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Prescribing in Palliative Care

In recent years there has been increased interest in providing better treatment and support for patients with terminal illness. The aim is to keep them as comfortable, alert, and free of pain as possible. It may also be necessary to direct attention to emotional, financial, social, or family problems. The patient's minister or the hospital chaplain may give invaluable help.

DOMICILIARY CARE. If they wish, whenever possible, patients should end their days in their own homes. Although families may at first be afraid of caring for the patient at home, they will usually do so if extra support from district nursing services, social services and voluntary agencies is provided. Families may be reassured if an assurance is given that the patient will be admitted to a hospital or hospice if they cannot cope.

HOSPITAL OR HOSPICE CARE. The most important lesson to be drawn from the experience of hospices is that both doctors and nurses must give time to listen to the patient. This gives great support and comfort to a patient who may otherwise suffer intolerable loneliness. Often problems come to light that can easily be dealt with—adjusting a blind in the late afternoon, an irritating noise to be avoided, drinks to be placed in easier reach, someone to read the newspaper, or the TV to be replaced by radio. The staff should not exclude the family from contributing to the patient's care; if prevented they may be resentful or subsequently suffer a feeling of guilt.

DRUG TREATMENT. The number of drugs should be as few as possible, for even the taking of medicine may be an effort. Oral medication is usually satisfactory unless there is severe nausea and vomiting, dysphagia, weakness, or coma, in which case parenteral medication may be necessary.

PAIN

Analgesics are always more effective in preventing the development of pain than in the relief of established pain.

The **non-opioid** analgesics aspirin or paracetamol given regularly will often make the use of opioids unnecessary. Aspirin (or other NSAIDs if preferred) may also control the pain of *bone secondaries*; naproxen, flurbiprofen, and indomethacin (see section 10.1.1) are valuable and if necessary can be given rectally. Radiotherapy, radioactive isotopes of **strontium** (Metastron® available from Amersham) and bisphosphonates (section 6.6.2) may also be useful for pain due to bone metastases.

Morphine is the most useful of the **opioid** analgesics. In addition to relief of pain, it confers a state of euphoria and mental detachment.

ORAL ROUTE. Morphine is given *by mouth* as an oral solution regularly every 4 hours, the initial dose depending largely on the patient's previous treatment. A dose of 5–10 mg is enough to replace a weaker analgesic (such as paracetamol or co-proxamol), but 10–20 mg or more is required to replace a strong one (comparable to morphine itself). If the first dose of morphine is no more effective than the previous analgesic it should be increased by 50%, the aim being to choose the lowest dose which prevents pain. Although a dose of 5–20 mg is usually adequate there should be no hesitation in increasing it stepwise according to response to 100 mg or occasionally up to 500 mg or higher if necessary. If pain occurs between doses the next dose due is increased; in the interim an additional dose is given. The dose should be adjusted with careful assessment of the pain and the use of other drugs (such as NSAIDs) should also be considered.

Modified-release preparations of morphine are an alternative to the oral solution. Depending on the formulation of the modified-release preparation, the total daily morphine requirement may be given in two equal doses or as a single dose.

Preparations suitable for twice daily administration include *MST Continus*® tablets or suspension and *Oramorph*® *SR* tablets. Preparations that allow administration of the total daily morphine requirement as a single dose include *MXL*® capsules. *Morcap SR*® capsules may be given either twice daily or as a single daily dose.

The starting dose of modified-release preparations designed for twice daily administration is usually 10–20 mg every 12 hours if no other analgesic (or only paracetamol) has been taken previously, but to replace a weaker opioid analgesic (such as co-proxamol) the starting dose is usually 20–30 mg every 12 hours. Increments should be made to the dose, not to the frequency of administration, which should remain at every 12 hours.

The effective dose of modified-release preparations can alternatively be determined by giving the oral solution of morphine every 4 hours in increasing doses until the pain has been controlled, and then transferring the patient to the same total 24-hour dose of morphine given as the modified-release preparation (divided into two portions for 12-hourly administration). The first dose of the modified-release preparation is given 4 hours after the last dose of the oral solution.[1]

Morphine, as oral solution or standard formulation tablets, should be prescribed for breakthrough pain.

PARENTERAL ROUTE. If the patient becomes unable to swallow, the equivalent intramuscular dose of morphine is half the oral solution dose; in the case of the modified-release tablets it is half the total 24-hour dose (which is then divided into 6 portions to be given every 4 hours). **Diamorphine** is preferred for injection because being more soluble it can be given in a smaller volume. The equivalent intramuscular (or subcutaneous) dose of diamorphine is only about a quarter to a third of the oral dose of morphine; *subcutaneous infusion via syringe driver* can be useful (for details, see p. 14).

1. Studies have indicated that administration of the last dose of the *oral solution* with the first dose of the *modified-release tablets* is not necessary.

RECTAL ROUTE. Morphine is also available for *rectal administration* as suppositories; alternatively oxycodone suppositories can be obtained on special order.

TRANSDERMAL ROUTE. Transdermal preparations of fentanyl are now available, see section 4.7.2. Careful conversion from oral morphine to transdermal fentanyl is necessary; a 25 micrograms/hr patch is equivalent to a total dose of morphine up to 135 mg/24 hours

GASTRO-INTESTINAL PAIN. The pain of *bowel colic* may be reduced by loperamide 2–4 mg 4 times daily. Hyoscine hydrobromide may also be helpful, given sublingually at a dose of 300 micrograms 3 times daily as Kwells® (Roche Consumer Health) tablets. For the dose by subcutaneous infusion using a syringe driver, see p. 14.

