

# 1: GASTRO-INTESTINAL SYSTEM

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## ANTACIDS

## BNF I.I.I

Antacids taken by mouth to neutralize gastric acid include:

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

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

The sodium content of some antacids may be detrimental in patients on salt-restricted diets, e.g. those with hypertension or heart failure; Gaviscon<sup>®</sup> Liquid (available OTC), Peptac<sup>®</sup> oral suspension and **magnesium trisilicate mixture BP** contain 6mmol/10ml compared with 0.1nmol/10ml in **co-magaldrox**. Regular use of **sodium bicarbonate** may cause sodium loading and metabolic alkalosis. **Calcium carbonate** may cause rebound acid secretion about 2h after each dose, and regular use may cause hypercalcaemia, particularly if taken with **sodium bicarbonate**.

**Aluminium hydroxide** binds dietary phosphate. It is of benefit in patients with hyperphosphataemia in renal failure. Long-term complications of phosphate depletion and osteomalacia are not an issue in advanced cancer. **Hydrotalcite** binds bile salts and is of specific benefit in patients with bile salt reflux, e.g. after certain forms of gastroduodenal surgery.

In post-radiation oesophagitis and candidosis which is causing painful swallowing, an **aluminium hydroxide-magnesium hydroxide** suspension containing **oxetacaine**, a local anaesthetic, can be helpful; this is unlicensed in the UK. Give 5–10ml (without fluid) 15min a.c. & o.n., and p.r.n. before drinks. This should be regarded as short-term symptomatic treatment while time and specific treatment of the underlying condition permits healing of the damaged mucosa. Alternatively, plain **benzocaine** suspension can be used (see p.427).

The following should be borne in mind:

- the administration of antacids should be separated from the administration of e/c tablets; direct contact between e/c tablets and antacids may result in damage to the enteric coating with consequential exposure of the drug to gastric acid, and of the stomach mucosa to the drug
- apart from **sodium bicarbonate**, antacids delay gastric emptying and may thereby modify drug absorption
- some proprietary products contain peppermint oil which masks the chalky taste of the antacid and helps belching by decreasing the tone of the lower oesophageal sphincter

- most antacid tablets feel gritty when sucked; some patients dislike this
- some proprietary products are fruit-flavoured, e.g. Tums<sup>®</sup> (chewable tablet)
- the cheapest single-ingredient products are **magnesium trisilicate mixture BP** and **aluminium hydroxide** chewable tablets; if a combination is required, the cheapest product is Mucogel<sup>®</sup>
- some antacids contain additional substances for use in specific situations, e.g. alginates (see below), **simeticone** (silica-activated **dimeticone**) (see p.3).

Nowadays, antacids are generally only used p.r.n. for occasional dyspepsia; H<sub>2</sub>-receptor antagonists (see p.15) and PPIs (see p.19) are used when continuous gastric acid reduction is indicated.<sup>1</sup>

## Supply

**Aluminium hydroxide** (non-proprietary)

**Tablets chewable** 500mg, 28 days @ 2 t.d.s. & o.n. = £3.

**Magnesium trisilicate mixture BP** (non-proprietary)

**Oral suspension** 28 days @ 10ml t.d.s. & o.n. = £3.50; *peppermint flavour.*

## Co-magaldrox

Maalox<sup>®</sup> (Sanofi-Aventis)

**Oral suspension (sugar-free) co-magaldrox** 195/220 (**magnesium hydroxide** 195mg, **aluminium hydroxide** 220mg/5ml), 28 days @ 10ml t.d.s. & o.n. = £6; *low Na<sup>+</sup>.*

Mucogel<sup>®</sup> (Forest)

**Oral suspension (sugar-free) co-magaldrox** 195/220 (**magnesium hydroxide** 195mg, **aluminium hydroxide** 220mg/5ml), 28 days @ 10ml t.d.s. & o.n. = £4; *low Na<sup>+</sup>.*

**Hydrotalcite** (non-proprietary)

**Oral suspension** 500mg/5ml, 28 days @ 10ml t.d.s. & o.n. = £4.50; *low Na<sup>+</sup>.*

With **oxetacaine**

**Oral suspension oxetacaine** 10mg, **aluminium hydroxide** 200mg, **magnesium hydroxide** 100mg/5ml, 28 days @ 10ml t.d.s. a.c. & o.n. = £41. (Unlicensed, available as a special order from Rosemont; see Special orders and named patient supplies, p.577). Available as *Mucaine<sup>®</sup> suspension (Wyeth) in some countries.*

<sup>1</sup> NICE (2004) *Dyspepsia. Management of dyspepsia in adults in primary care.* In: Clinical Guideline 17. National Institute for Clinical Excellence. Available from: [www.nice.org.uk/page.aspx?o=CG017](http://www.nice.org.uk/page.aspx?o=CG017)

## COMPOUND ALGINATE PRODUCTS

## BNF I.1.2

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

**Class:** Alginate.

**Indications:** Acid reflux ('heartburn').

### Pharmacology

Several antacid products containing alginic acid or its salts are available in the UK. They 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 an H<sub>2</sub>-receptor antagonist or a PPI (reduces acid) and/or an antifatulent (reduces air bubbles). Gaviscon<sup>®</sup> Liquid, Gaviscon<sup>®</sup> Advance and Peptac<sup>®</sup> oral suspension (sodium alginate products) are 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.<sup>1</sup> Compound alginate products have been largely superseded by acid suppression with H<sub>2</sub>-receptor antagonists and PPIs.

**Onset of action** < 5min.

**Duration of action** 1–2h.

### Cautions

Gaviscon<sup>®</sup> Liquid and Peptac<sup>®</sup> oral suspension contain Na<sup>+</sup> 6mmol/10ml dose, and Gaviscon<sup>®</sup> Advance oral suspension and tablets contain Na<sup>+</sup> 2.3mmol/5ml dose and Na<sup>+</sup> 2.3mmol/tablet respectively. They should not be used in patients requiring a salt-restricted diet, e.g. those with fluid retention, heart failure or renal impairment.

### Dose and use

Several preparations are available but none is recommended. For patients already taking Gaviscon<sup>®</sup> or Peptac<sup>®</sup> and who are reluctant to change to **co-magaldrox** (or similar option), prescribe Peptac<sup>®</sup> suspension 10–20ml, Gaviscon<sup>®</sup> Advance suspension 5–10ml or Gaviscon<sup>®</sup> Advance 1–2 tablets p.c. & o.n., and p.r.n.

### Supply

See BNF for products prescribable on the NHS; Gaviscon<sup>®</sup> Liquid is 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.

## SIMETICONE

## BNF I.I.I

**Class:** Antifoaming agent (antiflatulent).

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

### Pharmacology

Simeticone (silica-activated dimeticone or dimethylpolysiloxane) is a mixture of liquid dimeticones with silicon dioxide. It is an antifoaming agent present in several proprietary antacids, e.g. Asilone<sup>®</sup>. By facilitating belching, simeticone eases flatulence, distension and postprandial gastric discomfort. Simeticone-containing antacids are as effective as alginate-containing products in the treatment of acid reflux.<sup>1</sup> Asilone<sup>®</sup> should be used in preference to Gaviscon<sup>®</sup> Liquid, Gaviscon<sup>®</sup> Advance oral suspension or Peptac<sup>®</sup> oral suspension because it is cheaper and contains much less sodium.

**Onset of action** < 5min.

**Duration of action** 1–2h.

### Cautions

Although Asilone<sup>®</sup> contains both **aluminium** and **magnesium**, at higher doses (e.g. 30–60ml q.d.s. or more) the laxative effect of **magnesium** will override the constipating effect of **aluminium**.<sup>2</sup>

### Dose and use

- Start with Asilone<sup>®</sup> suspension 5ml p.r.n., or 5ml q.d.s. & p.r.n.
- if necessary, double dose to 10ml.

**Supply**Asilone<sup>®</sup> (Thornton & Ross)**Oral suspension (sugar-free)** simeticone 135mg, dried **aluminium hydroxide** 420mg, light **magnesium hydroxide** 70mg/5ml, 28 days @ 5ml q.d.s. = £4.50; low Na<sup>+</sup>.

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

**ANTIMUSCARINICS  
(ANTICHOLINERGICS)****BNF 1.2, 4.6 & 15.1.3****Indications:** Smooth muscle spasm (e.g. bladder, intestine), motion sickness (**hyoscine hydrobromide** TD), drying secretions (including surgical premedication, †sialorrhoea, †drooling, †death rattle and †inoperable intestinal obstruction), †paraneoplastic pyrexia and sweating.**Contra-indications:** See individual monographs.**Pharmacology**

Antimuscarinics are classified chemically as tertiary amines or quaternary ammonium compounds. The naturally-occurring belladonna alkaloids, **atropine**, **hyoscyamine (l-atropine)**, and **hyoscine hydrobromide**, are all tertiary amines, whereas the numerous semisynthetic and synthetic derivatives fall into both categories. Thus, **dicycloverine (dicyclomine)**, **oxybutynin** and **tolterodine** are tertiary amines, and **glycopyrronium**, **propantheline** and **hyoscine butylbromide** are quaternary ammonium compounds.

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

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

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

However, at least five different types of muscarinic receptors have been identified,<sup>2</sup> and newer drugs tend to be more selective in their actions. Thus, **oxybutynin** and **tolterodine** are relatively selective for muscarinic receptors in the urinary tract (see p.390).

Except when a reduction of oropharyngeal secretions is intended, dry mouth is an almost universal *undesirable* effect with this class of drugs. The secretion of saliva is mainly under the control of the autonomic nervous system. Food in the mouth causes reflex secretion of saliva, and so does stimulation by acid of afferent vagal fibres in the lower oesophagus. Stimulation of the parasympathetic nerves causes profuse secretion of watery saliva, whereas stimulation of the sympathetic nerve supply causes the secretion from only the submaxillary glands of small quantities of saliva rich in organic constituents.<sup>3</sup> If the parasympathetic supply is interrupted, the salivary glands atrophy, whereas interruption of the sympathetic supply has no such effect. The muscarinic receptors in salivary glands are very responsive to antimuscarinics and inhibition of salivation occurs at lower doses than required for other antimuscarinic effects.<sup>4</sup> This reduces the likelihood of undesirable effects when antimuscarinics are given to reduce salivation. In some patients, a reduction in excess saliva results in improved speech.<sup>5</sup>

To reduce the risk of undesirable effects, e.g. the development of an agitated delirium (central antimuscarinic syndrome), the concurrent use of two antimuscarinic drugs should generally be avoided (Box 1.B). Likewise, the concurrent use of an antimuscarinic and an opioid should be avoided as far as possible. Both cause constipation (by different mechanisms) and, if used together,

**Box 1.A** Peripheral antimuscarinic effects**Visual**

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

**Cardiovascular**

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

**Gastro-intestinal**

Dry mouth  
Heartburn (relaxation of lower oesophageal sphincter)  
Constipation

**Urinary tract**

Hesitancy of micturition  
Retention of urine

**Skin**

Reduced sweating  
Flushing

will result in an increased need for laxatives, and may even result in a paralytic ileus. On the other hand, **morphine** and **hyoscine butylbromide** or **glycopyrronium** are sometimes purposely combined in terminally ill patients with inoperable intestinal obstruction in order to prevent colic and to reduce vomiting.<sup>6</sup>

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

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

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

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

**Table 1.1** Pharmacokinetic features of antimuscarinic drugs used for death rattle

	Bio-availability	Plasma halflife	Duration of action (antisecretory)
Atropine	[readily absorbed]	4h	no data
Hyoscyamine (l-atropine) <sup>a</sup>	[readily absorbed]	3–5h	no data
Hyoscine hydrobromide	60–80% SL	5–6h	1–9h
Hyoscine butylbromide	8–10% PO	5–6h	<2h <sup>b</sup>
Glycopyrronium	<5% PO	1.7h	7h

a. not UK

b. in volunteers; possibly longer in moribund patients.

