ed not more often than every 4 hours; a dose of 2 mg/hour is the recommended starting dose as an intravenous infusion. The intravenous route may also be used for patient-controlled analgesia. When given subcutaneously, the starting dose is 5 mg every 4 hours; subcutaneous infusions should be started at 7.5 mg daily in opioid-naive patients. When transferring between oral and parenteral oxycodone, UK licensed product information advises that, as a guide, 2 mg of oral oxycodone is equivalent to about 1 mg of parenteral oxycodone.

Oxycodone has been given rectally as suppositories containing 30 mg of oxycodone (as the pectinate) or 10 or 20 mg of oxycodone hydrochloride; the dose may be repeated every 6 to 8 hours.

For doses in patients with hepatic or renal impairment, see below.

Oxycodone terephthalate is also used orally.

Administration in children. Although oxycodone hydrochloride is not licensed in the UK for use in children under 18 years old, the *BNFC* suggests that it may be given for the treatment of moderate to severe pain in palliative care. Those aged from 1 month to 12 years may be given initial oral doses of 200 micrograms/kg (up to 5 mg) every 4 to 6 hours increased thereafter as necessary according to response; older children may be given the usual adult dose (see above). Oxycodone hydrochloride may also be given orally as a modified-release preparation every 12 hours to those aged 8 years and older.

Administration in hepatic or renal impairment. The plasma concentrations of oxycodone may be increased in patients with hepatic or renal impairment and consequently dosage adjustment may be necessary in such patients. In the UK, licensed product information recommends that the oral starting dose for adult patients with mild hepatic impairment or mild to moderate renal impairment should be 2.5 mg given every 6 hours; it contra-indicates the use of oxycodone in those with moderate to severe hepatic impairment or severe renal impairment. US product information permits the cautious use of oxycodone in adult patients with severe hepatic or severe renal impairment.

Pain. References.

1. Sunshine A, *et al.* Analgesic efficacy of controlled-release oxycodone in postoperative pain. *J Clin Pharmacol* 1996; **36:** 595–603.
2. Curtis GB, *et al.* Relative potency of controlled-release oxycodone and controlled-release morphine in a postoperative pain model. *Eur J Clin Pharmacol* 1999; **55:** 425–9.
3. Gimbel JS, *et al.* Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology* 2003; **60:** 927–34.
4. Gammaitoni AR, *et al.* Randomized, double-blind, placebo-controlled comparison of the analgesic efficacy of oxycodone 10 mg/acetaminophen 325 mg versus controlled-release oxycodone 20 mg in postsurgical pain.*J Clin Pharmacol* 2003; **43:** 296–304.
5. Oldfield V, Perry CM. Oxycodone/ibuprofen combination tablet: a review of its use in the management of acute pain. *Drugs* 2005; **65:** 2337–54.
6. Kalso E. Oxycodone. *J Pain Symptom Manage* 2005; **29** (suppl): S47–S56.
7. Bercovitch M, Adunsky A. High dose controlled-release oxycodone in hospice care. *J Pain Palliat Care Pharmacother* 2006; **20:** 33–9.
8. Reid CM, *et al.* Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; **166:** 837–43. Correction. *ibid.*; 2387.
9. Portenoy RK, *et al.* Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain* 2007; **23:** 287–99.
10. Pan H, *et al.* Efficacy and tolerability of oxycodone hydrochloride controlled-release tablets in moderate to severe cancer pain. *Clin Drug Invest* 2007; **27:** 259–67.

