
- subsequently, use the lowest effective dose as long-term maintenance as necessary.

Peptic ulcer (including NSAID-related)

- stop any NSAIDs; if continuation is necessary, use long-term gastric protection after ulcer healing (see below)
- test for *H pylori*:
  - ▷ if negative, use standard dose PPI (or H_2 antagonist) for 4–8 weeks (8 weeks if continuing an NSAID)
  - ▷ if positive, and the ulcer is NSAID-related, use standard dose PPI (or H_2 antagonist) for 8 weeks, followed by eradication therapy (see BNF) *or*
  - ▷ if positive, and the ulcer is *not* NSAID-related, use eradication therapy first and then review (see BNF)
- if symptoms recur, use the lowest effective dose either as long-term maintenance or, when symptoms infrequent, p.r.n.

Gastric protection in patients taking an NSAID at high risk of peptic ulcer disease

- use standard dose PPI (or double-dose H_2 antagonist) *and*
- consider use of a COX-2 selective NSAID (continue gastric protection;[4] also see p.325).

Non-variceal upper-GI haemorrhage

- when bleeding or stigmata of recent bleeding is confirmed at endoscopy, use high-dose **omeprazole** 80mg PO/IV stat, followed by 8mg/h IVI (or 40mg b.d. PO) for 72h.[27]

For patients with swallowing difficulties, **lansoprazole** and **omeprazole** can be given as orodispersible or dispersible tablets respectively (Note. there is *no* SL absorption from orodispersible 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* (see Chapter 28, p.785).

Specific procedures are available from the manufacturers for administration by enteral feeding tubes (see Chapter 28, p.791). For patients with obstructive dysphagia and acid dyspepsia or with severe gastritis and vomiting, the rectal route has also been used.[28]

Parenteral administration

IV **omeprazole** (and **esomeprazole**) have been used in palliative care to treat painful reflux oesophagitis in patients unable to take PO medication.

Although PPIs are unauthorized for CSCI administration, there are case reports of such use:[29,30]

- **omperazole** 40mg for infusion diluted as per IVI (see supply) given by CSCI over 3–4h as a single daily dose for ≤4 days
- **esomeprazole** 40mg for infusion diluted in 50mL 0.9% normal saline and given by CSCI over 20min–1h as a single daily dose for ≤13 days.

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

Ranitidine given IV, SC or CSCI is an alternate, see p.28.

Supply

Lansoprazole (generic)
Capsules enclosing e/c granules 15mg, 30mg, 28 days @ 30mg each morning = £1.50.
Tablets orodispersible 15mg, 30mg, 28 days @ 30mg each morning = £5.50.

Zoton® (Pfizer)
Tablets orodispersible (FasTab®) 15mg, 30mg, 28 days @ 30mg each morning = £5.50.

Omeprazole (generic)
Capsules enclosing e/c granules or hard e/c capsule 10mg, 20mg, 40mg, 28 days @ 20mg each morning = £1.25.
Tablets e/c 10mg, 20mg, 40mg, 28 days @ 20mg each morning = £6.50.

Tablets dispersible enclosing e/c pellets 10mg, 20mg, 40mg, 28 days @ 20mg each morning = £12.
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 = £6.50.

Losec® (AstraZeneca)
Capsules enclosing e/c granules 10mg, 20mg, 40mg, 28 days @ 20mg each morning = £14.
Tablets dispersible (multiple-unit pellet system, MUPS®) ***enclosing e/c pellets*** 10mg, 20mg, 40mg, 28 days @ 20mg each morning = £12.

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

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

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LOPERAMIDE

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, in normal circumstances, 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 when used within the recommended dose range[2] (but see Drug interactions and Undesirable effects).

Unlike other drugs used for diarrhoea, e.g. **diphenoxylate** (in **co-phenotrope**) and **codeine**, loperamide has no analgesic effect in therapeutic or supratherapeutic doses. The lack of CNS effects is one reason why loperamide is a popular first-line choice for the control of diarrhoea, including that associated with short-bowel syndrome, radiotherapy or chemotherapy.[15,16]

However, **octreotide** (see p.544) 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.[15–17]

As an antidiarrhoeal, loperamide is about 3 times more potent mg for mg than **diphenoxylate** and 50 times more potent than **codeine**.[18] 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.[19,20] 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.[21]

Time to peak plasma concentration 2.5h (oral solution); 5h (capsules).[22]

Plasma halflife 11h[22] but up to 41h with doses of ≥16 mg/24h.[23]

Duration of action up to 3 days.[12]

Cautions

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.[24]

Patients with AIDS are at risk of toxic megacolon if loperamide is used in viral or bacterial colitis.