## Cautions

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

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

The increased gastro-intestinal transit time produced by antimuscarinics may allow increased drug absorption from some formulations, e.g. **digoxin** and **nitrofurantoin** from tablets and **potassium** from m/r tablets, but reduced absorption from others, e.g. **paracetamol** tablets. Dissolution and absorption of **glyceryl trinitrate** SL tablets may be reduced because of decreased saliva production.

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

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

## Dose and use

### Antispasmodic

Antimuscarinics are used to relieve smooth muscle spasm in the bladder (see **oxybutynin**, p.390) and rectum.

### Antispasmodic and antisecretory

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

**Table 1.2** Antisecretory and antispasmodic drugs: typical SC doses

Drug	Stat dose	CSCI drug/24h
Atropine	400microgram	1200–2000microgram
Hyoscine hydrobromide	400microgram	1200–2000microgram
Hyoscyamine (l-atropine) <sup>a</sup>	200microgram	600–1000microgram
Glycopyrronium	200microgram	600–1200microgram
Hyoscine butylbromide	20mg	20–300mg <sup>b</sup>

a. not UK

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

**Antisecretory****Sialorrhoea and drooling**

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

- **glycopyrronium** PO, solution and tablets (see p.441)
- **hyoscyamine** drops 125microgram/ml, 2ml SL q4h p.r.n. but the relatively large volume makes this less preferable (not UK; available in Canada, Hong Kong and the USA)
- **hyoscine hydrobromide** 1mg/3 days TD<sup>9</sup>
- **atropine** 1% ophthalmic solution, 4 drops SL q4h p.r.n. (Note: drop size varies with applicator and technique, dose per drop may vary from 200–500microgram, i.e. 800microgram–2mg/dose)

A regimen of atropine 1% 500microgram (1 drop) b.d. has been reported<sup>10</sup> but a controlled trial found 500microgram (2 drops) q.d.s. no better than placebo.<sup>11</sup>

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

**Death rattle**

In the UK, antimuscarinic drugs for death rattle are generally given SC.<sup>17</sup> See Table 1.2 and Guidelines, p.9.

In some countries, many centres use antimuscarinics SL for death rattle, thereby avoiding the need for injections. Treatment regimens, all unlicensed, are based mainly on local clinical experience:

- **atropine** 1% ophthalmic solution, 4 drops SL q4h p.r.n. (Note: drop size varies with applicator and technique, dose per drop may vary from 200–500microgram, i.e. 800microgram–2mg/dose)
- **hyoscyamine** drops 125microgram/ml, 2ml SL q4h p.r.n. but relatively large volume and thus less preferable (not UK; available in Canada, Hong Kong and the USA)
- **glycopyrronium** 100microgram SL q6h p.r.n.

**Paraneoplastic pyrexia and sweating**

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

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

Prescribe an antipyretic:

- paracetamol 500–1000mg q.d.s. or p.r.n. (generally less toxic than an NSAID)
- NSAID, e.g. ibuprofen 200–400mg t.d.s. or p.r.n. (or the locally preferred alternative).

If the sweating does not respond to an NSAID, prescribe an antimuscarinic drug:

- amitriptyline 25–50mg o.n. (may cause sedation, dry mouth and other antimuscarinic effects)
- hyoscine hydrobromide 1mg/3 days TD<sup>18</sup>
- glycopyrronium up to 2mg PO t.d.s.<sup>19</sup>

If an antimuscarinic fails, other options include:

- propranolol 10–20mg b.d.–t.d.s.
- cimetidine 400–800mg b.d.<sup>20</sup>
- olanzapine 5mg b.d.<sup>21</sup>
- thalidomide 100mg o.n.<sup>22,23</sup>

Thalidomide is generally seen as the last resort even though the response rate appears to be high.<sup>22</sup> This is because it can cause an irreversible painful peripheral neuropathy, and may also cause drowsiness (see p.385).

## Overdose

In the past, **physostigmine**, a cholinesterase inhibitor, was sometimes administered to correct antimuscarinic toxicity/poisoning. This is no longer recommended because **physostigmine** itself can cause serious toxic effects, including cardiac arrhythmias and seizures.<sup>24–26</sup> 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.545). Anti-arrhythmics are not advisable if arrhythmias develop; but hypoxia and acidosis should be corrected.

## Supply

See individual monographs: **glycopyrronium** (p.441), **hyoscine butylbromide** (p.10), **hyoscine hydrobromide** (p.190), **oxybutynin** (p.390), **propantheline** (p.12).

### Atropine sulphate (non-proprietary)

**Ophthalmic solution** 1%, 10ml bottle = £1.

Minims<sup>®</sup> atropine sulphate (Chauvin)

**Ophthalmic solution (single-dose units)** 1%, 0.5ml single-dose unit = £0.50.

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## PCF Guidelines: Management of death rattle

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

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

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

### Non-drug treatment

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

### Drug treatment

#### Saliva

Because they do not affect existing secretions, an antisecretory drug should be given SC (see Table) or SL (see Box), as soon as the onset of the rattle is detected. SL use is unlicensed and less well supported by the literature.

**Table** Antimuscarinic antisecretory drugs for death rattle: typical SC doses

Drug	Stat SC dose	CSCI dose/24h
Glycopyrronium	200microgram	600–1200microgram
Atropine	400microgram	1200–2000microgram
Hyoscine <i>hydrobromide</i>	400microgram	1200–2000microgram
Hyoscine <i>butylbromide</i>	20mg	20–120mg
Hyoscyamine (l-atropine; not UK)	200microgram	600–1000microgram

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

Glycopyrronium 0.01% oral solution, 1ml (100microgram) SL q6h p.r.n.; can be prepared extemporaneously from glycopyrronium powder (see Box B).

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

Hyoscyamine drops 125microgram/ml, 2ml (250microgram) SL q4h p.r.n. (not UK).

**Box B** Extemporaneous oral solution of glycopyrronium

Dissolve 100mg of glycopyrronium powder (obtainable from Antigen) in 100ml of sterile or distilled water (= 1mg/ml concentrated solution).

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

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

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

**Note:**

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

**Respiratory tract infection**

Occasionally it is appropriate to prescribe an antibiotic in an imminently dying patient if death rattle is caused by profuse purulent sputum associated with an underlying chest infection:

- e.g. ceftriaxone, mix 1g ampoule with 2.1ml lidocaine 1% (total volume 2.6–2.8ml), and give 250–1000mg SC/IM o.d.
- some centres use larger volumes of lidocaine 1% (up to 4ml) and administer a divided dose at separate SC/IM sites o.d. or give b.d.

**Pulmonary oedema**

Consider furosemide 20–40mg SC/IM/IV q2h p.r.n.

Note: beware precipitating urinary retention.

**Gastric reflux**

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

**Rattling breathing causing distress to a patient**

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

**HYOSCINE BUTYLBROMIDE****BNF 1.2**

**Class:** Antimuscarinic.

**Indications:** Smooth muscle spasm (e.g. bladder, intestine), ↑drying secretions (including ↑salorrhoea, ↑drooling, ↑death rattle and ↑inoperable intestinal obstruction), ↑paraneoplastic pyrexia and sweating.

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

## Pharmacology

Hyoscine *butylbromide* is an antimuscarinic (see p.10) and has both smooth muscle relaxant (antispasmodic) and antisecretory properties. Unlike **hyoscine hydrobromide** the *butylbromide* does not cross the blood-brain barrier and thus does not have a central anti-emetic effect or cause drowsiness. Because they are poorly absorbed, tablets of hyoscine *butylbromide* are of limited use, except perhaps for mild–moderate bowel colic.

In healthy volunteers a bolus injection of 20mg has a maximum antisecretory duration of action of 2h.<sup>1</sup> However, the same dose by CSCI is often effective for 24h in 'death rattle'. Hyoscine *butylbromide* and **hyoscine hydrobromide** act faster than **glycopyrronium** in death rattle,<sup>2,3</sup> but the overall efficacy is generally the same<sup>4</sup> with death rattle reduced in 1/2–2/3 of patients.

In inoperable gastro-intestinal obstruction in advanced cancer, the dose of hyoscine *butylbromide* is higher. In an open non-randomized trial of hyoscine *butylbromide* 60mg/24h CSCI vs. **octreotide** 300microgram/24h CSCI, **octreotide** resulted in a more rapid reduction in the volume of gastric aspirate (by 75% vs. 50%) and improvement in nausea, although it was possible to remove nasogastric tubes in both groups after about 5 days.<sup>5,6</sup> However, higher doses of hyoscine *butylbromide*, e.g. 120–200mg/24h, have not been compared with **octreotide**.

**Bio-availability** 8–10% PO.

**Onset of action** < 10min SC/IM/IV; 1–2h PO.

**Time to peak plasma concentration** 1–2h PO.

**Plasma half-life** 5–6h.

**Duration of action** <2h in volunteers; probably longer in moribund patients.

## Cautions

Competitively blocks the prokinetic effect of **metoclopramide** and **domperidone**.<sup>7</sup> Increases the peripheral antimuscarinic effects of antihistamines, phenothiazines and TCAs (see Antimuscarinics (anticholinergics), p.4).

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

## Undesirable effects

For full list, see manufacturers' SPCs.

Peripheral antimuscarinic effects (see p. 5).

## Dose and use

**Inoperable intestinal obstruction with colic**<sup>8,9</sup>

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

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

For patients with obstructive symptoms without colic, **metoclopramide** (see p.181) should be tried before an antimuscarinic drug because the obstruction is often more functional than organic.

## Death rattle

- start with 20mg SC stat, 20–60mg/24h CSCI, and 20mg SC q1h p.r.n.
- some centres use higher doses, namely 60–120mg/24h CSCI<sup>3</sup>

For use of alternative antimuscarinics, see p.4.

## Supply

Buscopan<sup>®</sup> (Boehringer Ingelheim)

**Tablets** 10mg, 28 days @ 20mg q.d.s. = £10. Also available OTC as Buscopan<sup>®</sup> IBS Relief.

**Injection** 20mg/ml, 1ml amp = £0.50.

- Herxheimer A and Haeefeli L (1966) Human pharmacology of hyoscine butylbromide. *Lancet*. **ii**: 418–421.
- Back I *et al.* (2001) A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. *Palliative Medicine*. **15**: 329–336.
- Bennett M *et al.* (2002) Using anti-muscarinic drugs in the management of death rattle: evidence based guidelines for palliative care. *Palliative Medicine*. **16**: 369–374.
- Hughes A *et al.* (2000) Audit of three antimuscarinic drugs for managing retained secretions. *Palliative Medicine*. **14**: 221–222.
- Mercadante S *et al.* (2000) Comparison of octreotide and hyoscine butylbromide in controlling gastrointestinal symptoms due to malignant inoperable bowel obstruction. *Supportive Care in Cancer*. **8**: 188–191.
- Ripamonti C *et al.* (2000) Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: a prospective randomized trial. *Journal of Pain and Symptom Management*. **19**: 23–34.
- Schuurkes JA *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
- De-Conno F *et al.* (1991) Continuous subcutaneous infusion of hyoscine butylbromide reduces secretions in patients with gastrointestinal obstruction. *Journal of Pain and Symptom Management*. **6**: 484–486.
- Ripamonti C *et al.* (2001) Clinical-practice recommendations for the management of bowel obstruction in patients with end-stage cancer. *Supportive Care in Cancer*. **9**: 223–233.