Gastric distension pain due to pressure on the stomach may be helped by a preparation incorporating an antacid with an antiflatulent (see section 1.1.1) and by domperidone 10 mg 3 times daily before meals.

MUSCLE SPASM. The pain of muscle spasm can be helped by a muscle relaxant such as diazepam 5–10 mg daily or baclofen 5–10 mg 3 times daily.

NERVE PAIN. Pain due to nerve compression may be reduced by a corticosteroid such as dexamethasone 8 mg daily, which reduces oedema around the tumour, thus reducing compression.

Dysaesthetic or stabbing pain resulting from nerve irritation may be reduced by amitriptyline 25–75 mg at night, or by carbamazepine 200 mg 3 times daily.

Nerve blocks may be considered when pain is localised to a specific area. **Transcutaneous electrical nerve stimulation** (TENS) may also provide useful relief of pain.

MISCELLANEOUS CONDITIONS

[redacted]

RAISED INTRACRANIAL PRESSURE. Headache due to raised intracranial pressure often responds to a high dose of a corticosteroid, such as dexamethasone 16 mg daily for 4 to 5 days, subsequently reduced to 4–6 mg daily if possible.

INTRACTABLE COUGH. Intractable cough may be relieved by moist inhalations or may require regular administration of an oral morphine hydrochloride (or sulphate) solution in an initial dose of 5 mg every 4 hours. Methadone linctus should be avoided as it has a long duration of action and tends to accumulate.

DYSPNOEA. Dyspnoea may be relieved by regular oral morphine hydrochloride (or sulphate) solution in carefully titrated doses, starting at 5 mg every 4 hours. Diazepam 5–10 mg daily may be helpful; a corticosteroid, such as dexamethasone 4–8 mg daily, may also be helpful if there is bronchospasm or partial obstruction.

EXCESSIVE RESPIRATORY SECRETION. Excessive respiratory secretion (death rattle) may be reduced by subcutaneous injection of hyoscine hydrobromide 400–600 micrograms every 4 to 8 hours; care must however be taken to avoid the discomfort of dry mouth. For the dose by subcutaneous infusion using a syringe driver, see next page.

RESTLESSNESS AND CONFUSION. Restlessness and confusion may require treatment with haloperidol 1–3 mg by mouth every 8 hours. Chlorpromazine 25–50 mg by mouth every 8 hours is an alternative, but causes more sedation. Methotrimeprazine is also used occasionally for restlessness. For the dose by subcutaneous infusion using a syringe driver, see next page

HICCUP. Hiccup due to gastric distension may be helped by a preparation incorporating an antacid with an antiflatulent (see section 1.1.1). If this fails, metoclopramide 10 mg every 6 to 8 hours by mouth or by intramuscular injection can be added; if this also fails, chlorpromazine 10–25 mg every 6 to 8 hours can be tried.

ANOREXIA. Anorexia may be helped by prednisolone 15–30 mg daily or dexamethasone 2–4 mg daily.

CONSTIPATION. Constipation is a very common cause of distress and is almost invariable after administration of an opioid. It should be prevented if possible by the regular administration of laxatives; a faecal softener with a peristaltic stimulant (e.g. co-danthramer), or lactulose solution with a senna preparation should be used (see sections 1.6.2 and 1.6.3).

FUNGATING GROWTH. Fungating growth may be treated by cleansing with a mixture of 1 part of 4% povidone–iodine skin cleanser solution and 4 parts of liquid paraffin. Oral administration of metronidazole (see section 5.1.11) may eradicate the anaerobic bacteria responsible for the odour of fungating tumours; topical application (see section 13.10.1.2) is also used.

CAPILLARY BLEEDING. Capillary bleeding may be reduced by applying gauze soaked in adrenaline solution (1 in 1000).

DRY MOUTH. Dry mouth may be relieved by good mouth care and measures such as the sucking of ice or pineapple chunks or the use of artificial saliva (section 12.3.5); dry mouth associated with candidiasis can be treated by oral preparations of nystatin or miconazole (section 12.3.2); alternatively, fluconazole can be given by mouth (section 5.2). Dry mouth may be caused by certain medication including opioids, antimuscarinic drugs (e.g. hyoscine), antidepressants and some anti-emetics; if possible, an alternative preparation should be considered.

PRURITUS. Pruritus, even when associated with obstructive jaundice, often responds to simple measures such as emollients. In the case of obstructive jaundice, further measures include administration of cholestyramine or an anabolic steroid, such as stanozolol 5–10 mg daily; antihistamines can be helpful (see section 3.4.1).

CONVULSIONS. Patients with cerebral tumours or uraemia may be susceptible to convulsions. Prophylactic treatment with phenytoin or carbamazepine (see section 4.8.1) should be considered. When oral medication is no longer possible, diazepam as suppositories 10–20 mg every 4 to 8 hours, or phenobarbitone by injection 50–200 mg twice daily is continued as prophylaxis. For the use of midazolam by subcutaneous infusion using a syringe driver, see next page.

DYSPHAGIA. A corticosteroid such as dexamethasone 8 mg daily may help, temporarily, if there is an obstruction due to tumour. See also under Dry Mouth.

NAUSEA AND VOMITING. Nausea and vomiting are very common in patients with advanced cancer. The cause should be diagnosed before treatment with anti-emetics (see section 4.6) is started. Octreotide (see section 8.3.4.3), which stimulates water and electrolyte absorption and inhibits water secretion in the small bowel, can be used by subcutaneous infusion, in a dose of 300–600 micrograms/24 hours to reduce intestinal secretions and vomiting.