Severe hepatic impairment (see Chapter 18, p.703) can increase plasma concentrations of loperamide and the risk of undesirable effects, including suppression of consciousness.[25] This may also occur in children, particularly <2 years, who receive excessive doses.[26–28] If **naloxone** is considered necessary, repeated doses may be needed because loperamide has a longer duration of action than **naloxone** (see, p.457).

Loperamide should be used with caution in patients who are at risk of *torsade de pointes* or other cardiac arrhythmias, and in patients who are using drugs which can alter the absorption or metabolism of loperamide.

Loperamide has become a drug of abuse, both to prevent withdrawal from other opioids and also to bring about euphoria in high doses.[29] High doses are associated with QT prolongation and potentially fatal cardiac arrhythmias, e.g. Torsade de Pointes (see Chapter 20, p.731).

Many of the reports of loperamide-induced cardiac arrhythmias occurred when taken in higher than recommended doses (median 250mg/24h, range 70–1600mg), either for the treatment of diarrhoea or as a drug of abuse.[30] Cardiac arrhythmias have also been reported rarely in patients taking therapeutic doses when taking a CYP3A4 inhibitor concurrently (see below).[23]

Cardiac arrhythmias may occur if absorption is enhanced or metabolism inhibited (see Drug interactions below). *Loperamide should be considered in any case of unexplained cardiac arrhythmia.* Blood concentrations can be measured.[23]

Drug interactions

Loperamide triples the PO bio-availability of **desmopressin**, possibly by both reducing GI enzymic degradation and slowing GI motility.[31]

Some CYP3A4 and P-glycoprotein inhibitors, e.g. **itraconazole**, increase plasma concentrations of loperamide significantly. Generally, these increases have not been associated with significant CNS effects. However, because of the risk of cardiac arrhythmia with high loperamide plasma concentrations, caution should be taken with potent CYP3A4 or P-glycoprotein inhibitors (see Chapter 19, Table 8, p.725).

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

Confirm that the diarrhoea is not secondary to faecal impaction.

In severe diarrhoea, ensure adequate fluid and electrolyte replacement is given, e.g. by using oral rehydration salts or IV fluids.

Note. For patients on a sodium-restricted diet, Imodium® *oral solution* contains Na^+ 4.85mg/5mL.

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.544)
- if severe, use **octreotide** first-line.

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. It is occasionally necessary to increase the dose to 32mg/24h; *this is twice the recommended maximum daily dose*. Such doses should *not* be used in conjunction with a CYP3A4 inhibitor (see Drug interactions above), or in someone at risk of a cardiac arrhythmia.

High-output stoma/ileostomy or intestinal fistula

Above-recommended doses of loperamide, e.g. 10mg q.d.s., may be necessary to reduce stoma or fistula output to manageable volumes. In specialist centres in the UK, 64mg/24h is regarded as the usual maximum dose, while recognizing that it may occasionally be beneficial to increase the dose to 96mg/24h.[1] Such doses should *not* be used in conjunction with a CYP3A4 inhibitor (see Drug interactions above), or in someone at risk of a cardiac arrhythmia. However, **octreotide** (± lower-dose loperamide) is probably a better option (see p.544).

Supply

Loperamide (generic)
Capsules 2mg, 5 days @ 2mg p.r.n., max 16mg/24h = £1.25.
Tablets 2mg, 5 days @ 2mg p.r.n., max 16mg/24h = £3.

Imodium® (Janssen)
Orodispersible tablets 2mg, 5 days @ 2mg p.r.n., max 16mg/24h = £5.
Oral solution (sugar-free) 1mg/5mL, 5 days @ 2mg p.r.n., max 16mg/24h = £11; *contains alcohol; also contains Na^+ 4.85mg/5mL.*

With **simeticone**
Imodium® Plus (McNeil)
Caplets (capsule-shaped tablets) containing loperamide 2mg, **simeticone** 125mg, 5 days @ 1 p.r.n., max 4 caplets/24h = £6.