Preparations

USP 31: Oxycodone and Acetaminophen Capsules; Oxycodone and Acetaminophen Tablets; Oxycodone and Aspirin Tablets; Oxycodone Hydrochloride Extended-Release Tablets; Oxycodone Hydrochloride Oral Solution; Oxycodone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Oxicalmans; Oxinovag; Oxycontin; ***Austral.:*** Endone; Oxycontin; Oxynorm; Proladone; ***Austria:*** Oxycontin; Oxynorm; ***Belg.:*** Oxycontin; ***Braz.:*** Oxycontin; ***Canad.:*** Oxy IR; Oxycontin; Supeudol; ***Chile:*** Oxycontin; ***Cz.:*** Oxycontin; ***Denm.:*** Oxycontin; Oxynorm; ***Fin.:*** Oxanest; Oxycontin; Oxynorm; ***Fr.:*** Eubine†; Oxycontin; Oxynorm; ***Ger.:*** Oxygesic; ***Hung.:*** Oxycontin; ***Irl.:*** Oxycontin; Oxynorm; ***Israel:*** Oxycod; Oxycontin; ***Ital.:*** Oxycontin; ***Jpn:*** Oxycontin; ***Malaysia:*** Oxycontin; ***Mex.:*** Oxycontin†; ***Neth.:*** Oxycontin; Oxynorm; ***Norw.:*** Oxycontin; Oxynorm; ***NZ:*** Oxycontin; Oxynorm; ***Philipp.:*** Oxycontin; ***Port.:*** Oxycontin; ***Singapore:*** Oxycontin; Oxynorm; ***Spain:*** Oxycontin; Oxynorm; ***Swed.:*** Oxycontin; Oxynorm; ***Switz.:*** Oxycontin; Oxynorm; ***UK:*** Oxycontin; Oxynorm; ***USA:*** Endocodone†; ETH-Oxydose; Oxycontin; Oxyfast; OxylR; Percolone†; Roxicodone; ***Venez.:*** Oxycontin.

Multi-ingredient: ***Arg.:*** Oxinovag Complex; ***Canad.:*** Endocet; Endodan; Percocet; Percodan; ratio-Oxycocet; ratio-Oxycodan; ***Israel:*** Percocet; Percodan; ***Ital.:*** Depalgos; ***USA:*** Combunox; Endocet; Magnacet; Narvox; Percocet; Percodan; Perloxx; Roxicet; Roxilox; Roxiprin†; Tylox.

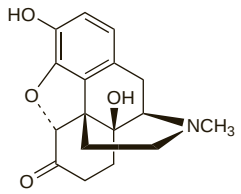
Oxymorphone Hydrochloride *(BANM, rINNM)* ⊗

7,8-Dihydro-14-hydroxymorphinone hydrochloride; Hidrocloruro de oximorfona; Oximorphone Hydrochloride; Oxymorphone, Chlorhydrate d'; Oxymorphoni Hydrochloridum. 6-Deoxy-7,8-dihydro-14-hydroxy-6-oxomorphine hydrochloride; (–)-(5*R*,6*S*,14*S*)-4,5-Epoxy-3,14-dihydroxy-9a-methylmorphinan-6-one hydrochloride.

Оксиморфона Гидрохлорид

$C_{17}H_{19}NO_4,HCl$ = 337.8.

CAS — 76-41-5 (oxymorphone); 357-07-3 (oxymorphone hydrochloride).



(oxymorphone)

Pharmacopoeias. In *US*.

USP 31 (Oxymorphone Hydrochloride). A white or slightly off-white odourless powder, darkening on exposure to light. Its aqueous solutions are slightly acidic. Soluble 1 in 4 of water, 1 in 100 of alcohol, and 1 in 25 of methyl alcohol; very slightly soluble in chloroform and in ether. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Dependence and Withdrawal

As for Opioid Analgesics in general, p.101.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p.102.

For details on the use of oxymorphone in patients with hepatic or renal impairment see below.

Interactions

For interactions associated with opioid analgesics, see p.103.

Licensed product information for a modified-release preparation of oxymorphone hydrochloride (*Opana ER; Endo, USA*) states that patients must not ingest alcohol, including alcohol-containing medicines, at the same time due to the risk of increased plasma concentrations and a potentially fatal overdose of oxymorphone.