Nausea and vomiting may also occur in the initial stages of morphine therapy but can be prevented by giving an anti-emetic such as haloperidol 1.5 mg daily (or twice daily if nausea continues) or prochlorperazine (see section 4.6). An anti-emetic is usually only necessary for the first 4 or 5 days therefore fixed-combination opioid preparations containing an anti-emetic are not recommended since they lead to unnecessary anti-emetic therapy (often with undesirable drowsiness). For the administration of anti-emetics by subcutaneous infusion using a syringe driver, see below.

For the treatment of nausea and vomiting associated with cancer chemotherapy, see section 8.1.

INSOMNIA. Patients with advanced cancer may not sleep because of discomfort, cramps, night sweats, joint stiffness, or fear. There should be appropriate treatment of these problems before hypnotics are used. Benzodiazepines, such as temazepam, may be useful (see section 4.1.1).

HYPERCALCAEMIA. See section 9.5.1.2.

SYRINGE DRIVERS

Although drugs can usually be administered *by mouth* to control the symptoms of advanced cancer, the parenteral route may sometimes be necessary. If the parenteral route is necessary, repeated administration of *intramuscular injections* can be difficult in a cachectic patient. This has led to the use of a portable syringe driver to give a *continuous subcutaneous infusion*, which can provide good control of symptoms with little discomfort or inconvenience to the patient.

Indications for the parenteral route are:

- the patient is unable to take medicines by mouth owing to *nausea and vomiting, dysphagia, severe weakness,* or *coma;*
- there is *malignant bowel obstruction* in patients for whom further surgery is inappropriate (avoiding the need for an intravenous infusion or for insertion of a nasogastric tube);
- occasionally when the patient *does not wish* to take regular medication by mouth.

NAUSEA AND VOMITING. **Haloperidol** is given in a *subcutaneous infusion* dose of 2.5–10 mg/24 hours.

Methotrimeprazine causes sedation in about 50% of patients; it is given in a *subcutaneous infusion dose* of 25–200 mg/24 hours, although lower doses of 5–25 mg/24 hours may be effective with less sedation.

Cyclizine is particularly liable to precipitate if mixed with diamorphine or other drugs (see under Mixing and Compatibility, below); it is given in a *subcutaneous infusion dose* of 150 mg/24 hours.

Metoclopramide may cause skin reactions; it is given in a *subcutaneous infusion dose* of 30–60 mg/24 hours.

BOWEL COLIC AND EXCESSIVE RESPIRATORY SECRETIONS. **Hyoscine hydrobromide** effectively reduces respiratory secretions and is sedative (but occasionally causes paradoxical agitation); it is given in a *subcutaneous infusion dose* of 0.6–2.4 mg/24 hours.

Hyoscine butylbromide is effective in bowel colic, is less sedative than hyoscine hydrobromide, but is not always adequate for the control of respiratory secretions; it is given in a *subcutaneous infusion dose* of 20–60 mg/24 hours (important: this dose of *hyoscine butylbromide* must not be confused with the much lower dose of *hyoscine hydrobromide*, above).

RESTLESSNESS AND CONFUSION. **Haloperidol** has little sedative effect; it is given in a *subcutaneous infusion dose* of 5–30 mg/24 hours.

Methotrimeprazine has a sedative effect; it is given in a *subcutaneous infusion dose* of 50–200 mg/24 hours.

Midazolam is a sedative and an antiepileptic, and is therefore suitable for a very restless patient; it is given in a *subcutaneous infusion dose* of 20–100 mg/24 hours.

CONVULSIONS. If a patient has previously been receiving an antiepileptic *or* has a primary or secondary cerebral tumour *or* is at risk of convulsion (e.g. owing to uraemia) antiepileptic medication should not be stopped. **Midazolam** is the benzodiazepine antiepileptic of choice for *continuous subcutaneous infusion*, and is given in a dose of 20–40 mg/24 hours.

PAIN CONTROL. **Diamorphine** is the preferred opioid since its high solubility permits a large dose to be given in a small volume (see under Mixing and Compatibility, below). The table on the next page gives the approximate doses of *morphine by mouth* (as oral solution or standard tablets or as modified-release tablets) equivalent to *diamorphine by injection* (intramuscularly or by subcutaneous infusion).

MIXING AND COMPATIBILITY. The general principle that injections should be given into separate sites (and should not be mixed) does not apply to the use of syringe drivers in palliative care. Provided that there is evidence of compatibility, selected injections can be mixed in syringe drivers. Not all types of medication can be used in a subcutaneous infusion. In particular, **chlorpromazine, prochlorperazine** and **diazepam** are **contra-indicated** as they cause skin reactions at the injection site; to a lesser extent **cyclizine** and **methotrimeprazine** may also sometimes cause local irritation.

In theory injections dissolved in **water for injections** are more likely to be associated with pain (possibly owing to their hypotonicity). The use of **physiological saline** (sodium chloride 0.9%) however increases the likelihood of precipitation when more than one drug is used; moreover subcutaneous infusion rates are so slow (0.1–0.3 mL/hour) that pain is not usually a problem when water is used as a diluent.

Diamorphine can be given by subcutaneous infusion in a strength of up to 250 mg/mL; up to a strength of 40 mg/mL either *water for injections* or *physiological saline* (sodium chloride 0.9%) is a suitable diluent—above that strength only *water for injections* is used (to avoid precipitation).

