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Menstrual disorders. Menorrhagia (p.2126) is thought to be associated with abnormalities of prostaglandin production. Treatment with NSAIDs such as ibuprofen, mefenamic acid, or naproxen during menstruation, can reduce uterine blood loss by an average of 30% in women with menorrhagia. There does not appear to be any evidence that one NSAID is more effective than another.

NSAIDs are usually the first choice for the pain of dysmenorrhoea (p.6). Mefenamic acid may have a theoretical advantage over other NSAIDs in being able to inhibit both the synthesis and the peripheral action of prostaglandins, but clinical studies have not shown fenamates to be more effective, and systematic review has suggested that ibuprofen may have the best risk/benefit ratio.

Migraine. See Headache, above.

Orthostatic hypotension. Fludrocortisone is usually the first drug tried in the treatment of orthostatic hypotension (p.1530) when nonpharmacological treatment has failed. NSAIDs such as flurbiprofen, ibuprofen, or indometacin may be used alone or added to treatment if the response is inadequate.

Pain. NSAIDs have a similar analgesic effect to aspirin and paracetamol in single doses but, in regular full dosage, they have both a lasting analgesic and an anti-inflammatory effect. They are used in the management of mild to moderate pain (see Choice of Analgesic, p.2) and are of particular value in pain due to inflammation. NSAIDs may be of benefit for inflammatory pain in infants and children (p.3), although paracetamol is generally the preferred non-opioid analgesic in this age group. NSAIDs may be used in the treatment of acute low back pain (p.7) if paracetamol fails to provide adequate pain relief. NSAIDs may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (p.5) and are particularly effective in bone pain of malignant origin. NSAIDs may be used for postoperative analgesia (p.4), and are of particular value after day-case surgery because of their lack of sedative effects. They are not usually considered to be strong enough as the sole analgesic after major surgery, but may be used with stronger analgesics and may allow dosage reduction of opioids. The pain of mild sickle-cell crises (p.9) may be controlled by analgesics such as NSAIDs or less potent opioids, for example codeine or dihydrocodeine; NSAIDs may be used with more potent opioids such as morphine for severe crises.

Dependence and tolerance are not a problem with non-opioid analgesics such as NSAIDs, but there is a ceiling of efficacy, above which, increasing the dose has no further therapeutic effect.

Rheumatic disorders. NSAIDs provide symptomatic relief for rheumatic disorders such as rheumatoid arthritis (p.11) and spondyloarthropathies (p.13), but they do not alter the course of the disease and additional antirheumatic drugs may need to be given to prevent irreversible joint damage. NSAIDs may also be used as an alternative to paracetamol for osteoarthritis (p.11). Short-term use of oral NSAIDs may help to relieve pain and reduce inflammation of soft-tissue rheumatism (p.13); topical formulations of some NSAIDs are also used.

Scleroderma. NSAIDs should be used with caution in scleroderma (p.1817) because of the risk of exacerbating renal and other problems.

Opioid Analgesics

Analgésicos opioides u opiáceos; Analgésiques Opioïdes; Opioid-analgetika.

Опиоидные Аналгетики

Dependence and Withdrawal

Repeated use of opioids is associated with the development of psychological and physical dependence. Although this is less of a problem with legitimate therapeutic use, dependence may develop rapidly when opioids are regularly abused for their euphoriant effects. Drug dependence of the opioid type is characterised by an overwhelming need to keep taking the drug (or one with similar properties), by a physical requirement for the drug in order to avoid withdrawal symptoms, and by a tendency to increase the dose owing to the development of tolerance.

Abrupt withdrawal of opioids from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose, and the duration of drug use. Withdrawal symptoms may also follow the use of an opioid antagonist such as naloxone or a mixed agonist and antagonist such as pentazocine in opioid-dependent persons. Neonatal abstinence syndrome may occur in the offspring of opioid-dependent mothers and these infants can suffer withdrawal symptoms at birth.

Opioid analgesics can be classified according to the receptors at which they act (see Uses and Administration, below) and withdrawal syndromes are characteristic for a receptor type. Cross-tolerance and cross-dependence can be expected between opioids acting at the same receptors. Dependence associated with morphine and closely related μ-agonists appears to result in more severe withdrawal symptoms than those associated with κ-receptor agonists. Onset and duration of withdrawal symptoms also vary according to the duration of action of the specific drug. With morphine and diamorphine *withdrawal symptoms* usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside; they develop more slowly with methadone. Withdrawal symptoms include yawning, mydriasis, lachrymation, rhinorrhoea, sneezing, muscle tremor, weakness, sweating, anxiety, irritability, disturbed sleep or insomnia, restlessness, anorexia, nausea, vomiting, loss of weight, diarrhoea, dehydration, leucocytosis, bone pain, abdominal and muscle cramps, gooseflesh, vasomotor disturbances, and increases in heart rate, respiratory rate, blood pressure, and temperature. Some physiological values may not return to normal for several months after the acute withdrawal syndrome.

Withdrawal symptoms may be terminated by a suitable dose of the original or a related opioid. Tolerance diminishes rapidly after withdrawal so that a previously tolerated dose may prove fatal.

For a discussion of the treatment of opioid dependence and neonatal abstinence syndrome, see below.

◊ Review.

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Diagnosis. Naloxone (p.1455) and other opioid antagonists have been used to diagnose opioid dependence.

Treatment of opioid dependence. The treatment of opioid dependence has been the subject of a number of reviews and discussions.[1-10]

Planned withdrawal (**detoxification**) may be effected slowly or rapidly. The usual method in many countries is to replace the drug of dependence with *methadone* (an opioid agonist) given as a liquid oral preparation, and then gradually withdraw the methadone if possible. Methadone is suitable for withdrawal therapy because it can be given orally and its long half-life allows once daily use. Oral *diamorphine* has been used similarly to methadone; reefers containing diamorphine have also been used in some centres. *Dihydrocodeine* tablets have been used successfully. The partial opioid agonist *buprenorphine*, given sublingually, is another alternative to methadone in the treatment of opioid dependence, and withdrawal symptoms may possibly resolve more quickly than with methadone.[11] However, it should only be given to patients with moderate dependence; those dependent on high doses of opioids may experience withdrawal symptoms when given buprenorphine. The methadone derivative *levacetylmethadol* was a more recent introduction but its proarrhythmic effects have led to its use being suspended.