Loperamide capsules are available to purchase OTC for acute diarrhoea.

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LAXATIVES

There is limited RCT evidence about laxative use in palliative care patients.[1] Consequently, guidelines for the management of constipation in palliative care are based largely on consensus best practice and expert opinion.[1–4]

Constipation is common in advanced cancer,[5] 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,[2] 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[6,7]
- *disordered rectal evacuation:* the need to strain when defaecating.[6]

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).

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[a] 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®)
Stimulant laxatives	Act via direct contact with the submucosal and myenteric plexus in the large bowel, resulting in rhythmic muscle contractions and improved intestinal motility. Also increase water secretion into the bowel lumen, thereby adding a degree of softening	Bisacodyl Dantron Senna Sodium picosulfate
Lubricants	Coat the surface of the stool to make it more slippery and easier to pass	Liquid paraffin[b] Arachis oil
Bulk-forming agents (fibre)	Increase 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®) Methylcellulose (e.g. Celevac®) Sterculia (e.g. Normacol®)

a. reflects predominant action; at doses >400mg/24h also has a stimulant effect

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

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.50).[8] Conversely, stimulant laxatives reduce water absorption from the faeces and thus have a softening action (see p.46).

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.49).

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

There is evidence for the benefit of some laxatives, e.g. **bisacodyl**, **sodium picosulphate**, **macrogols**, compared with placebo. However, these laxatives are rarely used as the comparator arm in RCTs of new medications.[9]

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

- an appreciation of the pathophysiology of constipation (particularly opioid-induced),[2,16] 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

- 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.[2,19] However, the results of the RCT which compared **senna** alone with **senna** and **docusate** in hospice patients (see Table 2)[15] and comparable results from a non-randomized non-blinded sequential cohort study in cancer inpatients[10] suggest that it is reasonable to prescribe a stimulant laxative alone, at least initially[20]
- 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.[2,3]

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

Rectal products available for the management of constipation include suppositories and enemas (see Rectal products, p.55). 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.

About one third of palliative care patients 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.44).

A Cochrane review of the management of constipation and faecal incontinence in patients with central neurological disease included 22 trials and 902 patients with diagnoses such as Parkinson's disease, multiple sclerosis and spinal cord injuries. The review concluded that there was limited evidence supporting bulk-forming laxatives (**ispaghula**) or **macrogols** (and also abdominal massage and transanal irrigation).[23]

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.[24–26] Opioids cause constipation by increasing ring contractions, decreasing propulsive intestinal activity, and by enhancing the resorption of fluid and electrolytes.[27,28] Tolerance does not develop to these effects.[29] 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.[30] Thus, as a general rule, all patients prescribed **morphine** (or other opioid) should also be prescribed a laxative (see p. 42).

Methylnaltrexone, a peripherally-acting opioid antagonist, represents an additional approach to the management of opioid-induced constipation (see p.42 and p.466). 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.[1]

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Quick Clinical Guide: Opioid-induced constipation

Generally, all patients prescribed an opioid should also be prescribed a stimulant laxative, with the aim of achieving 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 bisacodyl or senna and titrate the dose according to response:

Bisacodyl

If *not* constipated:

- generally start with 5mg at bedtime
- if no response after 24–48h, increase to 10mg at bedtime.

If already constipated:

- generally start with 10mg at bedtime
- if no response after 24–48h, increase to 20mg at bedtime
- if no response after a further 24–48h, consider adding a second daytime dose
- if necessary, consider increasing to a maximum of 20mg t.d.s.

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.

An oral solution (7.5mg/5mL) is an alternative to tablets; it is tasteless and generally cheaper.

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 and/or there has been no bowel evacuation within 3–4 days of commencing a stimulant, add a faecal softener laxative and titrate as necessary, e.g.:

- macrogols (e.g. Movicol®) one sachet each morning *or*
- lactulose 15mL once daily–b.d.

8 In a patient receiving opioids, if adequately titrated oral laxatives + rectal interventions fail to produce the desired response, consider SC methylnaltrexone.