The following can be mixed with *diamorphine:*

Cyclizine[1]
Dexamethasone[2]
Haloperidol[3]
Hyoscine butylbromide
Hyoscine hydrobromide
Methotrimeprazine
Metoclopramide[4]
Midazolam

1. Cyclizine may precipitate at concentrations above 10 mg/mL *or* in the presence of physiological saline *or* as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also liable to precipitate after 24 hours.
2. Special care is needed to avoid precipitation of dexamethasone when preparing.
3. Mixtures of haloperidol and diamorphine are liable to precipitate after 24 hours if haloperidol concentration is above 2 mg/mL.
4. Under some conditions metoclopramide may become discoloured; such solutions should be discarded.

Subcutaneous infusion solution should be monitored regularly both to check for precipitation (and discoloration) and to ensure that the infusion is running at the correct rate.

PROBLEMS ENCOUNTERED WITH SYRINGE DRIVERS. The following are problems that may be encountered with syringe drivers and the action that should be taken:

- if the subcutaneous infusion runs *too quickly* check the rate setting and the calculation;
- if the subcutaneous infusion runs *too slowly* check the start button, the battery, the syringe driver, the cannula, and make sure that the injection site is not inflamed;
- if there is an *injection site reaction* make sure that the site does not need to be changed—firmness or swelling at the site of injection is not in itself an indication for change, but pain or obvious inflammation is.

[redacted]

Equivalent doses of morphine sulphate by mouth (as oral solution or standard tablets *or* as modified-release tablets) *or* of diamorphine hydrochloride by intramuscular injection *or by* subcutaneous infusion

These equivalences are approximate only and may need to be adjusted according to response

ORAL MORPHINE		PARENTERAL DIAMORPHINE	
Morphine sulphate oral solution or standard tablets	Morphine sulphate modified-release tablets	Diamorphine hydrochloride by intramuscular injection	Diamorphine hydrochloride by subcutaneous infusion
every 4 hours	**every 12 hours**	**every 4 hours**	**every 24 hours**
5 mg	20 mg	2.5 mg	15 mg
10 mg	30 mg	5 mg	20 mg
15 mg	50 mg	5 mg	30 mg
20 mg	60 mg	7.5 mg	45 mg
30 mg	90 mg	10 mg	60 mg
40 mg	120 mg	15 mg	90 mg
60 mg	180 mg	20 mg	120 mg
80 mg	240 mg	30 mg	180 mg
100 mg	300 mg	40 mg	240 mg
130 mg	400 mg	50 mg	300 mg
160 mg	500 mg	60 mg	360 mg
200 mg	600 mg	70 mg	400 mg

If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection of diamorphine equivalent to one-sixth of the total 24-hour subcutaneous infusion dose. It is kinder to give an intermittent bolus injection *subcutaneously*—absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle).

To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.

Anadin Paracetamol® (paracetamol), Andrews Answer® (paracetamol, caffeine), Angettes 75® (aspirin), Askit® (aspirin, aloxiprin = polymeric product of aspirin, caffeine), Aspro® (aspirin), Aspro Clear® (aspirin)

Bayer Aspirin® (aspirin), Beechams All-in-One®, (paracetamol, guaphenesin, phenylephrine), Beechams Flu-Plus Powder®, Beechams Hot Lemon®, Hot Lemon and Honey®, Hot Blackcurrant® (all paracetamol, phenylephrine), Beechams Flu-Plus Caplets® (paracetamol, caffeine, phenylephrine), Beechams Powders® (aspirin, caffeine), Beechams Powders Capsules® With Decongestant (paracetamol, caffeine, phenylephrine), Beecham Aspirin®, Beechams Powders Tablets® (both aspirin), Benylin 4 Flu® (paracetamol, diphenhydramine, pseudoephedrine), Benylin Day and Night® (*day tablets*, paracetamol, phenylpropanolamine, *night tablets*, paracetamol, diphenhydramine), Boots Cold & Flu Relief Tablets® (paracetamol, caffeine, phenylephrine), Boots Children's Cold Relief®, Boots Cold Relief Hot Blackcurrant®, Hot Lemon® (paracetamol), Boots Day Cold Comfort® (paracetamol, pholcodine, pseudoephedrine), Boots Headache and Indigestion Relief® (paracetamol, caffeine), Boots Night-Cold Comfort® (diphenhydramine, paracetamol, pholcodine, pseudoephedrine), Boots Children's Pain Relief Syrup® (paracetamol), Boots Pain Relief Tablets® (paracetamol, caffeine), Boots Migraine Relief® (codeine, paracetamol)

Calpol Infant®, Calpol 6 Plus®, Calpol Paediatric® (all paracetamol), Ceprin® (aspirin), Catarrh-Ex® (paracetamol, caffeine, phenylephrine), Codis 500® (aspirin, codeine), Coldrex Blackcurrant Powders®, Hot Lemon Powders® (both paracetamol, phenylephrine), Coldrex Tablets® (paracetamol, caffeine, phenylephrine), Mrs. Cullen's® (aspirin), Cupanol Over 6®, Cupanol Under 6® (both paracetamol)

Day Nurse® (paracetamol, dextromethorphan, phenylpropanolamine), De Witt's Analgesic Pills® (paracetamol, caffeine), Disprin®, Disprin CV®, Disprin Direct® (all aspirin), Disprin Extra® (aspirin, paracetamol), Disprol® (paracetamol), Dristan Tablets® (aspirin, caffeine, chlorpheniramine, phenylephrine)

EP® (paracetamol, caffeine, codeine)