Iatrogenic opioid dependence may occur in patients receiving μ-agonists such as morphine, fentanyl, or pethidine for the management of acute pain or in an intensive care setting for more than 5 to 10 days. Methadone has been used successfully to manage opioid withdrawal in adult intensive care patients.[12] However, some[13] avoid using methadone to manage withdrawal in children because of the stigma of its associations with managing withdrawal in drug addicts. In physically dependent but non-addicted patients, gradual weaning using the same opioid that was used therapeutically is preferred where possible, although in some cases, it may be necessary to change to a different opioid because of ease of use, duration of action, and ability to taper the dose; virtually any opioid can be used.[13]

Other drugs used in the management of opioid withdrawal include alpha$_2$-adrenoceptor agonists such as *clonidine* and opioid antagonists such as *naltrexone* and *naloxone*. Clonidine may help to suppress symptoms of opioid withdrawal, such as anxiety, insomnia, and muscle aches. It appears to be more effective when used in the control of symptoms after abrupt withdrawal than when used during gradual withdrawal of methadone. Hypotension may limit its usefulness in some patients. The clonidine analogue *lofexidine* may produce similar results to those obtained with clonidine and appears to be less sedating and hypotensive.[14]

Naltrexone and naloxone block the euphoriant effects of opioids although their use as monotherapy in detoxification is limited by unacceptable opioid withdrawal effects. Naltrexone may be used with alpha$_2$-adrenoceptor agonists such as clonidine or lofexidine to ameliorate symptoms but there are insufficient data to determine whether such combinations reduce the duration of withdrawal treatment or increase the rate of transfer to maintenance therapy with an opioid antagonist.[15] Naloxone and naltrexone are also being used in the relatively new technique of rapid or ultra rapid opioid detoxification,[16-18] which is achieved while the patient is heavily sedated or under *general anaesthesia* and hence unaware of any unpleasant withdrawal symptoms. However, although detoxification may be achieved within 24 hours and has a high initial success rate, the technique itself is not without risks and it does not obviate the need for maintenance treatment (see below).

Concomitant counselling and other psychosocial services have been shown to be important in the outcome of withdrawal therapy.[19,20] Detoxification alone does not ensure long-term abstinence.

A number of other drugs may be of use as **adjuncts** in the management of withdrawal symptoms. *Diphenoxylate* with atropine or *loperamide* may be used for the control of diarrhoea. *Promethazine* has been used for its antiemetic and sedative actions. Beta blockers such as *propranolol* may be of use for patients with pronounced somatic anxiety symptoms. *Benzodiazepines* or *clomethiazole* can be given to relieve anxiety and associated insomnia but only short courses should be used in order to minimise the risk of dependence and abuse.

Long-term **maintenance** treatment (stabilisation treatment) with an opioid is sometimes used, in conjunction with psychosocial support, to enable the patient to acquire some form of social stability. *Methadone* is most commonly used; the use of *diamorphine* although feasible[21,22] is controversial[23] and is advocated by only a few individual centres. *Buprenorphine* is another possibility.[24] The use of methadone for maintenance has been reviewed.[25-27] *Naltrexone* can be effective in maintaining abstinence in opioid addicts after detoxification, especially after rapid or ultra rapid detoxification. It is considered that naltrexone would probably be of most use in highly motivated addicts with good sociological and psychological support to discourage impulsive use of opioids.[1,28,29]

The problems associated with the management of the **pregnant** patient with opioid dependence have been discussed.[30] The aim should be to stabilise the patient first using *methadone* since acute withdrawal can result in fetal death. Drug withdrawal is best done slowly during the second trimester. It has been suggest-

ed that if patients present during the final trimester and cannot be detoxified, maintenance with *diamorphine* might be preferable to the use of methadone as it might produce less severe withdrawal symptoms in the neonate.[31] The management of neonatal abstinence syndrome is discussed below.

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NEONATAL ABSTINENCE SYNDROME. Infants born to opioid-dependent mothers may suffer withdrawal, with signs including CNS hyperirritability, gastrointestinal dysfunction, respiratory distress, yawning, sneezing, mottling, and fever. Onset of symptoms is partly dependent on the drug and varies from shortly after birth to 2 weeks of age, although most symptoms appear within 72 hours. Some symptoms may persist for 3 months or more.

The American Academy of Pediatrics (AAP)[1] recommended that treatment of the neonate with abstinence syndrome should be primarily supportive and considered that many infants with signs of drug withdrawal could be managed in this way. They advised adoption of abstinence scoring methods to judge the need for drug therapy, although such systems do not appear to have been validated. Drugs that have been used for opioid withdrawal include paregoric (a USP 31 preparation containing opium), diluted tincture of opium, morphine, methadone, diazepam, chlorpromazine, phenobarbital, and clonidine. Naloxone should not routinely be given to infants of opioid-dependent mothers because of the risk of seizures with abrupt opioid withdrawal. The AAP[1] made no definite recommendations but considered that, when appropriate, specific drug therapy should be used for treatment of withdrawal symptoms. Thus for opioid withdrawal, tincture of opium was the preferred drug. Others favour treatment with oral morphine solution.[2] The *BNFC* notes that although morphine is widely used and the dose can be easily adjusted, methadone may provide smoother control of symptoms.

Practice varies widely and evidence for the efficacy of particular drugs in the management of neonatal abstinence syndrome is scanty and difficult to compare.[3,4] It has been suggested that diazepam may be less useful than phenobarbital or paregoric but the use of paregoric (which contains both camphor and alcohol) has been questioned. In the UK, chlorpromazine has also been widely used[5] although a systematic review[6] found insufficient evidence to support such use. The authors[6] also found that phenobarbital may reduce the severity of withdrawal symptoms in those receiving an opioid; there was insufficient evidence to support the use of clonidine.

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Adverse Effects

In usual doses the commonest adverse effects of opioid analgesics are nausea, vomiting, constipation, drowsiness, and confusion; tolerance to these (except constipation) generally develops with long-term use. Micturition may be difficult and there may be ureteric or biliary spasm; the latter may be associated with alterations in liver enzyme values. There is also an antidiuretic effect. Dry mouth, dizziness, sweating, facial flushing, headache, vertigo, bradycardia, tachycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, changes of mood, decreased libido or potency, hallucinations, and miosis also occur. These effects tend to occur more commonly in ambulant patients than in those at rest in bed and in those without severe pain. Raised intracranial pressure occurs in some patients. Muscle rigidity has been reported after high doses. The euphoric activity of opioids has led to their abuse. For a discussion of opioid dependence, see above.

Larger doses of opioids produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur, especially in infants and children. Rhabdomyolysis progressing to renal failure has been reported in overdosage. Death may occur from respiratory failure. Toxic doses of specific opioids vary considerably with the individual and regular users may tolerate large doses. The triad of coma, pinpoint pupils, and respiratory depression is considered indicative of opioid overdosage; dilatation of the pupils occurs as hypoxia develops. Pulmonary oedema after overdosage is a common cause of fatalities among opioid addicts.

Morphine and some other opioids have a dose-related histamine-releasing effect which may be responsible in part for reactions such as urticaria and pruritus as well as hypotension and flushing. Contact dermatitis has been reported and pain and irritation may occur on injection. Anaphylactic reactions after intravenous injection have been reported rarely.

◊ The adverse effects associated with individual opioid analgesics may reflect to some extent their activity at specific opioid receptors (see Uses and Administration, below) or may result from a direct toxic effect.[1,2] Some adverse effects of pure opioid agonists, such as the respiratory depressant effect of morphine, are dose related, whereas agonist-antagonists such as buprenorphine, butorphanol, and nalbuphine exhibit a 'ceiling effect' as the dose increases.