Methylnaltrexone

Methylnaltrexone is a peripherally acting opioid antagonist administered as a SC injection. It is relatively expensive and should be considered in patients with opioid-induced constipation only when the optimum use of laxatives is ineffective. In patients with advanced disease, because constipation is generally multifactorial in origin, methylnaltrexone is added to the existing laxative regimen.

- 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 and vomiting; these generally resolve after a bowel movement; postural hypotension can also occur
- about 1/3–1/2 of patients given methylnaltrexone have a bowel movement within 4h. The bowel movement can occur rapidly, consider having pads and a commode in place, particularly in those with poor mobility.

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.

Updated August 2016

Quick Clinical 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 1.5–2h
- 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 August 2017

ISPAGHULA (PSYLLIUM) HUSK

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

Ispaghula husk (generic)
Oral granules 3.5g/sachet, 28 days @ 1 sachet b.d. = £5; *low Na^+; sugar- and gluten-free; plain, lemon or orange flavour*.

Updated (minor change) July 2017

STIMULANT LAXATIVES

Indications: Prevention and treatment of constipation.

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

Pharmacology

Stimulant laxatives act through direct contact with the submucosal (Meissner's) plexus and the deeper myenteric (Auerbach's) plexus, resulting in both a motor and a secretory 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 and a pro-drug. It passes unabsorbed and unchanged through the small intestine as an inactive glycoside 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 is a synthetic anthranoid. It is not a glycoside, and has a direct action on 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.

Bisacodyl and **sodium picosulfate** are phenolics and are both pro-drugs. They are hydrolyzed to the same active metabolite bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM).[1] **Bisacodyl** is hydrolyzed by *intestinal enzymes* and, when applied directly to the intestinal mucosa in normal subjects, it induces powerful propulsive motor activity within minutes.[3] To ensure a laxative effect in the colon after oral intake, **bisacodyl** is formulated as an e/c tablet. **Sodium picosulfate** is hydrolyzed by *colonic bacteria*, and thus potentially has a more uncertain action because of its dependence on bacterial flora.

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]

There is convincing evidence supporting the efficacy of **bisacodyl** versus placebo and **sodium picosulphate** versus placebo in patients with chronic constipation.[5–7]

Phenolphthalein (not UK) is a stimulant laxative that is present in some proprietary laxatives, e.g. Fam-Lax. It is generally *not* recommended for use in palliative care as it can cause a drug rash or photosensitivity. Rarely, it causes encephalitis which can be fatal. It is also associated with increased risk of developing cancer. Laxatives containing this are prohibited in many countries.[8]

To date, RCTs of stimulant laxatives in palliative care patients have failed to show clinically meaningful differences (see Laxatives, Table 2, p.40). 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).[9]

In the past, a combination of a bowel stimulant with a stool softener was often prescribed in palliative care patients.[10,11] However, the results of the RCT which compared **senna** alone with **senna** and **docusate** in hospice patients (see Laxatives, Table 2, p.40)[12] and comparable results from a non-randomized non-blinded sequential cohort study in cancer inpatients suggest that *generally a stimulant laxative alone will be satisfactory*.[13] In countries where combined products are not available, this will also reduce the patient's tablet load.[14]

If a stimulant laxative is used alone but a satisfactory result is not achieved despite dose titration in a week, consider adding **docusate**. If faecal leakage occurs, the dose of this will need to be reduced.[10,15]

Onset of action

Bisacodyl tablets 6–12h;[4] suppositories 10–45min.[1]
Dantron 6–12h.
Senna 8–12h.
Sodium picosulfate 6–24h (median 12h).[9]

Cautions

Because very high doses in rodents revealed a carcinogenic risk,[16–18] 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.

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 QCG: Opioid-induced constipation, p.42).[19–22] Likewise, there is need for a protocol for patients with paraplegia and tetraplegia (see QCG: Bowel management in paraplegia and tetraplegia, p.44).

Bisacodyl

If *not* constipated:
- generally start with 5mg PO at bedtime
- if no response after 24–48h, increase to 10mg at bedtime.

If already constipated:
- generally start with 10mg PO at bedtime
- if no response after 24–48h, increase to 20mg at bedtime
- if no response after a further 24–48h, consider adding a second daytime dose
- if necessary, consider increasing to a maximum of 20mg t.d.s.