Fanalgic® (paracetamol), Femigraine® (aspirin, cyclizine), Feminax® (paracetamol, caffeine, codeine, hyoscine), Fennings Children's Cooling Powders® (paracetamol), Flurex Bedtime® (paracetamol, diphenhydramine, pseudoephedrine), Fynnon® Calcium Aspirin (aspirin)

Hedex® (paracetamol), Hedex Extra® (paracetamol, caffeine), Hedex Headcold Caplets® (paracetamol, caffeine, phenylephrine), Hedex Headcold Powders® (paracetamol, phenylephrine), Hill's Balsem Flu Strength Hot Lemon Powders® (paracetamol)

Infadrops® (paracetamol)

Lem-Plus Capsules® (paracetamol, caffeine, phenylephrine), Lem-Plus Powders® (paracetamol), Lemsip Lemcaps® (paracetamol, caffeine, phenylephrine), Lemsip Cool Lemon®, Lemsip Flu Strength®, Lemsip Lemon® or Blackcurrant®, Lemsip Max Strength®, Lemsip Menthol Extra® (all paracetamol, phenylephrine), Lemsip Flu Strength Nightime® (paracetamol, chlorpheniramine, dextromethorphan, phenylpropanolamine)

Maximum Strength Aspro Clear® (aspirin), Medinol® (paracetamol), Medleed® (paracetamol, promethazine), Migraleve® (paracetamol, isomethaptene mucate), Migraleve® (*pink tablets*, paracetamol, codeine, buclizine, *yellow tablets*, paracetamol, codeine), Miradol® (paracetamol), Mu-Cron Tablets® (paracetamol, phenylpropanolamine)

Night Nurse® (paracetamol, dextromethorphan, promethazine), Nurse Sykes' Powders® (aspirin, caffeine, paracetamol)

Paldesic® (paracetamol), Panadeine® (paracetamol, codeine), Panadol®, Panadol Baby and Infant® (both paracetamol), Panadol Extra® (paracetamol, caffeine), Panadol Junior® (paracetamol), Panadol Night® (paracetamol, diphenhydramine), Panadol Ultra® (paracetamol, codeine), Panaleve Junior®, Panaleve 6+® (both paracetamol), Panerel® (paracetamol, codeine), Paracets® (paracetamol), Paraclear Extra Strength® (paracetamol, caffeine), Paraclear® (paracetamol), Paracodol® (paracetamol, codeine), Paramin® (paracetamol), Paramol® (paracetamol, dihydrocodeine), Phensic® (aspirin, caffeine), Placidex® (paracetamol), Resolve® (aspirin, caffeine, paracetamol), Propain® (paracetamol, caffeine, codeine, diphenhydramine)

Resolve® (paracetamol)

Salzone® (paracetamol), Sinutab® (paracetamol, phenylpropanolamine), Sinutab Nightime® (paracetamol, phenylpropanolamine, phenyltoloxamine), Solpadeine® (paracetamol, caffeine, codeine), SP Cold Relief Capsules® (paracetamol, caffeine, phenylephrine), Sudafed Co® (paracetamol, pseudoephedrine), Syndol® (paracetamol, caffeine, codeine, doxylamine)

Toptabs® (aspirin, caffeine), Tramil® 500 (paracetamol), Triogesic® (paracetamol, phenylpropanolamine)

Unifflu with Gregovite C® (paracetamol, caffeine, codeine, diphenhydramine, phenylephrine)

Veganin® (aspirin, paracetamol, codeine), Vicks® Cold care (paracetamol, dextromethorphan, phenylpropanolamine), Vicks Medinite® (paracetamol, dextromethorphan, doxylamine, ephedrine)

IBUPROFEN

Indications: fever and pain in children; see also section 10.1.1

Cautions; Contra-indications; Side-effects: see section 10.1.1

Dose: see section 10.1.1; CHILD, fever and pain see below

Fever and pain in children

Junifen Sugar Free® (Crookes)

Suspension, sugar-free, ibuprofen 100 mg/5 mL, net price 150-mL pack = £2.37. Label: 21

Dose: fever and pain in children, under 1 year not recommended, 1–12 years 20 mg/kg daily in divided doses *or* 1–2 years 2.5 mL 3–4 times daily, 3–7 years 5 mL, 8–12 years 10 mL

Other preparations: see section 10.1.1

NEFOPAM HYDROCHLORIDE

Indications: moderate pain

Cautions: hepatic or renal disease, elderly, urinary retention; pregnancy and breast-feeding; interactions: Appendix 1 (nefopam)

Contra-indications: convulsive disorders; not indicated for myocardial infarction

Side-effects: nausea, nervousness, urinary retention, dry mouth, lightheadedness; less frequently vomiting, blurred vision, drowsiness, sweating, insomnia, tachycardia, headache; confusion and hallucinations also reported; may colour urine (pink)

Dose: by mouth, initially 60 mg (elderly, 30 mg) 3 times daily, adjusted according to response; usual range 30–90 mg 3 times daily; CHILD not recommended

By intramuscular injection, 20 mg every 6 hours; CHILD not recommended

Note. Nefopam hydrochloride 20 mg by injection = 60 mg by mouth

PoM **Acupan®** (3M)

Tablets, f/c, nefopam hydrochloride 30 mg. Net price 90-tab pack = £11.44. Label: 2, 14

Injection, nefopam hydrochloride 20 mg/mL. Net price 1-mL amp = 73p

4.7.2 Opioid analgesics

Opioid analgesics are used to relieve moderate to severe pain particularly of visceral origin. Repeated administration may cause dependence and tolerance, but this is no deterrent in the control of pain in terminal illness, for guidelines see Prescribing in Palliative Care, p. 12.