The type and extent of adverse effects experienced in practice may depend on whether or not opioid-sensitive pain is present, whether the opioid analgesic is being given for the control of chronic severe pain or acute pain, and the route used. In a review[3] of the use of opioids in *chronic pain* it was noted that, despite worries to the contrary, respiratory depression and dependence liability are not generally a problem when appropriate doses are used to treat opioid-sensitive pain. In fact the presence of opioid-sensitive pain appears to protect against the respiratory depressant effect, although it may occur if the source of opioid-sensitive pain is removed (e.g. by surgery) without adequate reduction in opioid dosage. The adverse effects of opioid analgesics when used in advanced cancer have also been discussed.[4] Constipation was considered to be the most troublesome adverse effect; significant respiratory depression was rarely seen with recommended regimens, since pain antagonises the central depressant effects of morphine.

In the context of *acute postoperative pain* opioid-induced respiratory depression is of concern but short-term postoperative use is unlikely to cause dependence (although see Treatment of Opioid Dependence, above for references to iatrogenic physical dependence).[5] It was hoped that giving opioids by the *spinal route* would result in fewer adverse effects, especially respiratory depression. In postoperative pain relief with spinal opioids, the incidence of adverse effects is said to be low when patients are properly monitored.[6] However, some[7] have reported pruritus, nausea and vomiting, and urinary retention to be common and respiratory depression to occur; more seriously the appearance of respiratory depression could be considerably delayed. These effects were more common with morphine, but all opioid analgesics had the propensity to produce respiratory depression when given spinally.[7] Delayed respiratory depression has been attributed to the poor lipid solubility of morphine, but does occur after other opioids. Some have considered that despite earlier worries, potentially fatal late respiratory depression was as rare with the spinal route as postoperative respiratory depression with the conventional route.[8,9] Disputes regarding the frequency of respiratory depression associated with even conventional use of opioid analgesics might be due to the methods used for measuring respiratory effects.[10] The incidence of ventilatory depression has been reported to be higher after intrathecal than epidural use of morphine.[11]

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Effects on the cardiovascular system. For reference to histamine release and cardiovascular effects following the intravenous administration of some opioids see under Pethidine, p.114.

Effects on the endocrine system. Endogenous opioid peptides may have a role in the regulation of endocrine function. Like endorphin and enkephalins, morphine has been found to stimulate prolactin release[1] and synthetic analogues of morphine are reported to have similar properties; long-term intrathecal opioids (morphine or hydromorphone) have been reported to produce hypogonadotrophic hypogonadism, adrenal insufficiency, and growth hormone deficiency, although tolerance to the effects on prolactin develops with long-term use.[2] Opioids such as morphine are also part of a large group of drugs implicated in causing hyperglycaemia.[3]

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Treatment of Adverse Effects

Activated charcoal may be given orally in conscious patients if a substantial overdose has been ingested within 1 hour provided that the airway can be protected (see below); it should be considered in all patients if a substantial amount of a modified-release preparation has been ingested.

Intensive supportive therapy may be required to correct respiratory failure and shock. In addition, the specific antagonist naloxone is used for rapid reversal of the severe respiratory depression and coma produced by excessive doses of opioid analgesics (see p.1454). Since naloxone has a shorter duration of action than

many opioids patients who have already responded should be kept under close observation for signs of relapse and repeated injections given according to the respiratory rate and depth of coma. Alternatively, in situations where repeated administration is required, such as where a longer acting opioid is known or suspected to be the cause of symptoms, a continuous intravenous infusion of naloxone, adjusted according to response, may be used. All patients should be observed for at least 6 hours after the last dose of naloxone.

The use of opioid antagonists such as naloxone in persons physically dependent on opioids may induce withdrawal symptoms.

Activated charcoal. The National Poisons Information Service in the UK considers the benefit of gastric decontamination in the management of overdosage with opioid analgesics to be uncertain. However, it is suggested that oral activated charcoal may be considered if given within 1 hour of ingestion and the quantity of opioid analgesic is substantial or, for these specific drugs, exceeds the following amount:

- buprenorphine: 100 micrograms/kg (adult); 100 micrograms/kg (child)
- codeine: 350 mg (adult); 5 mg/kg (child)
- dihydrocodeine: 420 mg (adult); 3 mg/kg (child)
- methadone: any amount in an opioid-naive patient or more than the prescribed daily dose if on methadone therapeutically
- tramadol: 500 mg (adult); 10 mg/kg (child)

See also under individual monographs.

Constipation. For reference to the use of opioid antagonists, particularly naloxone, to relieve opioid-induced constipation without compromising analgesic control in patients receiving long-term therapy with opioids, see Reversal of Opioid Effects under Uses and Administration of Naloxone, p.1454.

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Precautions

Opioid analgesics are generally contra-indicated in acute respiratory depression and obstructive airways disease, although opioids such as morphine are used in some forms of dyspnoea (see below). They are also contra-indicated or should be used with great caution in acute alcoholism, convulsive disorders, head injuries, and conditions in which intracranial pressure is raised. They should not be given to comatose patients.

Opioid analgesics should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, asthma or decreased respiratory reserve, renal or hepatic impairment, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders, or myasthenia gravis. Dosage should be reduced in elderly or debilitated patients.

Opioid analgesics should be given with great care to infants, especially neonates. Their use during labour may cause respiratory depression in the neonate. Babies born to opioid-dependent mothers may suffer withdrawal symptoms (see Neonatal Abstinence Syndrome, above).

Therapy with opioid analgesics should be stopped gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms (see Dependence, above). Opioid analgesics with some antagonist activity, such as buprenorphine, butorphanol, nalbuphine, or pentazocine, may precipitate withdrawal symptoms in physically dependent patients who have recently used pure agonists such as morphine.

Drowsiness may affect the ability to perform skilled tasks; those so affected should not drive or operate machinery.

Asthma. Opioids appear to be safe and may be used with caution in controlled asthma; however, they should be avoided during acute exacerbations.[1]

1. Barnes PJ, Chung KF. Difficult asthma. *BMJ* 1989; **299:** 1031–2.

Biliary-tract disorders. It is usually recommended that opioids such as morphine should either be avoided in patients with biliary disorders or that they should be given with an antispasmodic. Morphine can cause an increase in intrabiliary pressure as a result of effects on the sphincter of Oddi[1] and may therefore be expected to exacerbate rather than relieve pain in patients with biliary colic (p.5) or other biliary-tract disorders. Biliary-type pain after cholecystectomy has also been associated with codeine[2] and morphine.[3]

Morphine caused a more marked delay in gallbladder emptying than pethidine, pentazocine, or butorphanol in a study[4] in healthy subjects; this was considered confirmation that morphine should be avoided in biliary disorders. In another study[5] fentanyl and sufentanil did not constrict the common bile duct like morphine; they may be suitable for perioperative pain control in patients in whom spasm of the common bile duct is undesirable. The suggestion that pethidine should be preferred to morphine in patients with acute pancreatitis (p.9), because of its lesser effect on the bile duct, has been questioned.[6]

1. Helm JF, *et al.* Effects of morphine on the human sphincter of Oddi. *Gut* 1988; **29:** 1402–7.
2. Druart-Blazy A, *et al.* The underestimated role of opiates in patients with suspected sphincter of Oddi dysfunction after cholecystectomy. *Gastroenterol Clin Biol* 2005; **29:** 1220–3.
3. Roberts-Thomson IC, *et al.* Sympathetic activation: a mechanism for morphine induced pain and rises in liver enzymes after cholecystectomy? *Gut* 1990; **31:** 217–21.
4. Hahn M, *et al.* The effect of four narcotics on cholecystokinin octapeptide stimulated gall bladder contraction. *Aliment Pharmacol Ther* 1988; **2:** 129–34.
5. Vieira ZEG, *et al.* Evaluation of fentanyl and sufentanil on the diameter of the common bile duct by ultrasonography in man: a double blind, placebo controlled study. *Int J Clin Pharmacol Ther* 1994; **32:** 274–7.
6. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. *Am J Gastroenterol* 2001; **96:** 1266–72.