## PROPANTHELINE

## BNF 1.2 & 7.4.2

**Class:** Antimuscarinic.

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

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

### Pharmacology

Propantheline is a quaternary antimuscarinic (see p.4); it does not cross the blood–brain barrier and thus does *not* cause central effects. It doubles gastric emptying half-time<sup>1</sup> and slows gastrointestinal transit generally. It has variable effects on drug absorption (see Cautions). Propantheline is extensively metabolized in the small intestine before absorption. *If taken with food, the effect of propantheline by mouth is almost abolished.*<sup>2</sup>

**Bio-availability** <50% PO (much reduced if taken after food).

**Onset of action** 30–60min.

**Time to peak plasma concentration** no data.

**Plasma half-life** 3–4h.

**Duration of action** 4–6h.

### Cautions

Competitively blocks the prokinetic effect of **metoclopramide** and **domperidone**.<sup>3</sup> May reduce the rate of absorption of **paracetamol**, thereby delaying the onset of analgesia.<sup>4</sup>

Increases the peripheral antimuscarinic toxicity of antihistamines, phenothiazines and TCAs (see Antimuscarinics (anticholinergics), p.4). Use with caution in conditions predisposing to tachycardia (e.g. thyrotoxicosis, heart failure, β-adrenergic receptor agonists), and bladder outflow obstruction (prostatism). Likely to exacerbate acid reflux. Narrow-angle glaucoma may be precipitated in those at risk, particularly the elderly. Use in hot weather or pyrexia may lead to heatstroke.

### Undesirable effects

*For full list, see manufacturers' SPCs.*

Peripheral antimuscarinic effects (see p.4).

**Dose and use****Intestinal colic**

- start with 15mg t.d.s. 1h a.c. & 30mg o.n.
- maximum dose 30mg q.d.s.

**Urinary frequency**

- same as for colic, but largely replaced by **oxybutynin** (see p.390), **amitriptyline** (see p.154) and **imipramine**.

**Sweating**

Used as one of several alternatives to reduce paraneoplastic sweating (for other options, see Box 1.C, p.7):

- 15–30mg b.d.–t.d.s.

**Supply**

Pro-Banthine® (Concord)

**Tablets** 15mg, 28 days @ 15mg t.d.s. & 30mg o.n. = £19.

- 1 Hurwitz A *et al.* (1977) Prolongation of gastric emptying by oral propantheline. *Clinical Pharmacology and Therapeutics*. **22**: 206–210.
- 2 Ekenved G *et al.* (1977) Influence of food on the effect of propantheline and L-hyoscyamine on salivation. *Scandinavian Journal of Gastroenterology*. **12**: 963–966.
- 3 Schuurkes JA *et al.* (1986) Stimulation of gastroduodenal motor activity: dopaminergic and cholinergic modulation. *Drug Development Research*. **8**: 233–241.
- 4 Baxter K (ed) (2006) *Stockley's Drug Interactions (7e)*. Pharmaceutical Press, London.

**PROKINETICS****BNF 1.2**

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

Apart from **erythromycin**, prokinetics act by triggering a cholinergic system in the wall of the

**Table 1.3** Gastric prokinetics<sup>1</sup>

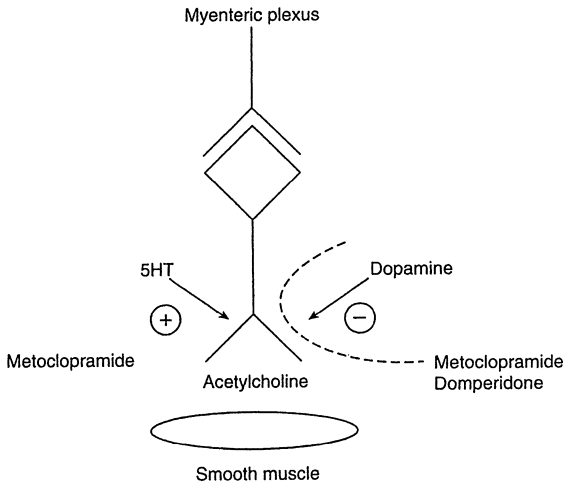
Class	Examples	Site of action
D <sub>2</sub> -receptor antagonist	Domperidone Metoclopramide	Stomach Stomach
5HT <sub>4</sub> -receptor agonist	Metoclopramide	Stomach → jejunum
Motilin agonist	Erythromycin	Stomach

gastro-intestinal tract (Table 1.4, Figure 1.1).<sup>2</sup> This action is impeded by opioids. Further, antimuscarinic drugs competitively block cholinergic receptors on the intestinal muscle fibres (and elsewhere).<sup>3</sup> Thus, all drugs with antimuscarinic properties reduce the impact of prokinetic drugs; the extent of this depends on several factors, including the respective doses of the interacting drugs and times of administration. Thus, generally, the concurrent administration of prokinetics and antimuscarinic drugs is best avoided. On the other hand, even if the peripheral prokinetic effect is completely blocked, **domperidone** and **metoclopramide** will still exert an anti-emetic effect at the dopamine receptors in the area postrema (see p.183).

**Table I.4** Comparison of prokinetic drugs<sup>2</sup>

Drug	Erythromycin	Domperidone	Metoclopramide
<b>Mechanism of action</b>			
Motilin agonist	+	-	-
D <sub>2</sub> -receptor antagonist	-	+	+
5HT <sub>4</sub> -receptor agonist	-	-	+
<b>Response to treatment<sup>3</sup></b>			
Gastric emptying (mean % acceleration)	45	30	20
Symptom relief (mean % improvement)	50	50	40

a. all percentages rounded to nearest 5%.



**Figure I.1** Schematic representation of drug effects on antroduodenal co-ordination via a postganglionic effect on the cholinergic nerves from the myenteric plexus.

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

**Erythromycin**, an antibiotic, is the only available motilin agonist.<sup>4</sup> It has been used mainly in diabetic gastroparesis when other prokinetics have proved inadequate.<sup>5,6</sup> A systematic review suggests that, overall, its prokinetic effect is greater than that of **metoclopramide** (Table I.4). However, it may cause intestinal colic and, in healthy people, it often causes diarrhoea. There is also concern about bacterial resistance developing. In some patients, tolerance to its prokinetic effects develops over time.<sup>7</sup> However, some patients have taken **erythromycin** 250mg b.d. for more than a year without apparent loss of its prokinetic effect.<sup>8</sup>

Prokinetics are used in various conditions in palliative care (Box I.D). D<sub>2</sub>-receptor antagonists block the dopaminergic 'brake' on gastric emptying induced by stress, anxiety and nausea from any cause. In contrast, 5HT<sub>4</sub>-receptor agonists have a direct excitatory effect which in theory gives them an advantage over the D<sub>2</sub>-receptor antagonists particularly for patients with gastric stasis or functional intestinal obstruction. However, when used for dysmotility dyspepsia, **metoclopramide** is no more potent than **domperidone** in standard doses.<sup>9,10</sup>

**Box 1.D** Indications for prokinetics in palliative care

## Gastro-oesophageal reflux

## Gastroparesis

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

## Functional gastro-intestinal obstruction

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

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

**H<sub>2</sub>-RECEPTOR ANTAGONISTS****BNF 1.3.1**

**Class:** Gastroprotective drugs.

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

**Pharmacology**

H<sub>2</sub>-receptor antagonists reduce both gastric acid output and the volume of gastric secretions.<sup>1</sup> **Ranitidine** is a good choice in terms of convenience and safety. **Cimetidine**, alone among H<sub>2</sub>-receptor antagonists, can cause serious cytochrome P450-related drug interactions (see Cautions below and Cytochrome P450, p.535). None of the H<sub>2</sub>-receptor antagonists, including **cimetidine**, alters the metabolism of **morphine**.<sup>2</sup>

Prophylactic treatment with a standard dose of an H<sub>2</sub>-receptor antagonist reduces the incidence of NSAID-induced *duodenal* ulcers.<sup>3</sup> Prevention of *gastric* erosions and ulcers is seen only with a double dose.<sup>4</sup> In patients taking NSAIDs, **ranitidine** (compared with **omeprazole**) is less effective and slower in *healing* gastroduodenal ulcers (63% vs. 80% at 8 weeks) and in *preventing* relapse (59% vs. 72% over 6 months) (Table 1.5).<sup>3,5</sup>

**Bio-availability** **cimetidine** 60–70% PO; **ranitidine** 50% PO.

**Onset of action** < 1h.

**Time to peak plasma concentration cimetidine** 1–3h PO, 15min IM; **ranitidine** 2–3h PO.  
**Plasma half-life cimetidine** 2h; **ranitidine** 2–3h.  
**Duration of action cimetidine** 7h; **ranitidine** 8–12h.

**Table 1.5** Comparison of gastroprotective agents<sup>3–7</sup>

	Prevent NSAID-GU	Prevent NSAID-DU	Heal NSAID-GU	Heal NSAID-DU
Misoprostol	+	+	+	+
H <sub>2</sub> -receptor antagonists	+ <sup>a</sup>	+	+ <sup>b</sup>	+ <sup>b</sup>
Proton pump inhibitors	+	+	+ <sup>c</sup>	+ <sup>c</sup>

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

## Cautions

**Serious drug interactions:** the increase in gastric pH caused by all H<sub>2</sub>-receptor antagonists decreases the absorption of **itraconazole** and **ketoconazole**; an increased dose may be needed to avoid antifungal treatment failure. **Cimetidine** binds to microsomal cytochrome P450 and inhibits the metabolism of **warfarin**, IV **lidocaine** (but not ED **lidocaine** or **bupivacaine**), some calcium antagonists (**diltiazem**, **isradipine**, **nifedipine**), **pentoxifylline**, **theophylline**, **clomethiazole**, **diazepam**, TCAs, **moclobemide**, **phenytoin**, **methadone** and **fluorouracil**. **Cimetidine** inhibits the renal clearance of **procaïnamide** and **quinidine**.<sup>8</sup>

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

## Undesirable effects

See *manufacturers' SPCs*.

**Cimetidine** occasionally causes gynaecomastia.

## Dose and use

**Cochrane review:** H<sub>2</sub>-receptor antagonists (double-dose), **misoprostol** and PPIs are effective at *preventing* chronic NSAID-related endoscopic peptic ulcers. **Misoprostol** 400microgram daily is less effective than 800microgram and is still associated with diarrhoea. Of all these treatments, only **misoprostol** 800microgram daily has been definitely shown to reduce the overall incidence of ulcer complications (perforation, haemorrhage or obstruction).<sup>4</sup> PPIs definitely reduce the incidence of re-bleeding from endoscopically confirmed peptic ulcers,<sup>10</sup> and may reduce the incidence of ulcer complications.<sup>7</sup>

Because **cimetidine** is responsible for several serious drug interactions, **ranitidine** is generally preferable in palliative care. However, PPIs are recommended by NICE as the gastroprotective drugs of choice (see p.19). H<sub>2</sub>-receptor antagonists are considered second-line treatment for gastro-oesophageal reflux disease, non-ulcer dyspepsia or uninvestigated dyspepsia, and as an OTC measure for mild dyspepsia.<sup>11</sup>

The dose and duration of treatment is least with duodenal ulceration and most with reflux oesophagitis and prophylaxis for NSAID-induced peptic ulcer, although the dose for ulcer healing can be doubled if the initial response is poor (Table 1.6). **Ranitidine** is more effective if taken o.n. rather than with the evening meal.<sup>12</sup> Parenteral formulations are available for IM and for IV use if treatment is considered necessary in a patient with severe nausea and vomiting (see BNF section 1.3.1).