By suppository: give 10–20mg PR once daily. For an optimal result, it is best to give **bisacodyl** suppositories *30min after breakfast* and thereby co-ordinate the drug response with the gastrocolonic reflex.[23]

Dantron

Because of the undesirable effects and cost (see Supply), other stimulant laxatives are preferred.

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.

Senna oral solution (7.5mg/5mL) can be used instead of tablets; it is tasteless and odourless.

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.[9]

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

Supply

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

Dantron
Co-danthramer (**dantron** and **poloxamer 188**) (generic)
***Oral suspension* co-danthramer** 25/200 in 5mL (**dantron** 25mg, **poloxamer 188** 200mg/5mL), 28 days @ 10mL at bedtime = £136.
***Strong oral suspension* co-danthramer** 75/1000 in 5mL (**dantron** 75mg, **poloxamer 188** 1g/5mL), 28 days @ 5mL at bedtime = £136.

Co-danthrusate (**dantron** and **docusate sodium**) (generic)
***Capsules* co-danthrusate** 50/60 (**dantron** 50mg, **docusate sodium** 60mg), 28 days @ 2 at bedtime = £46.
***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 b.d. = £3.75.

Senokot® (Reckitt Benckiser)
Oral solution (sugar-free) total **sennosides** 7.5mg/5mL, 28 days @ 10mL b.d.= £5.50.

Sodium picosulfate (generic)
Oral solution (elixir) 5mg/5mL, 28 days @ 10mL at bedtime = £6.50; *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.

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Updated August 2017

DOCUSATE SODIUM

Class: Surface-wetting agent (faecal softener).

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

Contra-indications: Fructose or sorbitol intolerance (capsules contain sorbitol).

Pharmacology

Although sometimes classified as a stimulant laxative, docusate sodium is principally an emulsifying and wetting agent. In most patients, it has a relatively weak effect on GI transit at doses commonly used (≤400mg/24h). 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

Despite evidence suggesting it is generally unnecessary, many centres still routinely use docusate in combination with a stimulant laxative, e.g. **senna**, **bisacodyl** (see p.46). Docusate is often used alone for patients with persistent partial bowel obstruction. Dose varies according to individual need:

- generally start with 100mg PO b.d.
- if necessary, increase to 200mg b.d.–t.d.s.; *the latter is higher than the authorized maximum dose of 500mg/day.*

Docusate can also be used as an enema (see Rectal products, p.55).

Supply

Docusate sodium (generic)

Capsules 100mg, 28 days @ 100mg b.d. = £4.

Oral solution (sugar-free) 12.5mg/5mL, 50mg/5mL, 28 days @ 100mg b.d. = £15.

For combination products containing docusate and **dantron** (**co-danthrusate**) or **poloxamer 188** and **dantron** (**co-danthramer**), see Stimulant laxatives, p.46.

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Updated August 2017

LACTULOSE

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.51), 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.
Oral solution (sachets) 10g/15mL sachet, 28 days @ one sachet b.d. = £14.

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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.* (2010) Lactulose versus polyethylene glycol for chronic constipation. *Cochrane Database of Systematic Reviews*. **7**: CD007570. www.thecochranelibrary.com

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MACROGOLS (POLYETHYLENE GLYCOLS)

Class: Osmotic laxative.

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

Contra-indications: Acute inflammatory bowel disease, bowel obstruction, paralytic ileus.

Pharmacology

Macrogol 3350 is available in the UK (the number refers to the molecular weight). It acts 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 **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] However, the volume per dose of macrogols is 5–10 times greater than **lactulose** (see p.50); this will be unacceptable to many patients.

A systematic review in children suggested that macrogols may be better than other treatments but the evidence is poor.[7] However, in faecal impaction in children, macrogols are no better than enemas, and cause more faecal incontinence.[8] Children also find macrogols less palatable than **lactulose**.[9] They are also more expensive.

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

Cautions

Stop treatment if symptoms of fluid and electrolyte shift occur (see Undesirable effects).

Macrogol 3350 *concentrated oral liquid* contains ethanol and a large amount of benzyl alcohol. 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.