Children. Children under 6 months of age may be more sensitive to opioids; neonates in particular may be more sensitive to respiratory depression with morphine than adults. Pharmacokinetic differences may contribute to this increased sensitivity. Nonetheless, neonates can be treated with opioids such as morphine (see p.90) if receiving respiratory support.

Older infants and children can be treated effectively with morphine or other opioid analgesics and from the age of 5 or 6 months morphine metabolism follows the course seen in adults.

For a discussion of the choice of analgesic in children see p.3. The use of opioids for sedation and analgesia in neonates in intensive care is mentioned on p.957.

References.

1. Choonara IA. Pain relief. *Arch Dis Child* 1989; **64:** 1101–2.
2. Lloyd-Thomas AR. Pain management in paediatric patients. *Br J Anaesth* 1990; **64:** 85–104.
3. Bhatt-Mehta V. Current guidelines for the treatment of acute pain in children. *Drugs* 1996; **51:** 760–76.
4. Marsh DF, *et al.* Opioid systems and the newborn. *Br J Anaesth* 1997; **79:** 787–95.

The elderly. Ageing can affect the pharmacokinetics and pharmacodynamics of opioids although the net effects of these changes on opioid analgesia in the elderly remain unclear.[1] Practical recommendations include careful review of indication for opioid use both initially and at regular intervals thereafter, starting opioids cautiously at lower doses and with longer dosing intervals, and regular consideration given to dose reduction and drug substitution or discontinuation. If possible, further drugs should not be prescribed to manage the adverse effects of opioids.

1. Wilder-Smith OHG. Opioid use in the elderly. *Eur J Pain* 2005; **9:** 137–40.

Hepatic impairment. The pharmacokinetics of opioids may be altered in patients with hepatic dysfunction. A review[1] of opioid use in this patient group considered that opioids such as morphine and hydromorphone that are metabolised by glucuronidation were relatively safe when compared with those metabolised by cytochrome P450 isoenzymes; the half-lives of glucuronidated opioids were found to be maintained until late disease whereas the prolonged half-lives seen with opioids metabolised by P450 isoenzymes were not accurately predicted by disease severity. It was also recommended that oral immediate-release or parenteral, short-acting opioids were preferable to long-acting preparations such as transdermal or modified-release formulations.

1. Davis M. Cholestasis and endogenous opioids: liver disease and exogenous opioid pharmacokinetics. *Clin Pharmacokinet* 2007; **46:** 825–50.

Phaeochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release. Both diamorphine[1] and pethidine[2] have been reported to cause hypertension when given to patients with phaeochromocytoma and histamine-releasing opioids should be avoided in such patients. Alfentanil, like fentanyl, does not release histamine and may be the opioid of choice in the anaesthetic management of patients with phaeochromocytoma.[3]

1. Chaturvedi NC, *et al.* Diamorphine-induced attack of paroxysmal hypertension in phaeochromocytoma. *BMJ* 1974; **2:** 538.
2. Lawrence CA. Pethidine-induced hypertension in phaeochromocytoma. *BMJ* 1978; **1:** 149–50.
3. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; **58:** 1453–68.

Renal impairment. A literature review[1] concluded that codeine and morphine are best avoided in patients with renal failure and/or on dialysis; hydromorphone may be used with caution and monitoring, and use of fentanyl and methadone appeared to be safe. Similar recommendations have been made for patients with end-stage renal disease who are not undergoing dialysis.[2] See also under the individual monographs.

1. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage* 2004; **28:** 497–504.
2. Murtagh FE, *et al.* The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother* 2007; **21:** 5–16.

Interactions

As serious and sometimes fatal reactions have followed use of pethidine in patients receiving MAOIs (including moclobemide), pethidine and related drugs are contra-indicated in patients taking MAOIs or within 14 days of stopping such treatment; other opioid analgesics should be avoided or given with extreme caution (for further details, see p.418). Life-threatening reactions have also been reported when selegiline, a selective inhibitor of monoamine oxidase type B, has been given with pethidine. The depressant effects of opioid analgesics are enhanced by other CNS depressants such as alcohol, anaesthetics, anxiolytics, hypnotics, tricyclic antidepressants, and antipsychotics. Cyclizine may counteract the haemodynamic benefits of opioids. Cimetidine inhibits the metabolism of some opioids, especially pethidine.

The actions of opioids may in turn affect the activities of other drugs. For instance, their gastrointestinal effects may delay absorption as with mexiletine or may be counteractive as with cisapride, metoclopramide, or domperidone. Opioid premedicants such as papaveretum have been reported to reduce serum concentrations of ciprofloxacin.

Alcohol. Rapid release or dose-dumping of hydromorphone from a modified-release preparation (*Palladone; Purdue Frederick, USA*) has been associated with the ingestion of alcohol (for further details, see under Interactions of Hydromorphone, p.63). Health Canada[1] has warned that this interaction may occur with all modified-release formulations of opioid analgesics. Licensed product information for some modified-release preparations of morphine sulfate also warns against such use (see Interactions of Morphine, p.88).

1. Health Canada. Potentially fatal interaction between slow-release opioid painkillers and alcohol (issued 3rd August, 2005). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2005/2005_84-eng.php (accessed 26/06/08)

Antivirals. Interactions between opioid analgesics and *HIV-protease inhibitors* or *reverse transcriptase inhibitors* are complex, and the results of the limited number of studies and reports *in vivo* have not always borne out predictions about the nature of potential interactions.