**Table 1.6** Recommended treatment regimens for H<sub>2</sub>-receptor antagonists

Indication	Cimetidine	Ranitidine
Duodenal ulcer <sup>a,b</sup>	400mg b.d. or 800mg o.n. for 4+ weeks	150mg b.d. or 300mg o.n. for 4–8 weeks
Gastric ulcer <sup>a,b</sup>	400mg b.d. or 800mg o.n. for 6+ weeks	150mg b.d. or 300mg o.n. for 4–8 weeks
Prophylaxis for NSAID-associated peptic ulcer	800mg b.d. indefinitely	300mg b.d. indefinitely
Reflux oesophagitis	400mg q.d.s. for 4–8 weeks	150mg b.d. or 300mg o.n. for 8–12 weeks
Short bowel syndrome	400mg b.d. or 800mg o.n. indefinitely	—
To reduce degradation of pancreatin supplements	200–400mg 1h a.c.	150mg 1h a.c.

a. 8 weeks for NSAID-induced ulcer

b. dose can be doubled if initial response is poor.

In renal impairment, the dose of **cimetidine** should be adjusted according to creatinine clearance (Table 1.7). **Cimetidine** is removed by haemodialysis, but not by peritoneal dialysis.

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

**Table 1.7** Dose adjustment for cimetidine in renal impairment

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

## Supply

**Cimetidine** (non-proprietary)

**Tablets** 200mg, 400mg, 800mg, 28 days @ 400mg b.d. or 800mg o.n. = £2 and £2.50 respectively.

**Oral solution (sugar-free)** 200mg/5ml, 28 days @ 400mg b.d. = £27; peach and peppermint flavour.

Dyspamet<sup>®</sup> (Goldshield)

**Oral suspension (sugar-free)** 200mg/5ml, 28 days @ 400mg b.d. = £22.

Tagamet<sup>®</sup> (Chemidex/GSK)

**Tablets** 200mg, 400mg, 800mg, 28 days @ 400mg b.d. or 800mg o.n. = £21.

**Oral syrup** 200mg/5ml, 28 days @ 400mg b.d. = £27; peach flavour.

**Injection** 100mg/ml, 2ml amp = £0.50.

**Ranitidine** (non-proprietary)

**Tablets** 150mg, 300mg, 28 days @ 150mg b.d. or 300mg o.n. = £2.

**Tablets effervescent** 150mg, 300mg, 28 days @ 150mg b.d. or 300mg o.n. = £19.

**Oral solution** 75mg/5ml, 28 days @ 150mg b.d. = £42.

Zantac<sup>®</sup> (GSK)

**Tablets** 75mg, 150mg, 300mg, 28 days @ 150mg b.d. or 300mg o.n. = £1.

**Tablets effervescent** 150mg, 300mg, 28 days @ 150mg b.d. or 300mg o.n. = £24; 150mg tablets contain 14.3mmol Na<sup>+</sup>/tablet, 300mg tablets contain 20.8mmol Na<sup>+</sup>/tablet.

**Oral solution (sugar-free)** 75mg/5ml, 28 days @ 150mg b.d. = £39; contains 8% alcohol, mint flavour.

**Injection** 25mg/ml, 2ml amp = £0.50.

- Williams JG and Strunin L (1985) Pre-operative intramuscular ranitidine and cimetidine. Double blind comparative trial, effect on gastric pH and volume. *Anaesthesia*. **40**: 242–245.
- Mojaverian P et al. (1982) Cimetidine does not alter morphine disposition in man. *British Journal of Clinical Pharmacology*. **14**: 809–813.
- Hollander D (1994) Gastrointestinal complications of nonsteroidal anti-inflammatory drugs: prophylactic and therapeutic strategies. *American Journal of Medicine*. **96**: 274–281.
- Rostom A et al. (2002) Prevention of NSAID-induced gastroduodenal ulcers. *The Cochrane Database of Systematic Reviews*. **10**: CD002296.
- Yeomans N et al. (1998) A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs. Acid suppression trial. *New England Journal of Medicine*. **338**: 719–726.
- Hawkins C and Hanks G (2000) The gastroduodenal toxicity of nonsteroidal anti-inflammatory drugs. A review of the literature. *Journal of Pain and Symptom Management*. **20**: 140–151.
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- Sorkin E and Ogawa C (1983) Cimetidine potentiation of narcotic action. *Drug Intelligence and Clinical Pharmacy*. **17**: 60–61.
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- Johnston DA and Wormsley KG (1988) The effect of food on ranitidine-induced inhibition of nocturnal gastric secretion. *Alimentary Pharmacology and Therapeutics*. **2**: 507–511.

## MISOPROSTOL

## BNF 1.3.4

**Class:** Prostaglandin analogue, gastroprotective drug.

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

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

### Pharmacology

Misoprostol is a synthetic PG analogue with gastric antisecretory and protective properties. After oral administration, it is rapidly converted to an active free acid. Misoprostol helps prevent NSAID-related gastroduodenal erosions and ulcers.<sup>1–3</sup> In relation to healing NSAID-related gastroduodenal injury, misoprostol and PPIs are equally effective.<sup>4</sup> In one RCT, PPIs were more effective at preventing relapse (relapse rate: PPI 39%, misoprostol 52%, placebo 73%).<sup>4</sup> However, a systematic review indicates that the evidence for prophylactic benefit is much stronger for misoprostol than for PPIs.<sup>3</sup> The use of misoprostol is limited by its tendency to cause intestinal colic and diarrhoea.

**Bio-availability** 90% PO.

**Onset of action** < 30min.

**Time to peak plasma concentration** 30min.

**Plasma half-life** 1–2h for free acid.

**Duration of action** 2–4h.

### Cautions

Women of childbearing age should use effective contraception.

Conditions where hypotension might precipitate severe complications, e.g. cerebrovascular disease, cardiovascular disease.

### Undesirable effects

For full list, see manufacturers' SPCs.

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

### Dose and use

**Cochrane review:** Misoprostol, PPIs, and double-dose H<sub>2</sub>-receptor antagonists are effective at preventing chronic NSAID-related endoscopic peptic ulcers. Misoprostol 400microgram daily is less effective than 800microgram and is still associated with diarrhoea. Of all these treatments, only misoprostol 800microgram daily has been definitely shown to reduce the overall incidence of ulcer complications (perforation, haemorrhage or obstruction).<sup>5</sup> PPIs definitely reduce the incidence of re-bleeding from endoscopically confirmed peptic ulcers,<sup>6</sup> and may reduce the incidence of ulcer complications.<sup>3</sup>

NSAID-associated ulcers may be treated with an H<sub>2</sub>-receptor antagonist, a PPI or misoprostol. In most cases, the causal NSAID need not be discontinued during treatment.<sup>4,7</sup> Consideration should be given to switching to a less toxic NSAID (see p.226).

### Prophylaxis against NSAID-induced ulcers

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

### NSAID-associated ulceration

- 200microgram t.d.s. with meals & o.n. or
- 400microgram b.d. (breakfast and bedtime) for 4–8 weeks.<sup>1</sup>

If causes diarrhoea, give 200microgram t.d.s. & o.n. and avoid **magnesium salts**.

### Supply

Cytotec® (Pharmacia)

**Tablets** 200microgram, 28 days @ 200microgram b.d. = £19.

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- 2 Silverstein FE *et al.* (1995) Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. *Annals of Internal Medicine*. **123**: 241–249.
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## PROTON PUMP INHIBITORS

## BNF 1.3.5

**Class:** Gastroprotective drugs.

**Indications:** Acid dyspepsia, acid reflux, peptic ulceration (including prevention and treatment of NSAID-induced ulceration), eradication of *Helicobacter pylori* (in combination with antibiotics).

### Pharmacology

Proton pump inhibitors (PPIs) reduce gastric acid output but, in contrast to H<sub>2</sub>-receptor antagonists, do not reduce the volume of gastric secretions. Because **lansoprazole**, **omeprazole**, **pantoprazole** and **rabeprazole** are all rapidly degraded by acid, they are formulated as e/c granules or tablets. These dissolve in the duodenum where the drug is rapidly absorbed to be selectively taken up by gastric parietal cells and converted into active metabolites.

These irreversibly inhibit the proton pump ( $H^+/K^+$ -ATPase) and thereby block gastric acid secretion. Elimination is predominantly by metabolism in the liver to inactive derivatives excreted mainly in the urine. The plasma half-lives of PPIs are all  $<2h$  but, because they irreversibly inhibit the proton pump, the antisecretory activity continues for several days until new proton pumps are synthesized.

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

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

**Onset of action**  $<2h$ .

**Duration of action**  $>24h$ .

**Table 1.8** Pharmacokinetic features of PPIs given PO

	Bio-availability (%)	Time to peak plasma concentration (h)	Plasma half-life (h)
Lansoprazole	80–90	1.5–2	1–2
Omeprazole	60	3–6	0.5–3
Pantoprazole	77	2–2.5	1 <sup>a</sup>

a. increases to 3–6h in cirrhosis.

## Cautions

**Serious undesirable drug reactions:** ocular damage,<sup>9</sup> impaired hearing, angina, hypertension. Most cases of ocular damage have been reported with IV **omeprazole**.<sup>10</sup> PPIs possibly cause vasoconstriction by blocking  $K^+/H^+$ -ATPase. Because the retinal artery is an end-artery, anterior ischaemic optic neuropathy may result. If the PPI is stopped, visual acuity may improve. Some patients have become permanently blind, in some instances after 3 days. Impaired hearing and deafness have also been reported, again mostly with IV **omeprazole**. A similar mechanism may be responsible for the angina and hypertension included in the US manufacturer's list of undesirable effects for **omeprazole**.

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

PPIs are metabolized by the cytochrome P450 family of liver enzymes (see Cytochrome P450, p.535). However, clinically important interactions are rare with PPIs.<sup>13,14</sup> Sedation and gait disturbances have been reported when **omeprazole** was given with **diazepam**, **flurazepam**, or **lorazepam**. **Omeprazole** levels are increased by some macrolides (**clarithromycin**, **erythromycin**) and azole antifungals (**fluconazole**, **ketoconazole**, **voriconazole**).<sup>12</sup> No significant interactions between **pantoprazole** and other drugs have been identified.<sup>12,15</sup>

## Undesirable effects

For full list, see manufacturers' SPCs.

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

## Dose and use

**Cochrane review:** PPIs, **misoprostol**, and double-dose H<sub>2</sub>-receptor antagonists are effective at preventing chronic NSAID-related endoscopic peptic ulcers. **Misoprostol** 400microgram daily is less effective than 800microgram and is still associated with diarrhoea. Of all these treatments, only **misoprostol** 800microgram daily has been definitely shown to reduce the overall incidence of ulcer complications (perforation, haemorrhage or obstruction).<sup>16</sup> PPIs definitely reduce the incidence of re-bleeding from endoscopically confirmed peptic ulcers,<sup>17</sup> and may reduce the incidence of ulcer complications.<sup>18</sup>

NICE guidelines state that PPIs are preferable to H<sub>2</sub>-receptor antagonists for the treatment of dyspepsia, gastro-oesophageal reflux disease and peptic ulcers, including NSAID-induced peptic ulcers (for comparison with H<sub>2</sub>-receptor antagonists, see Table 1.5, p.16).<sup>19</sup> PPIs are used in combination with antibiotics for the eradication of *Helicobacter pylori* (see p.345).