Pharmacokinetics

Oxymorphone hydrochloride is absorbed from the gastrointestinal tract after oral doses, but bioavailability is only about 10% because of first-pass metabolism. Absorption is increased after a high-fat meal. About 10% is bound to plasma proteins. Oxymorphone is extensively metabolised in the liver by glucuronidation and less than 1% of a dose appears in the urine and faeces as unchanged drug. With regard to its major metabolites between 33 and 38% of a dose is excreted in the urine as oxymorphone-3-glucuronide and less than 1% as 6-OH-oxymorphone. Oxymorphone crosses the placenta.

◊ References.

1. Adams MP, Ahdieh H. Pharmacokinetics and dose-proportionality of oxymorphone extended release and its metabolites: results of a randomized crossover study. *Pharmacotherapy* 2004; **24:** 468–76.
2. Adams MP, Ahdieh H. Single- and multiple-dose pharmacokinetic and dose-proportionality study of oxymorphone immediate-release tablets. *Drugs R D* 2005; **6:** 91–9.

Uses and Administration

Oxymorphone hydrochloride, a phenanthrene derivative, is an opioid analgesic (p.101) with actions and uses similar to those of morphine (p.86), apart from a lack of cough suppressant activity. Oxymorphone is given orally, parenterally, or rectally for the relief of moderate to severe pain, including pain in obstetrics, and is reported to provide analgesia for 3 to 6 hours. It may also be used parenterally for premedication, as an adjunct to anaesthesia, and to relieve dyspnoea due to pulmonary oedema resulting from left ventricular failure.

A usual *oral* starting dose for opioid-naive patients is 10 to 20 mg of oxymorphone hydrochloride every 4 to 6 hours adjusted thereafter as necessary; some patients may be started on lower doses of 5 mg. For patients who have been receiving a strong opioid analgesic the initial dose of oxymorphone should be based on the daily opioid requirement; licensed product information suggests that 10 mg of oral oxymorphone is equivalent to about 30 mg of oral morphine and recommends giving half the calculated equivalent dose of oxymorphone initially. Oxymorphone hydrochloride may also be given orally as a modified-release preparation every 12 hours. Oral preparations of oxymorphone should be taken on an empty stomach.

Oxymorphone hydrochloride is given by *intramuscular* or *subcutaneous injection* in initial doses of 1 to 1.5 mg, repeated every 4 to 6 hours as necessary; 500 micrograms may be given by intravenous injection. The usual dose for analgesia during labour is 0.5 to 1 mg intramuscularly. When transferring between oral and parenteral oxymorphone, licensed product information advises that, as a guide, 10 mg of oral oxymorphone is equivalent to about 1 mg of parenteral oxymorphone.

Oxymorphone hydrochloride is also given *rectally* as a suppository in a dose of 5 mg every 4 to 6 hours.

◊ References.

1. Prommer E. Oxymorphone: a review. *Support Care Cancer* 2006; **14:** 109–15.
2. Chamberlin KW, *et al.* Oral oxymorphone for pain management. *Ann Pharmacother* 2007; **41:** 1144–52.

Administration in hepatic impairment. Advice on the use of oxymorphone in patients with hepatic impairment is conflicting. Licensed product information for one range of preparations (*Opana* and *Opana ER tablets; Endo, USA*) recommends caution in patients with mild hepatic impairment; these patients should be started on the lowest oral dose and titrated slowly thereafter. In addition, it is stated that oxymorphone is contra-indicated in those with moderate or severe impairment. However, licensed information for another oxymorphone preparation (*Numorphan injection and suppositories; Endo, USA*) only recommends caution in hepatic disease although lower doses (unspecified) are advised in those patients with severe impairment.

Administration in renal impairment. In patients with moderate to severe renal impairment, the bioavailability of oxymorphone was found to increase by over 50%; consequently, it is recommended that oxymorphone is given with caution and in reduced doses (unspecified) to those with a creatinine clearance of less than 50 mL/minute.