- Substantial **decreases** in the area under the plasma concentration-time curve (AUC) and in the plasma concentration have been reported for pethidine when given with *ritonavir*; however, plasma concentrations of the toxic metabolite norpethidine are greatly **increased**, and licensed product information for ritonavir counsels against such combined use. Ritonavir is predicted to reduce plasma concentrations of morphine. Plasma concentrations of methadone may be reduced if given with HIV-protease inhibitors although the effect may not be clinically significant. The NNRTIs *nevirapine* and *efavirenz* have also been reported to reduce plasma-methadone levels and withdrawal symptoms have occurred when given to patients receiving methadone. (For further details on the interactions of methadone with antivirals, see p.84.) In addition, efavirenz has been reported to decrease the AUC of buprenorphine (see p.30).
- In contrast, an **increase** in AUC and in elimination half-life of fentanyl has been reported in subjects also receiving ritonavir (see p.57). Licensed product information for ritonavir also considers that increased plasma concentrations of buprenorphine (p.30), dextropropoxyphene, and tramadol, with an increased likelihood of opioid toxicity, may occur if these drugs are given during ritonavir treatment. Licensed information for meptazinol also states that increased plasma concentrations of meptazinol have been noted when given with ritonavir. The NNRTI *delavirdine* has been reported to increase the plasma concentrations of buprenorphine (see p.30) and methadone (p.84).

Histamine H_2-antagonists. Histamine H_2-antagonists may enhance the effects of some opioid analgesics. *Cimetidine* was reported to alter the clearance and volume of distribution of pethidine[1] whereas *ranitidine* did not.[2] Morphine has been considered less likely to interact with cimetidine than pethidine because of differences in metabolism. In a study[3] cimetidine did not affect the disposition of morphine in healthy subjects. A later study[4] in patients undergoing major surgery suggested that pre- or postoperative intravenous cimetidine did not significantly affect outcomes such as morphine consumption and incidence of adverse effects when compared with placebo. Nevertheless,

there have been isolated reports of possible interactions between morphine and H_2-antagonists; apnoea, confusion, and muscle twitching have been associated with cimetidine plus morphine,[5] and confusion associated with ranitidine plus morphine.[6] There has also been a report[7] of a patient receiving regular analgesia with oral methadone and subcutaneous morphine who became unresponsive 6 days after starting cimetidine for prophylaxis of peptic ulcer; treatment with naloxone was required.

1. Guay DRP, *et al.* Cimetidine alters pethidine disposition in man. *Br J Clin Pharmacol* 1984; **18:** 907–14.
2. Guay DRP, *et al.* Ranitidine does not alter pethidine disposition in man. *Br J Clin Pharmacol* 1985; **20:** 55–9.
3. Mojaverian P, *et al.* Cimetidine does not alter morphine disposition in man. *Br J Clin Pharmacol* 1982; **14:** 809–13.
4. Chia Y-Y, *et al.* Randomized, double-blind study comparing postoperative effects of treatment timing with histamine H -receptor antagonist cimetidine. *Acta Anaesthesiol Scand* 2005; **49:** 865–9.
5. Fine A, Churchill DN. Potentially lethal interaction of cimetidine and morphine. *Can Med Assoc J* 1981; **124:** 1434, 1436.
6. Martinez-Abad M, *et al.* Ranitidine-induced confusion with concomitant morphine. *Drug Intell Clin Pharm* 1988; **22:** 914–15.
7. Sorkin EM, Ogawa GS. Cimetidine potentiation of narcotic action. *Drug Intell Clin Pharm* 1983; **17:** 60–1.

Uses and Administration

Opioid analgesics possess some of the properties of naturally occurring or **endogenous opioid peptides**. Endogenous opioid peptides are widely distributed in the CNS and are also found in other parts of the body. They appear to function as neurotransmitters, modulators of neurotransmission, or neurohormones. Their presence in the hypothalamus suggests a role in the regulation of endocrine function. Opioids have been shown to stimulate the release of some pituitary hormones, including prolactin and growth hormone, and to inhibit the release of others, including corticotropin.

Endogenous peptides include the enkephalins, endorphins, and dynorphins; their polypeptide precursors may also be precursors for non-opioid peptides. Proenkephalin is the precursor of met- and leu-enkephalin; pro-opiomelanocortin is the precursor of beta-endorphin, beta-lipotrophin, melanocyte-stimulating hormone, and corticotropin; and prodynorphin is the precursor of dynorphins and neoendorphins.

Pharmacologically the opioid analgesics are broadly similar; qualitative and quantitative differences may be dependent on their interaction with **opioid receptors**. There are several types of opioid receptor and they are distributed in distinct patterns through the central and peripheral nervous systems. The three main types in the CNS were originally designated μ (mu), κ (kappa), and δ (delta) although they have been reclassified as OP_3, OP_2, and OP_1, respectively. Activities attributed to the stimulation of these receptors have been as follows:

- μ—analgesia (mainly at supraspinal sites), respiratory depression, miosis, reduced gastrointestinal motility, and euphoria; μ_1 (supraspinal analgesia) and μ_2 (respiratory depression and gastrointestinal activity) subtypes have been postulated
- κ—analgesia (mainly in the spinal cord); less intense miosis and respiratory depression, dysphoria and psychotomimetic effects
- δ—less certain in man, but probably analgesia; selective for enkephalins
- Other receptors include σ (sigma) and ε (epsilon) receptors. The psychotomimetic effects of agonist-antagonists such as pentazocine that are poorly antagonised by naloxone have been thought by some to be mediated by σ receptors

Opioids act at one or more of these receptors as full or partial agonists, or as antagonists. Morphine and similar opioid agonists (sometimes called μ agonists) are considered to act primarily at μ and perhaps at κ and δ receptors. Opioid agonist-antagonists such as pentazocine appear to act as κ agonists and μ antagonists whereas buprenorphine is a partial agonist at μ receptors with some antagonist activity at κ receptors. The opioid antagonist naloxone acts at μ, κ, and δ receptors.

In addition to differing affinities for particular receptors the degree of activation once bound also differs. The full agonist morphine produces maximum activation at the μ receptor and its effects increase with dose, whereas partial agonists and agonist-antagonists may demonstrate a 'ceiling effect' in that above a certain level their effects do not increase proportionately with dose.

Other differences between opioid analgesics may relate to their lipid solubility and pharmacokinetics; speed of onset and duration of action may influence the choice of analgesic.

Opioid analgesics were traditionally classified as weak or strong opioids; however this classification has largely been replaced by the one used in the WHO three-step analgesic ladder (see Cancer Pain, p.5). In this system opioids are divided into those that are used for **mild to moderate pain** and those that are used for **moderate to severe pain**. Examples of opioids in the first group include codeine, dextropropoxyphene, and dihydrocodeine; such opioids are distinguished by the existence of a ceiling effect and are often used with non-opioid analgesics. The principal opioid for the treatment of moderate to severe pain is morphine. Others include diamorphine, fentanyl, methadone, and pethidine.

In addition to the relief of pain, opioids are used in **anaesthesia** for premedication, induction, or maintenance; however, pre-operative use is generally limited to patients who require control of existing pain. In balanced anaesthesia they are used with an anaesthetic and a neuromuscular blocker. When used with an antipsychotic they can produce a state of mild sedation with analgesia called neuroleptanalgesia.

Some opioids are used for analgesia, sedation, and suppression of respiration in the management of mechanically ventilated patients under **intensive care** (p.957).

Opioids such as codeine, hydrocodone, and hydromorphone are used for the suppression of **cough**; for intractable cough in terminal illness morphine may be used.