### Lansoprazole

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

A higher dose, i.e. 30mg b.d., is recommended when **lansoprazole** is being used with antibiotics to eradicate *Helicobacter pylori* (see p.345). In severe hepatic impairment, the dose should be limited to 30mg/day. The SPC for **lansoprazole** states that administration should be o.m., a.c. in order to achieve 'optimal acid inhibition'. However, published data show that this precaution is unnecessary.<sup>7,8</sup> For patients with obstructive dysphagia and acid dyspepsia or with severe gastritis and vomiting, the rectal route can be used.<sup>20</sup>

### Omeprazole

- 20mg o.m. for both treatment and prevention of ulcer recurrence
- 40mg o.m. in reflux oesophagitis if poor response to standard dose.
- 20mg b.d. when **omeprazole** is being used with antibiotics to eradicate *Helicobacter pylori* (see p.345).

In severe hepatic impairment, the dose should be limited to 20mg/day.

For patients who cannot safely swallow tablets, **lansoprazole** and **omeprazole** can be given as orodispersible or dispersible tablets (Zoton Fastabs<sup>®</sup> and Losec MUPS<sup>®</sup> respectively), or the capsules can be opened and the e/c granules swallowed with water or fruit juice, or mixed with apple sauce or yoghurt. Specific procedures are available from the manufacturers for administration by enteral feeding tubes (see p.000).

**Omeprazole** has been used in the management of acute bleeding from an endoscopically proven peptic ulcer, either PO or IV.<sup>17</sup> **Omeprazole** has been used parenterally in palliative care to treat painful reflux oesophagitis in patients too ill or unable to take PO medication. Although not licensed for SC administration, it has been used successfully by this route for ≤4 days.<sup>21</sup>

**Omeprazole** is available in the UK as an injection (for IV administration over 5min) and an infusion (for IVI over 20–30min). The injection should be reconstituted only with the diluent provided. The infusion should be reconstituted and diluted with 0.9% saline or 5% glucose. After reconstitution, PPI injections/infusions are alkaline (pH 9–10.5) and should not be mixed with other drugs.

## Supply

**Omeprazole** (non-proprietary)

**Capsules enclosing e/c granules** 10mg, 20mg, 40mg, 28 days @ 20mg o.m. = £10.

**Tablets e/c** 10mg, 20mg, 40mg, 28 days @ 20mg o.m. = £19.

Losec<sup>®</sup> (AstraZeneca)

**Capsules enclosing e/c granules** 10mg, 20mg, 40mg, 28 days @ 20mg o.m. = £29.

**Tablets dispersible** (multiple-unit pellet system, MUPS<sup>®</sup>) 10mg, 20mg, 40mg, 28 days @ 20mg o.m. = £29.

**Injection** (powder for reconstitution and use as a slow IV injection) 40mg vial with diluent = £5.

**Infusion** (powder for reconstitution and use as an IV infusion) 40mg vial = £5.

**Lansoprazole** (non-proprietary)

**Capsules enclosing e/c granules** 15mg, 30mg, 28 days @ 30mg o.m. = £24.

Zoton<sup>®</sup> (Wyeth)

**Capsules enclosing e/c granules** 15mg, 30mg, 28 days @ 30mg o.m. = £24.

**Tablets orodispersible** (FasTab<sup>®</sup>) 15mg, 30mg, 28 days @ 30mg o.m. = £20.

**Oral suspension** (sachet of oral e/c granules to mix with water) 30mg/sachet, 28 days @ 30mg o.m. = £34; strawberry flavour.

**Pantoprazole**

Protium<sup>®</sup> (Altana)

**Tablets e/c** 20mg, 40mg, 28 days @ 40mg o.m. = £22.

**Injection** (powder for reconstitution with 0.9% saline and use as an IV injection/infusion) 40mg vial = £6.

- 1 DTB (1997) Pantoprazole—a third proton pump inhibitor. *Drug and Therapeutics Bulletin*. **35**: 93–94.
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- 3 Koop H et al. (1996) Intragastric pH and serum gastrin during administration of different doses of pantoprazole in healthy subjects. *European Journal of Gastroenterology and Hepatology*. **8**: 915–918.
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- 11 European Agency for the Evaluation of Medicinal Products (2004) Important new pharmacokinetic data demonstrating that REYATAZ (atazanavir sulphate) combined with NORVIR (ritonavir) and omeprazole should not be co-administered. In: EMEA public statement. Available from: [www.emea.europa.eu/pdfs/human/press/pus/20264904en.pdf](http://www.emea.europa.eu/pdfs/human/press/pus/20264904en.pdf)
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**LOPERAMIDE****BNF 1.4.2****Class:** Antidiarrhoeal.**Indications:** Acute and chronic diarrhoea,  $\ddagger$ ileostomy (to improve faecal consistency).**Contra-indications:** Colitis (ulcerative, infective, or antibiotic-associated).**Pharmacology**

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

Loperamide also has an effect on other peripheral  $\mu$ -opioid receptors, including those which are activated in the presence of inflammation.<sup>5</sup> Accordingly, it is currently under investigation as a possible topical analgesic for painful skin ulcers.

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

**Bio-availability** 10% PO.**Onset of action** about 1h; maximum effect 16–24h.<sup>14</sup>**Time to peak plasma concentration** 2.5h (oral solution); 5h (capsules).<sup>15</sup>**Plasma half-life** 11h.<sup>15</sup>**Duration of action** up to 3 days.<sup>16</sup>**Cautions**

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

**Undesirable effects**

For full list, see manufacturers' SPCs.

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

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

**Dose and use**

Ensure that the diarrhoea is not secondary to faecal impaction.

**Acute diarrhoea**

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

**Chronic diarrhoea**

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

**Supply**

Loperamide (non-proprietary)

**Capsules** 2mg, 28 days @ 2mg q.d.s. = £4.

Imodium® (Janssen-Cilag)

**Capsules** 2mg, 28 days @ 2mg q.d.s. = £4.50.

**Oral solution (sugar-free)** 1mg/5ml, 28 days @ 2mg q.d.s. = £11.

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**LAXATIVES****BNF 1.6**

Constipation is common in advanced cancer,<sup>1</sup> particularly in immobile patients with small appetites and those receiving constipating drugs such as opioids.<sup>2,3</sup> Exercise and increased dietary fibre are rarely feasible options.<sup>4</sup> Although some strong opioids are less constipating than **morphine** (e.g. **buprenorphine**, **fentanyl**, **methadone**, **tramadol**), most patients receiving any opioid regularly will need a laxative concurrently.<sup>1,5</sup> Thus, as a general rule, all patients prescribed **morphine** (or other opioid) should also be prescribed a laxative (see Guidelines, p.27).

About 1/3 of patients also need rectal measures<sup>6,7</sup> either because of failed oral treatment or electively, e.g. in bedbound debilitated elderly patients, or patients with paralysis (see Guidelines, p.28).

There are several classes of laxatives (Box 1.E).<sup>8,9</sup> In contrast to the BNF, **docusate sodium** is classed here as a surface-wetting agent, i.e. a faecal softener and not a contact (stimulant) laxative.

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

**Box 1.E** Classification of commonly used laxatives

**Bulk-forming agents (fibre)**

Ispaghula (psyllium) husk (e.g. Fybogel<sup>®</sup>, Regulan<sup>®</sup>)  
Methylcellulose (e.g. Celevac<sup>®</sup>)  
Sterculia (e.g. Normacol<sup>®</sup>)

**Lubricants**

Liquid paraffin

**Surface-wetting agents**

Docusate sodium  
Poloxamer 188 (in co-danthramer)

**Osmotic laxatives**

Lactulose syrup  
Macrogol (e.g. Movicol<sup>®</sup>, Idrolax<sup>®</sup>)  
Liquid paraffin and magnesium hydroxide oral emulsion BP  
Magnesium hydroxide suspension (Milk of Magnesia<sup>®</sup>)  
Magnesium sulphate (Epsom Salts)

**Contact (stimulant) laxatives**

Bisacodyl  
Dantron (in co-danthramer and co-danthrusate)  
Senna  
Sodium picosulfate

Opioids cause constipation by decreasing propulsive intestinal activity and increasing non-propulsive activity, and also by enhancing the absorption of fluid and electrolytes.<sup>2,10</sup> Colonic contact (stimulant) laxatives reduce intestinal ring contractions and thus facilitate propulsive activity. In this way, they provide a logical approach to the correction of opioid-induced constipation. In practice, a combination of a peristaltic stimulant and a faecal softener is often prescribed.<sup>1,11–13</sup>

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

- **senna vs. lactulose**<sup>14</sup>
- **senna vs. misrakasneham** (an Ayurvedic herbal remedy)<sup>15</sup>
- **senna and lactulose vs. co-danthramer** (dantron and poloxamer)<sup>16</sup>
- **senna and lactulose vs. magnesium hydroxide and liquid paraffin.**<sup>17</sup>

A significant difference between treatments was seen only in the third RCT.<sup>16</sup> The combination of **senna** and **lactulose** was significantly better at relieving constipation than **co-danthramer**. However, *PCF* generally discourages the use of **lactulose** because of its relative expense and its propensity for causing gastro-intestinal discomfort (see p.34).

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- 17 Sykes N (1991) A clinical comparison of lactulose and senna with magnesium hydroxide and liquid paraffin emulsion in a palliative care population. Unpublished data.

## PCF Guidelines: Opioid-induced constipation

Although some strong opioids are less constipating than morphine (e.g. buprenorphine, fentanyl, methadone, tramadol), most patients receiving any opioid regularly will need a laxative concurrently. Thus, as a general rule, all patients prescribed morphine (or other opioid) should also be prescribed a laxative. The aim is to achieve a regular bowel action without straining, generally every 1–3 days.

- 1 Ask about the patient's past (premorbid) and present bowel habit and use of laxatives; record the date of last bowel action.
- 2 Palpate for 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 co-danthramer *strong* or co-danthrusate:

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

- 6 It is sometimes appropriate to optimize a patient's existing laxative regimen, rather than change automatically to co-danthramer.
- 7 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.
- 8 If co-danthramer/co-danthrusate causes intestinal colic, divide the total daily dose into smaller more frequent doses, e.g. change from co-danthramer *strong* 2 capsules b.d. to 1 capsule q.d.s. Alternatively, change to an osmotic laxative, e.g. macrogol 3350 (Movicol<sup>®</sup>) or macrogol 4000 (Idrolax<sup>®</sup>) 1–2 sachets o.m.
- 9 If the maximum dose of co-danthramer/co-danthrusate is ineffective, halve the dose and add an osmotic laxative, e.g. macrogol 3350 (Movicol<sup>®</sup>) or macrogol 4000 (Idrolax<sup>®</sup>) 1 sachet o.m., and titrate as necessary.
- 10 An osmotic laxative, e.g. a macrogol may be preferable in patients with a history of colic with colonic stimulants, e.g. dantron, senna, bisacodyl.

## PCF Guidelines: Bowel management in paraplegia and tetraplegia

Management is governed by the level of the vertebral lesion:

- above T12–L1 = cauda equina intact → spastic bowel, generally with preserved sacral reflex; often responds to digital stimulation of the rectum; the presence of an anal reflex is indicative of an intact sacral reflex
- below T12–L1 = cauda equina involved → flaccid bowel; generally requires digital evacuation of the rectum.