Preparations

USP 31: Oxymorphone Hydrochloride Injection; Oxymorphone Hydrochloride Suppositories.

Proprietary Preparations (details are given in Part 3)

Canad.: Numorphan†; ***USA:*** Numorphan; Opana.

Oxyphenbutazone *(BAN, rINN)*

G-27202; Hydroxyphenylbutazone; Oksifenbutatsoni; Oxifenbutazon; Oxifenbutazona; Oxyphenbutazonum. 4-Butyl-1-(4-hydroxyphenyl)-2-phenylpyrazolidine-3,5-dione monohydrate.

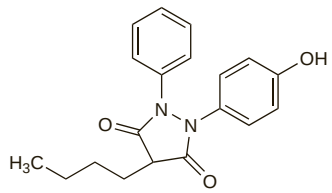
Оксифенбутазон

$C_{19}H_{20}N_2O_3,H_2O$ = 342.4.

CAS — 129-20-4 (anhydrous oxyphenbutazone); 7081-38-1 (oxyphenbutazone monohydrate).

ATC — M01AA03; M02AA04; S01BC02.

ATC Vet — QM01AA03; QM02AA04; QS01BC02.



Profile

Oxyphenbutazone, a metabolite of phenylbutazone (p.117), is an NSAID (p.96). It has been applied topically to the eye as an anti-inflammatory ointment in conditions such as episcleritis. Oxyphenbutazone was used systemically in disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis but such use is no longer considered justified because of the risk of severe haematological adverse effects (see also Effects on the Blood, under Phenylbutazone, p.117).

The piperazine salt has also been used.

Porphyria. Oxyphenbutazone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)

India: Sioril†; ***Mex.:*** Edefen†; Redolet†.

Multi-ingredient: ***Braz.:*** Algi Peralgin†; Algiflamanil; Analtrix†; Febupen; Flamanan; Reumazine†; ***Mex.:*** Dartrizon.

Paracetamol *(BAN, rINN)*

Acetaminofeno; Acetaminophen; *N*-Acetyl-*p*-aminophenol; Asetaminofen; Paracétamol; Paracetamolis; Paracetamolum; Parasetamol; Parasetamoli. 4′-Hydroxyacetanilide; *N*-(4-Hydroxyphenyl)acetamide.

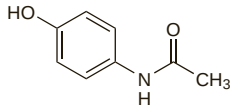
Парацетамол

$C_8H_9NO_2$ = 151.2.

CAS — 103-90-2.

ATC — N02BE01.

ATC Vet — QN02BE01.



NOTE. Compounded preparations of paracetamol may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine
- Co-codamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of codeine phosphate and paracetamol respectively
- Co-codAPAP (*PEN*)—paracetamol and codeine phosphate
- Co-dydramol (*BAN*)—dihydrocodeine tartrate 1 part and paracetamol 50 parts (w/w)
- Co-hycodAPAP (*PEN*)—hydrocodone tartrate and paracetamol
- Co-methiamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of DL-methionine and paracetamol, respectively
- Co-oxycodAPAP (*PEN*)—oxycodone and paracetamol
- Co-proxamol (*BAN*)—dextropropoxyphene hydrochloride 1 part and paracetamol 10 parts (w/w)
- Co-proxAPAP (*PEN*)—dextropropoxyphene napsilate and paracetamol.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Paracetamol). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol; very slightly soluble in dichloromethane. Protect from light.

USP 31 (Acetaminophen). A white odourless crystalline powder. Soluble 1 in 20 of boiling water, 1 in 10 of alcohol, and 1 in 15 of 1*N* sodium hydroxide. Store in airtight containers. Protect from light. Protect from moisture and heat.

Adverse Effects and Treatment

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Skin rashes and other hypersensitivity reactions occur occasionally. Hypotension has been reported rarely with parenteral use.