Opioids may relieve some forms of **dyspnoea**; morphine and diamorphine are probably the most commonly used in the UK, but dihydrocodeine, hydrocodone, and oxymorphone have also been tried.

Methadone and buprenorphine are used in the treatment of opioid **dependence** (see above).

◊ References.

1. Cherny NI. Opioid analgesics: comparative features and prescribing guidelines. *Drugs* 1996; **51:** 713–37.
2. Upton RN, *et al.* Pharmacokinetic optimisation of opioid treatment in acute pain therapy. *Clin Pharmacokinet* 1997; **33:** 225–44.
3. Walsh D. Advances in opioid therapy and formulations. *Support Care Cancer* 2005; **13:** 138–44.
4. Hanks GW, Reid C. Contribution to variability in response to opioids. *Support Care Cancer* 2005; **13:** 145–52.

Action. Some references to opioid receptors.

1. Pleuvry BJ. Opioid receptors and their ligands: natural and unnatural. *Br J Anaesth* 1991; **66:** 370–80.
2. Pleuvry BJ. Opioid receptors and awareness of the Greek alphabet. *Br J Hosp Med* 1992; **48:** 678–81.
3. Atcheson R, Lambert DG. Update on opioid receptors. *Br J Anaesth* 1994; **73:** 132–4.
4. Dhawan BN, *et al.* International Union of Pharmacology. XII. Classification of opioid receptors. *Pharmacol Rev* 1996; **48:** 567–86.
5. Inturrisi CE. Clinical pharmacology of opioids for pain. *Clin J Pain* 2002; **18** (4 suppl): S3–S13.
6. Gourlay GK. Advances in opioid pharmacology. *Support Care Cancer* 2005; **13:** 153–9.

Administration in children. See under Precautions, above.

Administration in the elderly. See under Precautions, above.

Anaesthesia. Opioid analgesics have been given intravenously as supplements during general anaesthesia with inhalational or intravenous drugs. They have also been widely used as premedication before surgery to reduce anxiety, for smooth induction of anaesthesia, to reduce overall anaesthetic requirements, and to provide postoperative pain relief. Such use of opioids is now rare and is restricted to patients already in pain or to those who will experience pain before induction of anaesthesia. Very high doses of morphine have been infused intravenously to produce anaesthesia for cardiac surgery, but shorter acting drugs such as fentanyl and related opioids are generally used now; some may prefer agonist-antagonist opioids. Sedation and respiratory depression may be prolonged necessitating assisted ventilation; reversal of these effects can be achieved by opioid antagonists such as naloxone. For a discussion of the various drugs used to achieve and maintain conditions suitable for surgery, including the use of opioids in the induction and maintenance of anaesthesia, see p.1780. Opioid analgesics, most commonly fentanyl, have been used with an antipsychotic to induce a state known as neuroleptanalgesia in which the patient is calm and indifferent to the surroundings yet is responsive to commands. For a brief discussion of neuroleptanalgesia and similar anaesthetic techniques, see p.1780.

POSTOPERATIVE SHIVERING. Pethidine appears to be effective in the treatment of postoperative shivering (see p.1779) but not all opioids are necessarily effective.

Cough. Opioids are used to suppress cough (p.1547). Pholcodine (p.1570) and dextromethorphan (p.1555), which lack classical analgesic activity and have fewer adverse effects, are the most commonly used opioids. Of the analgesic opioids, codeine is the most widely used as a cough suppressant. However, these opioids are seldom sufficiently potent to be effective in severe cough. Morphine and diamorphine are used for the relief of intractable cough in terminal illness, although morphine is now preferred. Methadone has also been used but should be avoided as it has a long duration of action and tends to accumulate.

Cough suppressants containing codeine or similar opioids are generally not recommended for use in children, and should be avoided in those under 2 years of age.

Diarrhoea. Oral rehydration therapy, which is the treatment of choice for acute diarrhoea (p.1694), prevents dehydration, but it does not necessarily shorten the duration of the diarrhoea. Preparations containing codeine, morphine, or other opioids have therefore been used for their antimotility action as adjuncts in the management of acute diarrhoea. However, the WHO considers that such antidiarrhoeal drug therapy is of limited value, and should never be given to children. Furthermore opioids should not be used in conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in diarrhoeal conditions such as severe ulcerative colitis or antibiotic-associated colitis.

Dyspnoea. Dyspnoea (a subjective feeling of abnormally uncomfortable, difficult, or laboured breathing) is associated with diseases that interfere with oxygenation of the blood. It is best relieved by treatment of the underlying disorder (the treatment of dyspnoea associated with asthma and chronic obstructive pulmonary disease is discussed on p.1108 and p.1112, respectively). Where this is impossible or ineffective, symptomatic management is required.

Oxygen may reduce dyspnoea in some patients even if dyspnoea is not related to hypoxia. A flow of air directed across the face by a fan can also be effective. Despite the hazards of using benzodiazepines in patients with any form of respiratory depression or pulmonary insufficiency (see under Precautions of Diazepam, p.989), drugs such as diazepam, lorazepam, or midazolam may be helpful in patients with advanced cancer who have rapid shallow respiration, especially when this is associated with anxiety.[1-3] Levomepromazine is occasionally used as an alternative.

Opioids may relieve some forms of dyspnoea,[2,4,5] such as those due to acute left ventricular failure, pulmonary oedema, and malignant chest disease. Guidelines[6] (based on the findings of systematic reviews[7]) issued for the management of dyspnoea in palliative care recommend that opioids should be considered in patients with severe and unrelieved dyspnoea. The cause of dyspnoea should be established since the use of opioids is generally not advised, or only with extreme caution, in patients with obstructive airways disease whose dyspnoea may be relieved by other means. In the UK, morphine and diamorphine are probably the most commonly used opioids for dyspnoea, but dihydrocodeine, hydrocodone, and oxymorphone have also been tried. It is unclear if all opioids are equally effective.[5]

Nebulised morphine, hydromorphone, or fentanyl have been tried for the management of dyspnoea, and there are anecdotal reports of benefit, especially in palliative care, but evidence from controlled studies to date does not support such use.[2-4,8-11] See also under Morphine, p.90.

In patients with advanced cancer and intractable dyspnoea unresponsive to the above measures, chlorpromazine may be useful to relieve air hunger and sedate dying patients who have unrelieved distress;[1] midazolam may be used as an alternative. Promethazine has also been used. High doses of a corticosteroid such as dexamethasone may help to relieve dyspnoea in patients with airways obstruction due to a tumour by reducing oedema around the tumour.

1. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342:** 450–1.
2. Davis CL. ABC of palliative care: breathlessness, cough, and other respiratory problems. *BMJ* 1997; **315:** 931–4.
3. American Thoracic Society. Dyspnea. Mechanisms, assessment, and management: a consensus statement. *Am J Respir Crit Care Med* 1999; **159:** 321–40. Also available at: http://www.thoracic.org/sections/publications/statements/pages/respiratory-disease-adults/dyspnea1-20.html (accessed 26/06/08)
4. Jennings AL, *et al.* Opioids for the palliation of breathlessness in terminal illness. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 26/06/08).