### Aim

To achieve controlled regular evacuation of soft formed faeces:

- every day in long-term paraplegia/tetraplegia (e.g. post-traumatic)
- every 1–3 days in late-stage cancer

and thus prevent either incontinence (faeces too soft; over-treatment with laxatives) or an anal fissure (faeces too hard; under-treatment with laxatives) which can cause autonomic dysreflexia in paraplegia above T7 vertebra and tetraplegia (see next page).

### Non-drug treatment

In patients with a good appetite:

- 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 (psyllium) husk.

In patients with a poor appetite, particularly if taking morphine or other opioid, a bulking agent is generally contra-indicated.

### Spastic bowel

- if rectum very full, consider a digital evacuation, otherwise
- insert 2 glycerol suppositories or a micro-enema deep into the rectum, and wait 30–60min
- if strong sacral reflex, some faeces will be expelled
- if necessary, proceed to digital stimulation:
  - ▷ insert gloved and lubricated finger
  - ▷ rotate finger clockwise 3–4 times
  - ▷ withdraw and wait 10min
  - ▷ if necessary, repeat 3–4 times.

If glycerol suppositories and micro-enemas do not work satisfactorily, substitute bisacodyl suppositories 10–20mg.

Patients who are unable to transfer to the toilet or a commode will need nursing assistance. Sometimes it is preferable for a patient to defaecate into strategically placed pads on the bed.

### Flaccid bowel

Generally requires digital evacuation. A pattern will emerge for each patient, allowing the rectal measures to be adjusted to the individual patient's needs and response.

### Use of laxatives

- some people with paraplegia/tetraplegia, particularly if taking opioids or other constipating drugs, require oral laxatives in addition to the rectal measures described above. Which laxative is used depends partly on local availability, fashion, and individual preference
- for someone taking opioids, cautiously prescribe a colonic stimulant laxative, e.g. senna 15mg b.d., bisacodyl 5–10mg b.d. Adjust the dose as necessary to produce soft formed faeces in the rectum
- beware:
  - ▷ docusate, 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.

*continued*

**Autonomic dysreflexia**

This is a potential problem in paraplegia above T7 vertebra and in tetraplegia, and it:

- is caused typically by a distended bladder, constipation/faecal impaction, or anal fissure
- manifests as headache (often pounding), profuse sweating, nasal stuffiness, facial flushing, and bradycardia
- is caused by a stimulus below the level of the lesion causing sympathetic autonomic overactivity → vasoconstriction and hypertension; this stimulates parasympathetic overactivity above the lesion via the carotid and aortic baroreceptors.

As a general rule, headache in someone with paraplegia/tetraplegia should lead to action: check the urinary catheter and, if draining satisfactorily, proceed to rectal examination.

**ISPAGHULA (PSYLLIUM) HUSK****BNF 1.6.1**

Included for general information. Isphaghula husk is *not recommended* as a laxative in palliative care patients. It may sometimes 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, intestinal obstruction, colonic atony, faecal impaction.

**Pharmacology**

Isphaghula (psyllium) is derived from the husks of an Asian plant, *Plantago ovata*. It has very high water-binding capacity, is partly fermented in the colon, and increases bacterial cell mass. Like other bulk-forming laxatives, isphaghula 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 intestinal obstruction.

**Undesirable effects**

For full list, see manufacturers' SPCs.

Flatulence, abdominal distension, faecal impaction, intestinal obstruction.

**Dose and use**

Isphaghula 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, and followed by 100–200ml of water. Give 1 sachet o.m.–t.d.s., preferably after meals; not immediately before going to bed.

**Supply**

Fybogel<sup>®</sup> (Reckitt Benckiser)

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

Regulan<sup>®</sup> (Procter & Gamble)

**Oral powder** 3.4g/sachet, 28 days @ 1 sachet b.d. = £4; sugar- and gluten-free; orange or lemon-lime flavour.

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

## CONTACT (STIMULANT) LAXATIVES

## BNF 1.6.2

**Indications:** Prevention and treatment of constipation.

**Contra-indications:** Large intestinal obstruction.

### Pharmacology

Anthranoïd laxatives such as **senna** are derived from plants. They are inactive glycosides which pass unabsorbed and unchanged through the small intestine and are hydrolyzed by bacterial glycosidases in the large intestine to yield active compounds.<sup>1</sup> Thus, glycosides have no effect on the small intestine but become active in the large intestine. **Dantron**, a synthetic anthranoid, is not a glycoside and has a direct action on the small intestine as well as the large intestine.<sup>2</sup> Systemic absorption of sennosides or their metabolites is small, whereas **dantron** is absorbed to some extent from the small intestine with subsequent significant urinary excretion. The laxative effect is through direct contact with the submucosal (Meissner's) plexus and the deeper myenteric (Auerbach's) plexus, resulting in both a secretory and a motor effect in the large intestine. The motor effect precedes the secretory effect, and is the more important laxative action. There is a decrease in segmenting muscular activity and an increase in propulsive waves. Differences in bacterial flora may explain differences in individual response to anthranoid laxatives.

Phenolics such as **bisacodyl** and **sodium picosulfate** have a similar laxative effect to the anthranoids. **Bisacodyl** and **sodium picosulfate** are hydrolyzed to the same active metabolite but the mode of hydrolysis differs.<sup>1</sup> **Bisacodyl** is hydrolyzed by intestinal enzymes and thus acts on both the small and large intestines. When applied directly to the intestinal mucosa in normal subjects, **bisacodyl** induces powerful propulsive motor activity within minutes.<sup>3</sup> **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.<sup>4</sup>

In contrast, **sodium picosulfate** is hydrolyzed by colonic bacteria and its action is thus confined to the large intestine. Its activity is potentially more uncertain because it depends on bacterial flora. Nonetheless, an open study in palliative care patients reported a satisfactory response (normal stool consistency, no need for enemas, suppositories or manual evacuation, and no significant undesirable effects) in 15/20 patients.<sup>5</sup>

**Phenolphthalein** is another contact laxative, and is present in some proprietary laxatives. **Phenolphthalein** exists in two forms: white and yellow. The yellow form contains several impurities produced during manufacture. These impurities enhance the laxative effect of **phenolphthalein** such that the comparable dose of the yellow form is only 2/3 that of the pure white form. The active constituent of **phenolphthalein** is released in two stages: by metabolism in the liver and subsequently in the colon, and it probably undergoes enterohepatic circulation.<sup>6</sup> Some people respond to small doses. However, it can cause a drug rash (see Undesirable effects) and is generally not considered a first-line laxative.

Several RCTs of contact laxatives have been completed in palliative care patients:

- **senna** vs. **lactulose**<sup>7</sup>
- **senna** vs. **misrakasneham** (an Ayurvedic herbal remedy)<sup>8</sup>
- **senna** and **lactulose** vs. **co-danthramer (dantron and poloxamer)**<sup>9</sup>
- **senna** and **lactulose** vs. **magnesium hydroxide and liquid paraffin**.<sup>10</sup>

A significant difference between treatments was seen only in the third RCT.<sup>9</sup> The combination of **senna** and **lactulose** was significantly better at relieving constipation than **co-danthramer**. However, *PCF* generally discourages the use of **lactulose** because of its relative expense and its propensity for causing gastro-intestinal discomfort (see p.34).

### Onset of action

**Bisacodyl** tablets 6–12h; suppositories 20min–3h (mean 1h).<sup>4</sup>

**Dantron** 6–12h.

**Senna** 6–12h.

**Sodium picosulfate** 6–24h (median 12h).<sup>5</sup>

### Cautions

Because very high doses in rodents revealed a carcinogenic risk,<sup>11–13</sup> UK licences for laxatives containing **dantron** are limited to constipation in terminally ill patients.

### Undesirable effects

*For full list, see manufacturers' SPCs.*

Intestinal colic, diarrhoea. **Bisacodyl** suppositories may cause local rectal inflammation. **Dantron** discolours urine, typically red but sometimes green or bluish. 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 become excoriated. **Phenolphthalein** occasionally causes a drug rash or photosensitivity. Rarely, it causes encephalitis which can be fatal.

### Dose and use

*The doses recommended here for opioid-induced constipation are higher (often much higher) than those featured in the BNF and the respective SPCs.* Because round-the-clock opioids constipate, b.d. or t.d.s. laxatives may well be necessary, rather than the traditional daily (o.n. or o.m.) dose. 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 Guidelines, p.27).<sup>14–17</sup> Likewise, there is need for a protocol for patients with paraplegia and tetraplegia (see Guidelines, p.28).

### Bisacodyl

- start with 10–20mg PO o.n.
- if necessary, increase by stages to 20mg PO t.d.s.
- by suppository: 10–20mg PR o.d.

### Dantron

Variable, according to preparation, individual need and patient acceptance (see Guidelines, p.27)

### Senna

- start with 15mg o.n. or, if taking opioids, 15mg b.d.
- if necessary, increase to 15–22.5mg t.d.s.

### Sodium picosulfate

- start with 5–10mg o.n.; 10mg if taking regular opioids
- if necessary, increase daily by 5mg until a satisfactory result is achieved
- median satisfactory dose = 15mg o.n.
- typical maximum dose = 30mg.<sup>5</sup>

### Supply

**Bisacodyl** (non-proprietary)

**Tablets e/c** 5mg, 28 days @ 10mg o.n. = £1.

**Suppositories** 10mg, 28 days @ 10mg o.d. = £2.

### Dantron

**Co-danthramer** (**dantron** and **poloxamer 188**) (non-proprietary)

**Co-danthramer** suspension 5ml = 1 **co-danthramer** capsule.

**Co-danthramer** suspension 15ml = 5ml **strong co-danthramer** suspension.

**Strong co-danthramer** suspension 5ml = 2 **strong co-danthramer** capsules.

**Capsules co-danthramer** 25/200 (**dantron** 25mg, **poloxamer 188** 200mg), 28 days @ 2 o.n. = £12.

**Strong capsules co-danthramer** 37.5/500 (**dantron** 37.5mg, **poloxamer 188** 500mg), 28 days @ 2 o.n. = £15.

**Oral suspension co-danthramer** 25/200 in 5ml (**dantron** 25mg, **poloxamer 188** 200mg/5ml), 28 days @ 10ml o.n. = £11.

**Strong oral suspension co-danthramer** 75/1000 in 5ml (**dantron** 75mg, **poloxamer 188** 1g/5ml), 28 days @ 5ml o.n. = £14.

**Co-danthrusate (dantron and docusate sodium)** (non-proprietary)

**Capsules co-danthrusate** 50/60 (**dantron** 50mg, **docusate sodium** 60mg), 28 days @ 2 o.n. = £12.

**Oral suspension co-danthrusate** 50/60 in 5ml (**dantron** 50mg, **docusate sodium** 60mg/5ml), 28 days @ 10ml o.n. = £12.

**Senna** (non-proprietary)

**Tablets** total **sennosides**/tablet 7.5mg, 28 days @ 15mg o.n. = £2.

Senokot<sup>®</sup> (Reckitt Benckiser)

**Tablets** total **sennosides**/tablet 7.5mg NHS.

**Oral solution (sugar-free)** total **sennosides** 7.5mg/5ml, 28 days @ 10ml o.n. = £1.50.

**Sodium picosulfate** (non-proprietary)

**Oral syrup** 5mg/5ml, 28 days @ 10ml o.n. = £5.

The proprietary names Laxoberal<sup>®</sup> NHS and Dulco-lax<sup>®</sup> Liquid are used for **sodium picosulfate** oral syrup 5mg/5ml, the proprietary name Dulco-lax<sup>®</sup> NHS is used for **bisacodyl** tablets and suppositories.