Overdosage with paracetamol can result in severe liver damage and sometimes acute renal tubular necrosis. Prompt treatment with acetylcysteine or methionine is essential and is discussed under Overdosage, below.

◊ References.

1. Graham GG, *et al.* Tolerability of paracetamol. *Drug Safety* 2005; **28:** 227–40.

Effects on the kidneys. For reference to evidence that abuse or prolonged excessive use of analgesics, including paracetamol, can produce nephropathy, see under NSAIDs, p.98.

See also under Overdosage, below.

Effects on the respiratory tract. The results of a case-control study[1] have suggested that the frequent (daily or weekly) use of paracetamol may be associated with asthma. However, the UK CSM has commented that the results of this study do not alter any advice regarding the use of paracetamol and that it remains a safe and effective pain killer for many patients including asthmatics.

Subsequently, a further study and a review have found an increase in the prevalence of asthma[2,3] and COPD[2] with frequent (daily or weekly) use of paracetamol. A link between paracetamol use in pregnancy and asthma in children has also been suggested (see Pregnancy under Precautions, below). However, another review[4] stated that there have been very few actual reports of paracetamol causing asthma; furthermore, bronchospasm is not a recognised feature of paracetamol overdosage. The review concluded that a strong link between paracetamol use and asthma was unlikely.

1. Shaheen SO, *et al.* Frequent paracetamol use and asthma in adults. *Thorax* 2000; **55:** 266–70.
2. McKeever TM, *et al.* The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med* 2005; **171:** 966–71.
3. Eneli I, *et al.* Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005; **127:** 604–12.
4. Nuttall SL, *et al.* Does paracetamol cause asthma? *J Clin Pharm Ther* 2003; **28:** 251–7.

Hypersensitivity. Reactions characterised by urticaria, dyspnoea, and hypotension have occurred after use of paracetamol in adults[1-4] and children.[5,6] Angioedema has also been reported.[7] Fixed drug eruptions, confirmed by rechallenge, have been described,[8-11] and toxic epidermal necrolysis has occurred.[12]

1. Stricker BHC, *et al.* Acute hypersensitivity reactions to paracetamol. *BMJ* 1985; **291:** 938–9.
2. Van Diem L, Grilliat JP. Anaphylactic shock induced by paracetamol. *Eur J Clin Pharmacol* 1990; **38:** 389–90.
3. Kumar RK, Byard I. Paracetamol as a cause of anaphylaxis. *Hosp Med* 1999; **60:** 66–7.
4. Bachmeyer C, *et al.* Acetaminophen (paracetamol)-induced anaphylactic shock. *South Med J* 2002; **95:** 759–60.
5. Ellis M, *et al.* Immediate adverse reactions to acetaminophen in children: evaluation of histamine release and spirometry. *J Pediatr* 1989; **114:** 654–6.
6. Bousetta K, *et al.* Hypersensitivity reactions to paracetamol in children: a study of 25 cases. *Allergy* 2005; **60:** 1174–7.
7. Idoko JA, *et al.* Angioneurotic oedema following ingestion of paracetamol. *Trans R Soc Trop Med Hyg* 1986; **80:** 175.
8. Thomas RHM, Munro DD. Fixed drug eruption due to paracetamol. *Br J Dermatol* 1986; **115:** 357–9.
9. Cohen HA, *et al.* Fixed drug eruption caused by acetaminophen. *Ann Pharmacother* 1992; **26:** 1596–7.
10. Harris A, Burge SM. Vasculitis in a fixed drug eruption due to paracetamol. *Br J Dermatol* 1995; **133:** 790–1.
11. Hern S, *et al.* Bullous fixed drug eruption due to paracetamol with an unusual immunofluorescence pattern. *Br J Dermatol* 1998; **139:** 1129–31.
12. Halevi A, *et al.* Toxic epidermal necrolysis associated with acetaminophen ingestion. *Ann Pharmacother* 2000; **34:** 32–4.