5. Kvale PA, *et al.* American College of Chest Physicians. Lung cancer: palliative care. *Chest* 2003; **123** (suppl): 284S–311S. Also available at: http://www.chestjournal.org/cgi/reprint/123/1_suppl/284S.pdf (accessed 26/06/08)
6. Qaseem A, *et al.* Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2008; **148:** 141–6. Also available at: http://www.annals.org/cgi/reprint/148/2/141.pdf (accessed 28/08/08)
7. Lorenz KA, *et al.* Evidence for improving palliative care at the end of life: a systematic review. *Ann Intern Med* 2008; **148:** 147–59.
8. Chandler S. Nebulized opioids to treat dyspnea. *Am J Hosp Palliat Care* 1999; **16:** 418–22.
9. Foral PA, *et al.* Nebulized opioids use in COPD. *Chest* 2004; **125:** 691–4.
10. Brown SJ, *et al.* Nebulized morphine for relief of dyspnea due to chronic lung disease. *Ann Pharmacother* 2005; **39:** 1088–92.
11. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnea. *Respir Care* 2007; **52:** 900–10.

Pain. Opioid analgesics are used for the relief of acute and chronic pain (see Choice of Analgesic, p.2). Not every type of pain responds; neuropathic pain, for example, may not be alleviated by opioid therapy. For further discussion of specific pain states and the role of opioid analgesics in their treatment see p.5 onwards.

There has also been interest in the local analgesic effects of opioids themselves.[1,2]

The use of opioid analgesics in opioid-dependent patients receiving maintenance treatment with an opioid is the subject of much debate; however, some consider such use to be appropriate in the management of acute pain in these patients and recommendations have been issued.[3]

1. Thompson DF, Pierce DR. Local analgesia with opioid drugs. *Ann Pharmacother* 1995; **29:** 189–90.
2. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med* 1995; **332:** 1685–90.
3. Alford DP, *et al.* Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med* 2006; **144:** 127–34.

HEADACHE. Opioid analgesics such as codeine are sometimes included in oral compound analgesic preparations used in the initial treatment of migraine (see p.616) or tension-type headache (see p.617), but are best avoided, especially in patients who experience frequent attacks.

Restless legs syndrome. Some opioids may be beneficial in the treatment of restless legs syndrome (see Sleep-associated Movement Disorders, p.958), although evidence is scanty.

Sedation. In addition to their analgesic action opioids have been used for their sedative properties. Mention of this use of opioids can be found in the discussions of anaesthesia (p.1780), endoscopy (p.956), and intensive care (p.957).

Tetanus. Opioid analgesics can be used to provide analgesia and additional sedation in patients undergoing treatment for tetanus (p.196 and p.1901). Opioids such as fentanyl, morphine, and sufentanil have also been given to control the sympathetic overactivity in such patients.[1-3]

1. Rocke DA, *et al.* Morphine in tetanus—the management of sympathetic nervous system overactivity. *S Afr Med J* 1986; **70:** 666–8.
2. Moughabghab AV, *et al.* Management of autonomic dysfunction in severe tetanus: the use of fentanyl. *Can J Anaesth* 1995; **42:** 955.
3. Bhagwanjee S, *et al.* Management of sympathetic overactivity in tetanus with epidural bupivacaine and sufentanil: experience with 11 patients. *Crit Care Med* 1999; **27:** 1721–5.

Opium

Gum Opium; Nyers ópium; Opijus, žaliavinis; Opio; Opium brut; Opium crudum; Opium surové; Raakaopiumi; Råopium; Raw Opium.

Опиум

ATC — A07DA02; N02AA02.
ATC Vet — QA07DA02; QN02AA02.

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of opium:
Ah-pen-yen; Aunti; Aunti Emma; Big O; Black; Black pill; Black shit; Black stuff; Black tar opium; Block; Boulette; Chandoo; Chandu; China; Chinese molasses; Chinese tobacco; Chocolate; Cruz; Dopium; Dover's deck; Dover's powder; Dream gum; Dream gun; Dream stick; Dreams; Dutch courage; Easing powder; Fi-do-nie; Gee; God's medicine; Goma; Gondola; Gong; Goric; Great tobacco; Gum; Guma; Hard stuff; Hocus; Hop; Hops; Incense; Indonesian bud; Joy plant; Midnight oil; Mira; Mud; O; O.P.; Ope; O-Rock DC; Pen yan; Pin gon; Pin yen; Pox; Skee; Tar; Toxy; Toys; When-shee; Ze; Zero.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.
Chin., *Eur.*, and *US* include a monograph for prepared or powdered opium. *Eur.* also contains monographs for standardised opium dry extract or standardised opium tincture. *Jpn* includes prepared opium and a diluted opium powder containing 1% of anhydrous morphine.
Ph. Eur. 6.2 (Opium, Raw; Opium BP 2008). The air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum* L. It has a characteristic odour and a blackish-brown colour. It should contain not less than 10% of anhydrous morphine, not less than 2% of anhydrous codeine, and not more than 3% of anhydrous thebaine. Protect from light.
Ph. Eur. 6.2 (Opium, Prepared; Opii Pulvis Normatus). Raw opium powdered and dried at a temperature not exceeding 70°. It is a yellowish-brown or dark brown powder and contains 9.8 to 10.2% of morphine and not less than 1.0% of codeine, calculated with reference to the dried drug. The content may be adjusted by adding a suitable excipient or raw opium powder.
USP 31 (Opium). The air-dried milky exudate obtained by incising the unripe capsules of *Papaver somniferum* (Papaveraceae). Externally it is pale olive-brown or olive-grey; internally it is reddish-brown. It has a very characteristic odour and a very bitter taste. It yields not less than 9.5% of anhydrous morphine.
USP 31 (Powdered Opium). Opium dried at a temperature not exceeding 70°, and reduced to a very fine light brown or moderately yellowish-brown powder that yields not less than 10% and not more than 10.5% of anhydrous morphine. It may contain any of the permitted diluents with the exception of starch.

Profile

Opium is the air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum* (Papaveraceae). It contains morphine, codeine, and thebaine and a variable mixture of other alkaloids including noscapine and papaverine. The exuded latex is dried and manipulated to form cakes of uniform composition, variously shaped according to the country of origin, and known in commerce as Turkish, Indian, or European opium.

Opium has the properties of opioid analgesics (p.101). Its analgesic and sedative actions are due mainly to its content of morphine (p.89). It acts less rapidly than morphine since opium appears to be more slowly absorbed; the relaxing action of the papaverine and noscapine on intestinal muscle makes it more constipating than morphine.

Opium is intended only as the starting material for the manufacture of galenical preparations and is not dispensed as such. It is used as Prepared Opium (Ph. Eur. 6.2), as Powdered Opium (USP 31), as Opium Tincture (BP 2008 or USP 31), or as Camphorated Opium Tincture (BP 2008) or Paregoric (USP 31) in various oral preparations. These have included Opiate Squill Linctus (BP 2008) (Gee's linctus) for cough.