SIDE-EFFECTS. Opioid analgesics share many side-effects though qualitative and quantitative differences exist. The most common include nausea, vomiting, constipation, and drowsiness. Larger doses produce respiratory depression and hypotension. Overdosage, see Emergency Treatment of Poisoning, p. 22.

INTERACTIONS. See Appendix 1 (opioid analgesics) (important: special hazard with *pethidine and possibly other opioids* and MAOIs).

DRIVING. Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

CHOICE. **Morphine** remains the most valuable opioid analgesic for severe pain although it frequently causes nausea and vomiting. It is the standard against which other opioid analgesics are compared. In addition to relief of pain, morphine also confers a state of euphoria and mental detachment.

Morphine is the opioid of choice for the oral treatment of *severe pain in palliative care*. It is given regularly every 4 hours (or every 12 or 24 hours as modified-release preparations). For guidelines on dosage adjustment in palliative care, see p. 12.

Buprenorphine has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in patients dependent on other opioids. It has abuse potential and may itself cause dependence. It has a much longer duration of action than morphine and sublingually is an effective analgesic for 6 to 8 hours. Vomiting may be a problem. Unlike most opioid analgesics its effects are only partially reversed by naloxone.

Codeine is effective for the relief of mild to moderate pain but is too constipating for long-term use.

Dextromoramide is less sedating than morphine and has a short duration of action.

Diphenoxylate (in combination with atropine, as co-phenotrope) is used in acute diarrhoea (see section 1.4.2).

Dipipanone used alone is less sedating than morphine but the only preparation available contains an anti-emetic and is therefore not suitable for regular regimens in palliative care (see p. 14).

Dextropropoxyphene given alone is a very mild analgesic somewhat less potent than codeine. Combinations of dextropropoxyphene with paracetamol (co-proxamol) or aspirin have little more analgesic effect than paracetamol or aspirin alone. An important disadvantage of co-proxamol is that overdosage (which may be combined with alcohol) is complicated by respiratory depression and acute heart failure due to the dextropropoxyphene and by hepatotoxicity due to the paracetamol. Rapid treatment is essential (see Emergency Treatment of Poisoning, p. 22).

Diamorphine (heroin) is a powerful opioid analgesic. It may cause less nausea and hypotension than morphine. In *palliative care* the greater solubility of diamorphine allows effective doses to be injected in smaller volumes and this is important in the emaciated patient.

Dihydrocodeine has an analgesic efficacy similar to that of codeine. The dose of dihydrocodeine by mouth is usually 30 mg every 4 hours; doubling the dose to 60 mg may provide some additional pain relief but this may be at the cost of more nausea and vomiting. A 40-mg tablet is now also available.

Alfentanil, fentanyl and **remifentanil** are used by injection for intra-operative analgesia (section 15.1.4.3); fentanyl has been introduced recently in a transdermal drug delivery system as a self-adhesive patch which is changed every 72 hours.

Meptazinol is claimed to have a low incidence of respiratory depression. It has a reported length of action of 2 to 7 hours with onset within 15 minutes, but there is an incidence of nausea and vomiting.

Methadone is less sedating than morphine and acts for longer periods. In prolonged use, methadone should not be administered more often than twice daily to avoid the risk of accumulation and opioid overdosage. Methadone may be used instead of morphine in the occasional patient who experiences excitation (or exacerbation of pain) with morphine.

Nalbuphine has a similar efficacy to that of morphine for pain relief, but may have fewer side-effects and less abuse potential. Nausea and vomiting occur less than with other opioids but respiratory depression is similar to that with morphine.

Oxycodone is used as the pectinate in suppositories (special order from BCM Specials) for the control of *pain in palliative care*.

Papaveretum is used peri-operatively, section 15.1.4.3.

Pentazocine has both agonist and antagonist properties and precipitates withdrawal symptoms, including pain in patients dependent on other opioids. By injection it is more potent than dihydrocodeine or codeine, but hallucinations and thought disturbances may occur. It is not recommended and, in particular, should be avoided after myocardial infarction as it may increase pulmonary and aortic blood pressure as well as cardiac work.

Pethidine produces prompt but short-lasting analgesia; it is less constipating than morphine, but even in high doses is a less potent analgesic. It is not suitable for severe continuing pain. It is used for analgesia in labour, and in the neonate is associated with less respiratory depression than other opioid analgesics (probably because its action is weaker).

Phenazocine is effective in severe pain and has less tendency to increase biliary pressure than other opioid analgesics. It can be administered sublingually if nausea and vomiting are a problem.

Phenoperidine is used for intra-operative analgesia, section 15.1.4.3.

Tramadol has been introduced recently and is claimed to produce analgesia by two mechanisms: an opioid effect and an enhancement of serotoninergic and adrenergic pathways. It is reported to have fewer of the typical opioid side-effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported.

ADDICTS. Although caution is necessary addicts (and ex-addicts) may be treated with analgesics in the same way as other people when there is a real clinical need. Doctors are reminded that they do not require a special licence to prescribe opioid analgesics for addicts for relief of pain due to organic disease or injury.