- 1 Jauch R et al. (1975) Bis-(p-hydroxyphenyl)-pyridyl-2-methane: the common laxative principle of bisacodyl and sodium picosulfate. *Arzneimittel-Forschung Drug Research*. **25**: 1796–1800.
- 2 Lennard-Jones J (1994) Clinical aspects of laxatives, enemas and suppositories. In: M Kamm and J Lennard-Jones (eds) *Constipation*. Wrightson Biomedical Publishing, Petersfield, pp. 327–341.
- 3 De Schryver AM et al. (2003) Effects of a meal and bisacodyl on colonic motility in healthy volunteers and patients with slow-transit constipation. *Digestive Diseases and Sciences*. **48**: 1206–1212.
- 4 Flig E et al. (2000) Is bisacodyl absorbed at all from suppositories in man? *International Journal of Pharmaceutics*. **196**: 11–20.
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- 9 Sykes N (1991) A clinical comparison of laxatives in a hospice. *Palliative Medicine*. **5**: 307–314.
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- 14 Levy MH (1996) Pharmacologic treatment of cancer pain. *New England Journal of Medicine*. **335**: 1124–1132.
- 15 Pappagallo M (2001) Incidence, prevalence, and management of opioid bowel dysfunction. *American Journal of Surgery*. **182 (suppl 5A)**: 11s–18s.
- 16 Bouvy ML et al. (2002) Laxative prescribing in relation to opioid use and the influence of pharmacy-based intervention. *Journal of Clinical Pharmacy and Therapeutics*. **27**: 107–110.
- 17 Herndon CM et al. (2002) Management of opioid-induced gastrointestinal effects in patients receiving palliative care. *Pharmacotherapy*. **22**: 240–250.

**DOCUSATE SODIUM****BNF I.6.2**

**Class:** Surface-wetting agent (faecal softener).

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

**Pharmacology**

Although sometimes classified as a stimulant laxative, docusate sodium (docusate) is principally an emulsifying and wetting agent and has a relatively weak effect on gastro-intestinal transit. Other wetting agents include **poloxamer 188** (in **co-danthramer**). Docusate lowers surface tension, thereby allowing water and fats to penetrate hard, dry faeces. It also stimulates fluid secretion by the small and large intestines.<sup>1,2</sup> Docusate does not interfere with protein or fat absorption.<sup>3</sup> Docusate has been evaluated in several groups of elderly patients; frequency of defaecation increased and the need for enemas decreased almost to zero.<sup>4-6</sup> Given these clinical results, it is surprising that, in a study in normal subjects, docusate did not increase faecal weight.<sup>7</sup> In palliative care, docusate is not recommended as the sole laxative except in patients with partial bowel obstruction.<sup>8</sup> The routine combination of docusate (or alternative surface-wetting agent) and a contact (stimulant) laxative has been criticized because of a lack of published data supporting such a regimen.<sup>9</sup> However, in the UK, such a combination is widely used with good effect in patients with opioid-induced constipation.

**Onset of action** 12–72h.

**Cautions**

Docusate enhances the absorption of **liquid paraffin**;<sup>10</sup> combined preparations of these substances are prohibited in some countries.

**Undesirable effects**

For full list, see manufacturers' SPCs.

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

**Dose and use**

At many centres, docusate is used in combination with **dantron** in **co-danthrusate** as the laxative of choice for opioid-induced constipation (see Guidelines, p.27). Docusate is often used alone for patients with persistent partial bowel obstruction. Dose varies according to individual need:

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

**Supply**

Diocetyl® (Schwarz)

**Capsules** 100mg, 28 days @ 100mg b.d. = £4.50.

Docusol® (Typharm)

**Oral solution (sugar-free)** 50mg/5ml, 28 days @ 10ml b.d. = £4.50.

- 
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  - 4 Cass L and Frederik W (1956) Doxinate in the treatment of constipation. *American Journal of Gastroenterology*. **26**: 691–698.
  - 5 Harris R (1957) Constipation in geriatrics. *American Journal of Digestive Diseases*. **2**: 487–492.
  - 6 Hyland C and Foran J (1968) Dioctyl sodium sulphosuccinate as a laxative in the elderly. *Practitioner*. **200**: 698–699.
  - 7 Chapman R et al. (1985) Effect of oral dioctyl sodium sulfosuccinate on intake-output studies of human small and large intestine. *Gastroenterology*. **89**: 489–493.

- 8 Twycross RG and Wilcock A (2001) *Symptom Management in Advanced Cancer* (3e). Radcliffe Medical Press, Oxford.
- 9 Hurdon V *et al.* (2000) How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. *Journal of Pain and Symptom Management*. **19**: 130–136.
- 10 Godfrey H (1971) Dangers of dioctyl sodium sulfosuccinate in mixtures. *Journal of the American Medical Association*. **215**: 643.

## LACTULOSE

BNF 1.6.4

**Class:** Osmotic laxative.

**Indications:** Constipation, hepatic encephalopathy.

**Contra-indications:** Intestinal obstruction, galactosaemia.

### Pharmacology

Lactulose is a synthetic disaccharide, a combination of galactose and fructose, which is not absorbed by the small intestine.<sup>1</sup> It is a 'small bowel flusher', i.e. through an osmotic effect, lactulose deposits a large volume of fluid into the large intestine. Lactulose is fermented in the large intestine to acetic, formic and lactic acids, hydrogen and carbon dioxide, with an increase in faecal acidity, which also stimulates peristalsis. The low pH discourages the proliferation of ammonia-producing organisms and thereby reduces the absorption of ammonium ions and other nitrogenous compounds; hence its use in hepatic encephalopathy.<sup>2</sup> Lactulose does not affect the management of diabetes mellitus; 5ml contains 19 calories, but because bio-availability is negligible, the number of calories absorbed is much lower. Although lactulose is cheaper than **macrogol 3350** (another osmotic laxative, see p.35), it is less effective and less well tolerated.<sup>3</sup> A systematic review found only moderate evidence in favour of lactulose (grade IIB), whereas the evidence in favour of **macrogol 3350** was graded as good (grade IA).<sup>4</sup>

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

- lactulose vs. **senna**<sup>5</sup>
- lactulose and **senna** vs. **co-danthramer (dantrolone and poloxamer)**<sup>6</sup>
- lactulose and **senna** vs. **magnesium hydroxide and liquid paraffin**.<sup>7</sup>

A significant difference between treatments was seen only in the second RCT.<sup>6</sup> The combination of lactulose and **senna** was significantly better at relieving constipation than **co-danthramer**. However, *PCF* generally discourages the use of lactulose because of its relative expense and its propensity for causing gastro-intestinal discomfort (see p.34).

**Onset of action** up to 48h.

### Cautions

Lactose intolerance.

### Undesirable effects

*For full list, see manufacturers' SPCs.*

Abdominal bloating, flatulence, nausea, intestinal colic.

### Dose and use

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

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

### Supply

Lactulose (non-proprietary)

**Oral solution** 10g/15ml, 28 days @ 15ml b.d. = £5.

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## MACROGOLS (POLYETHYLENE GLYCOLS) BNF 1.6.4

**Class:** Osmotic laxative.

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

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

### Pharmacology

Macrogols have an osmotic action and retain water in the intestines. In constipated patients, this will hydrate hardened faeces, increase faecal volume, and stimulate and ease defaecation. Macrogol 3350 and 4000 are available in the UK (the numbers refer to their respective molecular weights).

Macrogol 3350 was developed from large-volume pre-operative bowel clearing solutions, and contains electrolytes to ensure that there is virtually no net gain or loss of sodium and potassium from the body. However, the *rate of administration* should be restricted in patients with cardiovascular impairment when taking high doses for faecal impaction (see Dose and use below). Macrogol 4000 contains no electrolytes because they are unnecessary for the laxative effects of macrogols, and are possibly disadvantageous in patients on salt-restricted diets.<sup>1</sup>

Macrogols are unchanged in the GI tract, virtually unabsorbed and have no known pharmacological activity. Any traces of absorbed macrogol are excreted via the urine; no dose reduction is required in renal impairment.

Although more expensive than **lactulose** (see p.34), macrogols are more effective in the management of chronic constipation in adults and better tolerated.<sup>2,3</sup> At some centres, macrogol 3350 is a first-line laxative for opioid-induced constipation, often supplemented with a contact (stimulant) laxative.<sup>4</sup> In an open study in 27 adults of its use in faecal impaction without concurrent rectal measures, macrogol 3350 cleared the impaction in 44% in  $\leq 1$  day, 85% in  $\leq 2$  days, and 89% in  $\leq 3$  days.<sup>5,6</sup> There are no published studies of macrogol 4000 in palliative care.

Some patients who dislike the sweetness or syrupy texture of **lactulose** find macrogols more palatable. Similarly, some patients prefer macrogol 4000 because they dislike the saltiness of macrogol 3350.

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

### Undesirable effects

For full list, see manufacturers' SPCs.

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

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

### Dose and use

Macrogols are supplied as powder in sachets. Each sachet is dissolved in water:

- macrogol 3350, dissolve in half a glass of water (about 125ml)
- macrogol 4000, dissolve in a glass of water (about 250ml).

A half-strength macrogol 3350 product is available for fine-tuning the dose.

**Constipation**

The solution is used immediately after reconstitution:

- start with 1 sachet daily
- if necessary, increase to:
  - ▷ 1 sachet b.d.–t.d.s. (macrogol 3350)
  - ▷ 2 sachets o.m. or 1 sachet b.d. (macrogol 4000).

**Faecal impaction**

Macrogol 3350:

- start with 8 sachets on day 1, each dissolved in 125ml of water, and taken in < 6h (total 1L)
  - patients with cardiovascular impairment should restrict intake to 2 sachets/h, i.e. 250ml/h
  - if necessary, repeat on days 2 and 3; most patients do not need the full dose on the second day.
- For convenience, all 8 sachets can be made up together in 1L of water and kept in a refrigerator for a maximum of 6h, after which any remaining solution should be discarded.

**Supply**

Macrogol 3350

Movicol<sup>®</sup> (Norgine)

**Oral powder** macrogol 3350 13.125g, sodium bicarbonate 178.5mg, sodium chloride 350.7mg, potassium chloride 46.6mg/sachet, 28 days @ 1 sachet o.d. = £6; lime-lemon flavour.

Movicol-Half<sup>®</sup> (Norgine)

**Oral powder** macrogol 3350 6.563g, sodium bicarbonate 89.3mg, sodium chloride 175.4mg, potassium chloride 23.3mg/sachet, 28 days @ 1 sachet o.d. = £4; lime-lemon flavour.

Macrogol 4000

Idrolax<sup>®</sup> (Ipsen)

**Oral powder** macrogol 4000 10g/sachet, 28 days @ 1 sachet o.d. = £7; orange-grapefruit flavour.

- 1 Hudziak H et al. (1996) [Low-dose polyethylene glycol 4000: digestive effects. Randomized double-blind study in healthy subjects]. *Gastroenterologie Clinique et Biologique*. **20**: 418–423.
- 2 Attar A et al. (1999) Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. *Gut*. **44**: 226–230.
- 3 Ramkumar D and Rao SS (2005) Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. *American Journal of Gastroenterology*. **100**: 936–971.
- 4 Wirz S and Klaschik E (2005) Management of constipation in palliative care patients undergoing opioid therapy: is polyethylene glycol an option? *American Journal of Hospice and Palliative Care*. **22**: 375–381.
- 5 Culbert P et al. (1998) Highly effective oral therapy (polyethylene glycol/electrolyte solution) for faecal impaction and severe constipation. *Clinical Drug Investigation*. **16**: 355–360.
- 6 Culbert P et al. (1998) Highly effective new oral therapy for faecal impaction. *British Journal of General Practice*. **48**: 1599–1600.