Paregoric (USP 31) has been advocated in the USA for the treatment of neonatal abstinence syndrome.

Abuse. Reports of squill-associated cardiac toxicity resulting from the abuse of opiate squill linctus (Gee's linctus).[1,2]

1. Thurston D, Taylor K. Gee's linctus. *Pharm J* 1984; **233:** 63.
2. Smith W, *et al.* Wenckebach's phenomenon induced by cough linctus. *BMJ* 1986; **292:** 868.

Preparations

BP 2008: Camphorated Opium Tincture; Concentrated Camphorated Opium Tincture; Opium Tincture;
Ph. Eur.: Opium Dry Extract, Standardised; Opium Tincture, Standardised;
USP 31: Opium Tincture; Paregoric.

Proprietary Preparations (details are given in Part 3)
Braz.: Elixir Paregorico.

Multi-ingredient: ***Braz.:*** Camomila; Elixir de Marinheiro†; ***Denm.:*** Pectyl; ***Fin.:*** Tannopon; ***Fr.:*** Colchimax; Lamaline; Paregorique; ***Hong Kong:*** Brown Mixture; ***Israel:*** Davilla; Doveri; ***Mex.:*** Reglosedyl†; ***S.Afr.:*** Paragoriese-Elikser; Tandpyndruppels; ***Spain:*** Digestovital†; Tanagel; ***Switz.:*** Bromocod N; Pectocalmine; ***USA:*** B & O Supprettes No. 15A; B & O Supprettes No. 16A; ***Venez.:*** Atrobel.

Hydrochlorides of Mixed Opium Alkaloids

Alkaloidosum Opii Hydrochloridum; Extractum Concentratum Opii; Mezclas de hidrocloruros de alcaloides del opio; Omnoponum; Opialum; Opium Concentratum.

Гидрохлориды Смешанных Алкалоидов Опия

Pharmacopoeias. Preparations of the hydrochlorides of mixed opium alkaloids are included in *Jpn.*

Papaveretum *(BAN)*

A mixture of 253 parts of morphine hydrochloride, 23 parts of papaverine hydrochloride, and 20 parts of codeine hydrochloride.

Папаверетум

CAS — 8002-76-4.
ATC — N02AA10.
ATC Vet — QN02AA10.

NOTE. Do not confuse papaveretum with papaverine (p.2191).

Pharmacopoeias. In *Br.*
BP 2008 (Papaveretum). It contains 80.0 to 88.4% of anhydrous morphine hydrochloride, 8.3 to 9.2% of papaverine hydrochloride, and 6.6 to 7.4% of anhydrous codeine hydrochloride. A white or almost white crystalline powder. Soluble in water, sparingly soluble in alcohol. A 1.5% solution in water has a pH of 3.7 to 4.7. Protect from light.

Profile

The opium alkaloids are the prototypical opioid analgesics (p.101). Mixtures of opium alkaloids such as papaveretum have the analgesic and sedative properties of morphine (p.89) and are used in the treatment of moderate to severe pain including postoperative and severe chronic pain. They may also be used for pre-operative sedation and as an adjunct to anaesthesia. Papaveretum (BP 2008) 15.4 mg contains the equivalent of about 10 mg of the major component, anhydrous morphine.

- In the UK, papaveretum formerly contained the hydrochlorides of morphine, codeine, noscapine, and papaverine. However, because of concern over the potential genotoxicity of noscapine (p.1566) UK preparations containing papaveretum were reformulated to exclude the noscapine component and the name papaveretum was redefined in the BP 1993 to reflect this change of formulation. It is possible that in other countries the term papaveretum is still being used to describe a mixture containing noscapine.

Doses. Papaveretum is generally given by subcutaneous or intramuscular injection in doses of 7.7 to 15.4 mg every 4 hours if necessary. The initial dose in the elderly or debilitated patients should not exceed 7.7 mg.

In the treatment of pain and as an adjunct in anaesthesia, papaveretum may also be given intravenously in doses of one-quarter to one-half the corresponding subcutaneous or intramuscular dose. For pre-operative medication papaveretum is given intramuscularly or subcutaneously sometimes with hyoscine hydrobromide.

For details of doses in children, see below.

Oral preparations containing papaveretum with aspirin have been given for the management of moderate to severe pain.

◊ Papaveretum has been confused with papaverine (p.2191) and in one such case[1] a patient became unconscious after self-injection of papaveretum in mistake for papaverine.

1. Robinson LQ, Stephenson TP. Self injection treatment for impotence. *BMJ* 1989; **299:** 1568.

Administration in children. Papaveretum may be given to children in the treatment of moderate to severe pain including postoperative and severe chronic pain. It is also used for pre-operative sedation and as an adjunct to anaesthesia. Papaveretum is generally given by subcutaneous or intramuscular injection every 4 hours if necessary, according to age as follows:

- neonates: 115 micrograms/kg
- 1 to 12 months: 154 micrograms/kg
- 1 to 6 years: 1.93 to 3.85 mg
- 6 to 12 years: 3.85 to 7.7 mg

Older children may be given the usual adult dose (see above).

In the treatment of pain and as an adjunct to anaesthesia papaveretum may also be given intravenously in doses of one-quarter to one-half the corresponding subcutaneous or intramuscular dose.

Preparations

BP 2008: Papaveretum Injection.

Proprietary Preparations (details are given in Part 3)
S.Afr.: Omnopon.

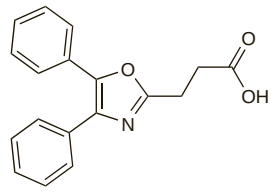
Multi-ingredient: ***UK:*** Aspav.

Oxaprozin *(BAN, USAN, rINN)*

Oksaprotsiini; Oxaprozina; Oxaprozine; Oxaprozinum; Wy-21743. 3-(4,5-Diphenyloxazol-2-yl)propionic acid.

Оксапрозин

$C_{18}H_{15}NO_3$ = 293.3.
CAS — 21256-18-8.
ATC — M01AE12.
ATC Vet — QM01AE12.



Pharmacopoeias. In *Chin.*, *Jpn.*, and *US*.
USP 31 (Oxaprozin). A white to yellowish-white, crystalline powder. Store in airtight containers at a temperature of 20° to 25°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Diagnosis and testing. False-positive results for testing of benzodiazepines in urine have been reported in patients taking oxaprozin.[1] The manufacturer[2] has commented that the interaction occurs with some immunoassay tests and that thin-layer chromatography can successfully discriminate between benzodiazepines and oxaprozin. False-positive results for a fluorescence polarisation immunoassay for phenytoin have also been reported in patients receiving oxaprozin.[3]

1. Pulini M. False-positive benzodiazepine urine test due to oxaprozin. *JAMA* 1995; **273:** 1905.
2. Raphan H, Adams MH. False-positive benzodiazepine urine test due to oxaprozin. *JAMA* 1995; **273:** 1905–6.
3. Patel T, *et al.* Assay interaction between oxaprozin and phenytoin. *Ann Pharmacother* 1997; **31:** 254.