Drug interactions

There are reports of decreased effect of other drugs when taken at the same time as macrogols, e.g. anti-epileptics. Accordingly, other drugs should not be taken within an hour of taking macrogol.[10]

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

Macrogol 3350 is generally formulated with electrolyes and is available as an oral powder sachet, a concentrated oral liquid and an oral solution sachet. The powder and concentrated liquid products need to be dissolved or diluted in water:

- dissolve one sachet of oral powder in half a glass of water (about 125mL) *or*
- dilute 25mL of the concentrated oral liquid with 100mL water (total volume 125mL).

Half-strength macrogol 3350 (with electrolytes) and Paediatric oral powder sachets are available for fine-tuning the dose and should be dissolved in a quarter of a glass of water (about 60mL).

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

Note. Although the 25mL oral solution sachet (Movicol® Ready to Take) does not require further dilution, it is recommended that patients drink 2–2.5L fluid/24h to maintain good health.

Constipation

- start with one sachet or 125mL of *diluted* oral liquid concentrate PO once daily
- if necessary, increase to b.d. or t.d.s.

Faecal impaction

The concentrated oral liquid is not authorized for faecal impaction (see Cautions).

- start with eight sachets PO on day 1, taken in <6h
- patients with cardiovascular impairment should restrict intake to two sachets/h
- if necessary, repeat on days 2 and 3; most patients do not need the full dose on the second day.

For convenience, all eight oral powder 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.

Note. For Movicol® Ready to take sachets, although the product itself does not require dilution, patients are recommended to take an additional 1L fluid.

Supply

Macrogol 3350 with electrolytes: sodium bicarbonate, sodium chloride and potassium chloride *(Containing per sachet or 25mL dose of oral liquid: Na^+ = 8mmol, K^+ = 0.7mmol, Cl^- = 7mmol and bicarbonate = 2mmol)*.

Movicol® (Norgine)
Oral powder macrogol 3350 = 13.125g, 28 days @ one sachet once daily = £7; *available in plain (sugar-free), lime-lemon and chocolate flavour. Other brands include CosmoCol®, Laxido®, Macilax®, Molaxole®, Molative®; not all have the full range of flavours available.*
Concentrated oral liquid macrogol 3350 = 13.125g/25mL, 28 days @ 25mL (diluted with 100mL water) once daily = £7; *orange flavour, contains ethanol and benzyl alcohol.*

Movicol® Ready to take (Norgine)
Oral solution (sachet) macrogol 3350 = 13.125g, 25mL sachet, 28 days @ one sachet once daily = £3.50

Movicol-Half® (Norgine)
Oral powder macrogol 3350 = 6.563g, 28 days @ one sachet once daily = £4: *lime-lemon flavour (sugar-free).*
Other brands include CosmoCol-Half®.

Paediatric sachets are also available for children aged ≤12 years (see *BNFc*).

Note. Magrogol 3350 (with other salts and electrolytes) is available as Moviprep® and Klean-prep®; authorized for bowel cleansing before radiological examination, colonoscopy or surgery.

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. www.thecochranelibrary.com
7 Gordon M *et al.* (2016) Osmotic and stimulant laxatives for the management of childhood constipation. *Cochrane Database of Systematic Reviews*. **8**: CD009118. www.thecochranelibrary.com
8 Bekkali NL *et al.* (2009) Rectal fecal impaction treatment in childhood constipation: enemas versus high doses oral PEG. *Pediatrics*. **124**: e1108–1115.
9 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.
10 Galen (2015) Laxido orange, powder for oral solution SPC, www.medicines.org.uk

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MAGNESIUM SALTS

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 (see p.589).

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.1).

Dose and use

For the treatment of hypomagnesaemia, see p.588.
For use of magnesium in antacids, see p.1.

Magnesium hydroxide

For opioid-induced constipation (see QCG: Opioid-induced constipation, p.42), 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; mix with water before administration
- 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.46).

Magnesium sulfate

A typical dose is 5–10g of crystals/powder (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

Oral suspension hydrated magnesium oxide 415mg (7.1mmol elemental magnesium)/5mL, 28 days @ 15mL b.d. = £14; available OTC as Phillips' Milk of Magnesia®; *do not store in a cold place*.

Magnesium sulfate

Oral powder (Epsom Salts) 4mmol/g elemental magnesium, 28 days @ 5g once daily = £1; also Original Andrew's Salts® (magnesium sulfate, citric acid, sodium bicarbonate).