**MAGNESIUM SALTS****BNF 1.6.4**

**Class:** Osmotic laxative.

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

**Pharmacology**

Magnesium and sulphate ions are poorly absorbed from the gut. Their action is mainly osmotic but other factors may be important, e.g. the release of cholecystokinin.<sup>1,2</sup> Magnesium ions also decrease absorption or increase secretion in the small bowel. Total faecal PGE<sub>2</sub> increases progressively as the dose of magnesium hydroxide is raised from 1.2 to 3.2g daily.<sup>3</sup> Also see **Magnesium**, p.407.

An RCT of magnesium hydroxide and **liquid paraffin** vs. **senna** and **lactulose** failed to differentiate between the two combination treatments.<sup>4</sup>

**Cautions**

Risk of hypermagnesaemia in patients with renal impairment.

**Dose and use**

**Magnesium hydroxide** mixture contains about 8% of hydrated magnesium oxide and the usual dose is 25–50ml. **Magnesium sulphate** is a more potent laxative which tends to produce a large volume of liquid stool. The compound is not popular with patients because it often leads to a sense of distension and the sudden passage of offensive liquid faeces which is socially inconvenient; it is very difficult to adjust the dose to produce a normal soft stool. The usual dose is 5–10g of crystals o.m., preferably before breakfast, dissolved in warm water and taken with extra fluid.

**Supply**

All the preparations below are available OTC.

**Magnesium Hydroxide Mixture BP**

**Oral suspension** contains about 8% hydrated magnesium oxide 415mg (7.1mmol elemental magnesium)/5ml, available OTC as Milk of Magnesia<sup>®</sup>; *do not store in a cold place.*

**Magnesium sulphate**

**Oral powder** (Epsom Salts), also Andrew's Liver salts<sup>®</sup> (magnesium sulphate, citric acid, sodium bicarbonate).

**Oral solution** magnesium sulphate (Epsom Salts) 4–5g/10ml prepared extemporaneously.

- 
- 1 Donowitz M (1991) Magnesium-induced diarrhea and new insights into the pathobiology of diarrhea. *New England Journal of Medicine*. **324**: 1059–1060.
  - 2 Harvey R and Read A (1975) Mode of action of the saline purgatives. *American Heart Journal*. **89**: 810–813.
  - 3 Donowitz M and Rood R (1992) Magnesium hydroxide: new insights into the mechanism of its laxative effect and the potential involvement of prostaglandin E<sub>2</sub>. *Journal of Clinical Gastroenterology*. **14**: 20–26.
  - 4 Sykes N A clinical comparison of lactulose and senna with magnesium hydroxide and liquid paraffin emulsion in a palliative care population.; 1991.

**RECTAL PRODUCTS****BNF 1.6.2, 1.6.3 & 1.6.4**

**Indications:** Constipation and faecal impaction if oral laxatives are ineffective.

**Treatment strategy**

One third of patients receiving **morphine** continue to need rectal measures (laxative suppositories, enemas and/or digital evacuation) either regularly or intermittently despite oral laxatives.<sup>1,2</sup> Sometimes these measures are elective, e.g. in paraplegics and in the very old and debilitated (Box 1.F; also see Guidelines, p.28).

In the UK, most patients needing laxative suppositories receive both **glycerol** and **bisacodyl**. **Glycerol** is hygroscopic, and draws fluid into the rectum, thereby softening and lubricating any faeces in the rectum. The laxative effect of **bisacodyl** is the result of local direct contact with the rectal mucosa after dissolution of the suppository and after metabolism by intestinal bacteria to an active metabolite (see p.30). The minimum time for response is thus generally >20min, and may be up to 3h.<sup>3</sup> (Defaecation a few minutes after the insertion of a **bisacodyl** suppository is the result of ano-rectal stimulation.) **Bisacodyl** suppositories occasionally cause faecal leakage, even after a successful evacuation.

Faecal softener micro-enemas contain **docusate sodium**, a wetting agent (see p.33), which allows water to permeate into hard faeces. Osmotic micro-enemas contain mainly **sodium citrate** and **sodium lauryl sulphoacetate** with several excipients, including **glycerol** and sorbitol. **Sodium lauryl sulphoacetate** is a wetting agent (similar to **docusate sodium**), whereas **sodium citrate** draws fluid into the intestine by osmosis, an action enhanced by sorbitol, and displaces bound water from the faeces. Osmotic standard enemas contain phosphates, which

draw fluid into the rectum by osmosis. Digital evacuation is the ultimate approach to faecal impaction; the need for this can be reduced by using oral **macrogols** (see p.35).<sup>4,5</sup>

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

**Suppositories**

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

Bisacodyl 10mg, after hydrolysis by enteric enzymes, stimulates propulsive activity.<sup>6</sup>

Carbalax<sup>®</sup>, a mixture of anhydrous sodium acid phosphate and sodium bicarbonate which reacts in the rectum, releasing 200ml of carbon dioxide and stimulating evacuation by rectal distension.

**Enemas**

Faecal softener micro-enema, contains docusate sodium 120mg per unit.

Lubricant enema (130ml), contains arachis (peanut) oil; this is generally instilled and left overnight before giving a stimulant laxative suppository or an osmotic enema. *Do not use in patients with peanut allergy.*

Osmotic micro-enemas (5ml), contain sodium citrate, sodium lauryl sulphoacetate, glycerol and sorbitol.

Osmotic standard enemas (118–128ml), contain phosphates.

**Supply**

Suppositories

**Glycerol Suppositories BP**

**Suppositories glycerol** 700mg, gelatin 140mg/1g, adult suppositories 4g, 28 days @ 4g o.d. = £4.50.

**Bisacodyl** (non-proprietary)

**Suppositories** 10mg, 28 days @ 10mg o.d. = £2.

Dulco-lax<sup>®</sup> (Boehringer Ingelheim)

**Suppositories** 10mg, 28 days @ 10mg o.d. = £4.50.

**Sodium acid phosphate**

Carbalax<sup>®</sup> (Forest)

**Suppositories sodium acid phosphate** (anhydrous) 1.3g, **sodium bicarbonate** 1.08g, 28 days @ 1 o.d. = £4.50.

Faecal softener enema

Norgalax Micro-enema<sup>®</sup> (Norgine), **docusate sodium** 120mg in 10g single-use disposable pack, 1 enema = £0.50.

Lubricant enema

Fletcher's Arachis Oil Retention Enema<sup>®</sup> (Forest), **arachis** (peanut) **oil** in 130ml single-dose disposable pack, 130ml = £1; *do not use in patients with peanut allergy.*

Osmotic micro-enemas

These all contain **sodium citrate**, **sodium lauryl sulphoacetate**, **glycerol** and sorbitol and are supplied in 5ml single-dose disposable packs with nozzle:

Micolette<sup>®</sup> (Pinewood), 5ml = £0.50.

Micralax<sup>®</sup> (Celltech), 5ml = £0.50.

Relaxit<sup>®</sup> (Crawford), 5ml = £0.50.

Osmotic standard enemas

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

Fletcher's Phosphate enema<sup>®</sup> (Forest), **sodium acid phosphate** 12.8g, **sodium phosphate** 10.24g in 128ml, 1 enema with standard tube = £0.50, 1 enema with long rectal tube = £0.50.

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

## PRODUCTS FOR HAEMORRHOIDS

## BNF 1.7 & 15.2

Because haemorrhoids are often more troublesome if associated with the evacuation of hard faeces, constipation must be corrected (see Laxatives, p.24). Peri-anal pruritus, soreness and excoriation are best treated by the application of a bland ointment or cream. Soothing products containing mild astringents such as **bismuth subgallate**, **zinc oxide** and **witch hazel (hamamelis)** all give symptomatic relief in haemorrhoids. Many proprietary products also contain lubricants, vasoconstrictors and antiseptics.

Local anaesthetics relieve pruritus ani as well as pain associated with haemorrhoids. **Lidocaine** ointment can be used before defaecation to relieve pain associated with an anal fissure. Local anaesthetic ointments are absorbed through the rectal mucosa and could produce a systemic effect if applied excessively. They should be used for only a few days because, apart from **lidocaine**, they can cause contact dermatitis. Corticosteroids can be combined with local anaesthetics and astringents; suitable for short-term use after exclusion of infection, such as *Herpes simplex*. Pain associated with spasm of the internal anal sphincter may be helped by topical **glyceryl trinitrate** ointment (see p.55).

### Dose and use

#### Anusol<sup>®</sup>

For haemorrhoids, pruritus ani and peri-anal excoriation:

- apply cream or ointment topically b.d. and after defaecation
- insert suppository after defaecation and o.n.

#### Lidocaine ointment 5%

For pain from haemorrhoids, pruritus ani and anal fissure:

- apply topically p.r.n. and before defaecation.

#### Scheriproct<sup>®</sup>

For anal pain:

- apply ointment topically b.d. for 5–7 days (t.d.s.–q.d.s. on first day if necessary), then daily for a few days after symptoms have cleared
- insert suppository o.d. after defaecation for 5–7 days (in severe cases initially b.d.–t.d.s.).

#### Xyloproct<sup>®</sup>

For pain from haemorrhoids, pruritus ani and anal fissure:

- apply ointment topically p.r.n. for up to 3 weeks.

### Supply

Anusol<sup>®</sup> (Pfizer Consumer Healthcare)

**Cream, ointment and suppositories bismuth oxide, bismuth subgallate, Peru balsam, zinc oxide**, all available OTC.

**Lidocaine** (non-proprietary)

**Ointment 5%**, 15g = £1.

With corticosteroids

Scheriproct<sup>®</sup> (Schering Health)

**Ointment cinchocaine 0.5%, prednisolone hexanoate 0.19%, 30g = £3.**

**Suppositories cinchocaine 1mg, prednisolone hexanoate 1.3mg, pack of 12 = £1.50.**

Xyloproct<sup>®</sup> (AstraZeneca)

**Ointment (water-miscible) aluminium acetate 3.5%, hydrocortisone acetate 0.275%, lidocaine 5%, zinc oxide 18%, 20g (with applicator) = £2.50.**

## PANCREATIN

## BNF 1.9.4

**Class:** Enzyme supplement.

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

### Pharmacology

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

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

### Cautions

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

If mixing with food or drinks:

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

### Undesirable effects

For full list, see manufacturers' SPCs.

**Very common (>10%):** abdominal pain.

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

### Dose and use

There are several different proprietary preparations of pancreatin, of which Creon<sup>®</sup> is a good choice. Capsule strength denotes lipase unit content.

In adults, start with Creon<sup>®</sup> 10 000. The granules in the capsules are e/c and, if preferred, may be added to fluid or soft food and *swallowed without chewing*:

- Creon<sup>®</sup> 10 000, initially give 1–2 capsules with each meal
- Creon<sup>®</sup> 25 000, initially give 1 capsule with each meal.

The dose is adjusted upwards according to faecal size, consistency, and number. Extra capsules may be needed if snacks are taken between meals. If the pancreatin continues to seem ineffective, prescribe a PPI or H<sub>2</sub>-receptor antagonist concurrently, and review.

### Supply

Creon<sup>®</sup> (Solvay)

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

**Capsules enclosing e/c granules** Creon 10 000, 28 days @ 2 t.d.s. = £28.

**Capsules enclosing e/c pellets** Creon 25 000, 28 days @ 1 t.d.s. = £25.