MORPHINE SALTS

Indications: see notes above; acute pulmonary oedema; peri-operative analgesia see section 15.1.4.3

Cautions: hypotension, hypothyroidism, asthma (avoid during attack) and decreased respiratory reserve, prostatic hypertrophy; pregnancy and breast-feeding; may precipitate coma in hepatic impairment (reduce dose or avoid but many such patients tolerate morphine well); reduce dose or avoid in renal impairment (see also Appendix 3), elderly and debilitated (reduce dose); dependence (severe withdrawal symptoms if withdrawn abruptly); use of cough suppressants containing opioid analgesics not generally recommended in children and should be avoided altogether in those under at least 1 year; interactions: Appendix 1 (opioid analgesics)

PALLIATIVE CARE. In the control of pain in terminal illness these cautions should not necessarily be a deterrent to the use of opioid analgesics

Contra-indications: avoid in acute respiratory depression, acute alcoholism and where risk of paralytic ileus; not indicated for acute abdomen; also avoid in raised intracranial pressure or head injury (in addition to interfering with respiration, affect pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma (risk of pressor response to histamine release)

Side-effects: nausea and vomiting (particularly in initial stages), constipation, and drowsiness; larger doses produce respiratory depression and hypotension; other side-effects include difficulty with micturition, ureteric or biliary spasm, dry mouth, sweating, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitations, postural hypotension, hypothermia, hallucinations, dysphoria, mood changes, dependence, miosis, decreased libido or potency, rashes, urticaria and pruritus; overdosage: see Emergency Treatment of Poisoning, p. 22; for reversal of opioid-induced respiratory depression, see section 15.1.7.

Dose: acute pain, *by subcutaneous injection* (or suitable for oedematous patients) *or by intramuscular injection*, 10 mg every 4 hours if necessary (15 mg for heavier well-muscled patients); CHILD up to 1 month 150 micrograms/kg, 1–12 months 200 micrograms/kg, 1–5 years 2.5–5 mg, 6–12 years 5–10 mg

Postoperative pain, see section 15.1.4.3

By slow intravenous injection, quarter to half corresponding intramuscular dose

Patient controlled analgesia (PCA), consult hospital protocols

Myocardial infarction, *by slow intravenous injection* (2 mg/minute), 10 mg followed by a further 5–10 mg if necessary; elderly or frail patients reduce dose by half

Acute pulmonary oedema, *by slow intravenous injection* (2 mg/minute) 5–10 mg

Chronic pain, *by mouth or by subcutaneous injection* (not suitable for oedematous patients) *or by intramuscular injection*, 5–20 mg regularly every 4 hours; dose may be increased according to needs; oral dose should be approximately double corresponding intramuscular dose and triple or quadruple corresponding intramuscular diamorphine dose (see also Prescribing in Palliative Care, p. 12); *by rectum*, as suppositories, 15–30 mg regularly every 4 hours

Note. The doses stated above refer equally to morphine hydrochloride, sulphate, and tartrate; see below for doses of modified-release preparations.

Oral solutions

Note. For advice on transfer from oral solutions of morphine to modified-release preparations of morphine, see Prescribing in Palliative Care, p. 12

PoM or **CD Morphine Oral Solutions**

Oral solutions of morphine can be prescribed by writing the formula:

Morphine hydrochloride 5 mg

Chloroform water to 5 mL

Note. The proportion of morphine hydrochloride may be altered when specified by the prescriber; if above 13 mg per 5 mL the solution becomes CD. For sample prescription see Controlled Drugs and Drug Dependence, p. 7.1. It is usual to adjust the strength so that the dose volume is 5 or 10 mL.

Oramorph® (Boehringer Ingelheim)

PoM *Oramorph® oral solution*, morphine sulphate 10 mg/5 mL. Net price 100-mL pack = £2.10; 250-mL pack = £5.36; 500-mL pack = £9.71. Label: 2

PoM *Oramorph® Unit Dose Vials 10 mg* (oral vials), sugar-free, morphine sulphate 10 mg/5-mL vial, net price 25 vials = £3.31. Label: 2

CD *Oramorph® Unit Dose Vials 30 mg* (oral vials), sugar-free, morphine sulphate 30 mg/5-mL vial, net price 25 vials = £9.30. Label: 2

CD *Oramorph® concentrated oral solution*, sugar-free, morphine sulphate 100 mg/5 mL. Net price 30-mL pack = £6.47; 120-mL pack = £24.13 (both with calibrated dropper). Label: 2

CD *Oramorph® Unit Dose Vials 100 mg* (oral vials), sugar-free, morphine sulphate 100 mg/5-mL vial, net price 25 vials = £31.00. Label: 2

Tablets

CD **Sevredol®** (Napp)

Tablets, all f/c, scored, morphine sulphate 10 mg (blue), net price 56-tab pack = £6.31; 20 mg (pink), 56-tab pack = £12.62; 50 mg (pale green), 56-tab pack = £31.55. Label: 2

Dose: severe pain uncontrolled by weaker opioid, 10–30 mg every 4 hours (dose adjusted according to need and tolerance); CHILD 3–5 years, 5 mg; 6–12 years, 5–10 mg

Modified release

CD **Morcap® SR** (Sanofi Winthrop)

Capsules, m/r, clear enclosing ivory and brown pellets, morphine sulphate 20 mg, net price 30-cap pack = £5.71, 60-cap pack = £11.42; 50 mg, 30-cap pack = £13.84, 60-cap pack = £27.68; 100 mg, 30-cap pack = £27.68, 60-cap pack = £55.37. Label: 2, counselling, see below

Dose: prolonged severe pain uncontrolled by weaker opioids, 40 mg once daily or 20 mg every 12 hours, increased in increments of 25–50% as necessary (24-hour interval between dosage adjustment); in patients already receiving oral morphine substitute same total daily dose as Morcap SR capsules in single or 2 divided doses