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 methylnaltrexone for the management of constipation in palliative care patients. *Cochrane Database of Systematic Reviews*. CD003448. www.thecochranelibrary.com

Updated August 2017

RECTAL PRODUCTS FOR CONSTIPATION

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.51).[2,3]

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

Rectal laxative	*Dose/volume*	*Predominant mode of action*	*Time to effect*[b]
Suppositories[c]			
Bisacodyl	10mg	Stimulates propulsive activity after hydrolysis by enteric enzymes[4]	10–45min
Glycerol	4g	Hygroscopic; softens and lubricates	15–30min
Enemas[d]			
Osmotic micro-enema	5mL	Faecal softener and osmotic effect (see text below)	15min
Osmotic standard phosphate enema	118–128mL	Osmotic effect	2–5min
Docusate sodium micro-enema	120mg in 10g	Faecal softener (surface-wetting agent), some direct stimulant action	5–20min
Arachis (peanut) oil retention enema	130mL	Faecal softener	Overnight retention enema

a. PR digital examination will indicate the most appropriate intervention
b. as stated in SPC
c. suppositories should be administered only if there are faeces in the rectum; place in contact with the rectal mucosa
d. warm enemas to room temperature before use.

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.46). 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.49), whereas **sodium citrate** draws fluid into the bowel 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
Bisacodyl (generic)
Suppositories 5mg,10mg, 12 = £3.50.

Glycerol (generic)
Suppositories glycerol 700mg/1g, gelatin 140mg/1g, adult suppositories 4g, 12= £1.25.

Enemas
Docusate sodium (generic)
Norgalax® (Essential Pharma)
Micro-enema 120mg in 10g single-use disposable pack, one enema = £4.50.

Sodium citrate (generic)
Micro-enema 90mg/mL with **sodium lauryl sulfoacetate**, **glycerol** and **sorbitol**, supplied in 5mL single-dose disposable packs with nozzle, 5mL = £0.50.

Phosphate enema BP Formula B (generic)
Enema **sodium phosphate** 10.24g, **sodium acid phosphate** 12.8g, in 128mL, standard tube = £4, long rectal tube = £28.

Cleen Ready-to-use® (Casen Recordati)
Enema **sodium phosphate** 9.4g, **sodium acid phosphate** 21.4g, in 118mL, standard tube = £0.75.

Arachis (peanut) oil (generic)
Retention enema 1mg/mL, single-dose disposable pack, 130mL = £48; *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.

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PRODUCTS FOR HAEMORRHOIDS

Because haemorrhoids can be more troublesome if associated with the evacuation of hard faeces, constipation must be corrected (see Laxatives, p.38).

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; see p.81).

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 = £6.25.

Corticosteroid plus astringent
Anusol HC® (McNeil)
***Ointment* hydrocortisone acetate** 0.25%, **zinc oxide**, **benzyl benzoate**, **bismuth oxide**, **bismuth subgallate**, **Peru balsam** 30g = £2.50. (Also available OTC as Anusol Plus HC ointment).

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

Corticosteroid plus local anaesthetic and astringent
Xyloproct® (Astra Zeneca)
Ointment (water miscible) **hydrocortisone acetate** 0.275%, **lidocaine** 5%, **aluminium acetate** 3.5%, **zinc oxide**, 20g (with applicator) = £4.25.

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 May 2015

PANCREATIN

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 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.

Pancreatin has been used to clear feed-related blockages in enteral feeding tubes. However, this should only be considered when other options have failed (see Chapter 28, p.791).[5]

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; higher strength Creon® 25,000 and Creon® 40,000 have 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, all derived from pigs. Creon® is a good choice in terms of cost and range of strengths available. 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 starts to dissolve 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)

Granules **(*gastro-resistant*)** Creon® Micro, lipase 5,000 units, amylase 3,600 units, protease 200 units in 100mg (measuring scoop provided), 28 days @ 100mg t.d.s. = £13.

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.

Higher strength capsules (enclosing gastro-resistant granules)

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. = £70.

See BNF for other products available.

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.

5 White R and Bradnam V. *Handbook of Drug Administration via Enteral Feeding Tubes*. London: Pharmaceutical Press www.medicinescomplete.com (accessed June 2015).

Updated July 2015