CHILD not recommended

COUNSELLING. Swallow whole or open capsule and sprinkle contents on soft food

Note. Prescription must also specify 'capsules' (i.e. 'Morcap SR capsules')

CD **MST Continus®** (Napp)

Tablets, all m/r, f/c, morphine sulphate 5 mg (white), net price 60-tab pack = £4.50; 10 mg (brown), 60-tab pack = £7.51; 15 mg (green), 60-tab pack = £13.16; 30 mg (purple), 60-tab pack = £18.03; 60 mg (orange), 60-tab pack = £35.16; 100 mg (grey), 60-tab pack = £55.67; 200 mg (green), 60-tab pack = £111.35. Label: 2, 25

Suspension (= sachet of granules to mix with water), m/r, pink, morphine sulphate 20 mg/sachet, net price 30-sachet pack = £28.60; 30 mg/sachet, 30-sachet pack = £29.72; 60 mg/sachet, 30-sachet pack = £59.44; 100 mg/sachet, 30-sachet pack = £99.07; 200 mg/sachet pack, 30-sachet pack = £198.14. Label: 2, 13

Dose: (suspension or tablets) severe pain uncontrolled by weaker opioids, 30 mg every 12 hours, increased to 60 mg every 12 hours when required, then further increments of 30–50% if necessary. For lower initial doses in patients who have not received other opioids, see Prescribing in Palliative Care, p. 12

CHILD severe, intractable pain in cancer, initially 200–800 micrograms/kg every 12 hours, then further increments of 30–50% if necessary

Note. Prescriptions must also specify 'tablets' or 'suspension' (i.e. 'MST Continus tablets' or 'MST Continus suspension').

CD **MXL®** (Napp)

Capsules, m/r, morphine sulphate 30 mg (light blue), net price 30-cap pack = £13.16; 60 mg (brown), 30-cap pack = £18.03; 90 mg (pink), 30-cap pack = £26.59; 120 mg (green), 30-cap pack = £35.16; 150 mg (blue), 30-cap pack = £43.95; 200 mg (red-brown), 30-cap pack = £55.67. Label: 2, counselling, see below

Dose: prolonged severe pain uncontrolled by weaker opioids, 60 mg once daily increased in increments of 30–50% if necessary; in patients already receiving oral morphine substitute same total daily dose as MXL capsules once daily

CHILD severe, intractable pain in cancer, initially 0.4–1.6 mg/kg daily, then further increments of 30–50% if necessary

COUNSELLING. Swallow whole or open capsule and sprinkle contents on soft food

Note. Prescriptions must also specify 'capsules' (i.e. 'MXL capsules')

CD **Oramorph® SR** (Boehringer Ingelheim)

Tablets, all m/r, f/c, morphine sulphate 10 mg (buff), net price 60-tab pack = £5.75; 30 mg (violet), 60-tab pack = £13.80; 60 mg (orange), 60-tab pack = £26.89; 100 mg (grey), 60-tab pack = £42.59. Label: 2, 25

Dose: severe pain uncontrolled by weaker opioids, 30 mg every 12 hours, increased to 60 mg every 12 hours when sequired, then further increments of 25–50% if necessary. For lower initial doses in patients who have not received other opioids, see Prescribing in Palliative Care, p. 12

CHILD not recommended

Note. Prescriptions must also specify 'tablets' (i.e. 'Oramorph SR tablets')

Injections

CD Morphine Sulphate (Non-proprietary)

Injection, morphine sulphate 10, 15, 20, and 30 mg/mL, net price 1- and 2-mL amp (all) = 64–96p

CD Min-I-Jet® Morphine Sulphate (IMS)

Injection, morphine sulphate 10 mg/mL, net price 2-mL disposable syringe = £10.85

CD Morphine and Atropine Injection

See section 15.1.4.3

CD Morphine Sulphate Rapiject® (IMS)

Injection, morphine sulphate 1 mg/mL, net price 50-mL disposable syringe = £9.50; 2 mg/mL, 50-mL disposable syringe = £10.50

Injection with anti-emetic

CAUTION. In myocardial infarction cyclizine may aggravate severe heart failure and counteract the haemodynamic benefits of opioids, see section 4.6. Not recommended in palliative care, see p. 14

CD **Cyclimorph®** (GlaxoWellcome)

Cyclimorph-10® Injection, morphine tartrate 10 mg, cyclizine tartrate 50 mg/mL. Net price 1-mL amp = £1.28

Dose: by subcutaneous, intramuscular, or intravenous injection, 1 mL, repeated not more often than every 4 hours, with not more than 3 doses in any 24-hour period; CHILD 1–5 years 0.25–0.5 mL as a single dose, 6–12 years 0.5–1 mL as a single dose

Cyclimorph-15® Injection, morphine tartrate 15 mg, cyclizine tartrate 50 mg/mL. Net price 1-mL amp = £1.33

Dose: by subcutaneous, intramuscular, or intravenous injection, 1 mL, repeated not more often than every 4 hours, with not more than 3 doses in any 24-hour period

Suppositories

CD Morphine (Non-proprietary)

Suppositories, morphine hydrochloride or sulphate 10 mg, net price 12 = £6.12; 15 mg, 12 = £5.54; 20 mg, 12 = £7.45; 30 mg, 12 = £8.10. Label: 2

Available from Aurum, Evans, Martindale

Note. Both the strength of the suppositories and the morphine salt contained in them must be specified by the prescriber