Overdosage. Acute ***oral*** overdosage with paracetamol, whether accidental or deliberate, is relatively common and can be extremely serious because of the narrow margin between therapeutic and **toxic doses**. Ingestion of as little as 10 to 15 g of paracetamol by adults may cause severe hepatocellular necrosis and, less often, renal tubular necrosis. Patients should be considered at risk of severe liver damage if they have ingested more than 150 mg/kg of paracetamol or 12 g or more in total, whichever is the smaller. The risk of severe toxicity after acute paracetamol overdose appears to be less in children than in adults at comparable doses; however, chronic use of supratherapeutic doses in children has resulted in unintentional overdoses and severe hepatotoxicity.[1,2]

Patients receiving enzyme-inducing drugs or those with a history of alcohol abuse are at special risk of hepatic damage, as may be patients suffering from malnutrition such as those with anorexia or AIDS. It has also been suggested that fasting may predispose to hepatotoxicity.[3]

Early **signs** of overdosage (very commonly nausea and vomiting although they may also include lethargy and sweating) usually settle within 24 hours. Abdominal pain may be the first indication of liver damage, which is not usually apparent for 24 to 48 hours and sometimes may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Hepatic failure, encephalopathy, coma, and death may result. Complications of hepatic failure include acidosis, cerebral oedema, haemorrhage, hypoglycaemia, hypotension, infection, and renal failure. Prothrombin time increases with deteriorating liver function and some recommend that it be measured regularly. However, as both paracetamol[4] and acetylcysteine[5] can independently affect prothrombin time in the absence of hepatic injury, the use of prothrombin time as a marker for hepatotoxicity has been questioned and it has been recommended that treatment decisions are based on the entire liver biochemistry.[6]

Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage. Other non-hepatic symptoms that have been reported following paracetamol overdosage include myocardial abnormalities and pancreatitis.

The **mechanism** of toxicity in overdosage with paracetamol is thought to be the production of a minor but highly reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine (NABQI) by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4)[2] in the liver and kidney. The amount of NABQI produced after normal doses of paracetamol is usually completely detoxified by conjugation with glutathione and excreted as mercaptopurine and cysteine conjugates. In paracetamol overdosage, tissue stores of glutathione become depleted, allowing NABQI to accumulate and bind to sulfhydryl groups within hepatocytes causing cell damage. Substances capable of replenishing depleted stores of glutathione, such as acetylcysteine or methionine, are therefore used as antidotes in paracetamol overdosage. Acetylcysteine may also be involved in the repair of damaged tissue.

Treatment of oral paracetamol overdosage. The management of paracetamol overdosage as practised in the UK and US has been the subject of numerous reviews.[3,6-13] Guidelines have also been issued in the UK by the Paracetamol Information Centre.[14] Separate consensus guidelines have also been issued by clinical toxicologists in Australia and New Zealand.[15]

Prompt treatment is essential, even when there are no obvious symptoms, and all patients should be admitted to hospital; full supportive measures should also be instituted.

- Activated charcoal may be used to reduce gastrointestinal absorption, if it can be given within 1 hour of the overdose, and if more than 150 mg/kg of paracetamol has been ingested. However, if acetylcysteine or methionine is to be given by mouth the charcoal is best cleared from the stomach to prevent it reducing the absorption of the antidote.
- There is little evidence that gastric lavage is of benefit in those who have overdosed solely with paracetamol.
- The plasma-paracetamol concentration should be determined as soon as possible, but not within 4 hours of ingestion, to ensure that peak concentrations are recorded. The risk of liver damage is determined by comparison with a nomogram reference line on a plot of plasma-paracetamol concentration against hours after ingestion. A semi-logarithmic plot or a linear plot may be used, see Figure 1 (p.109) and Figure 2 (p.109). Generally, antidote treatment is required if the patient's plasma-paracetamol concentration is higher than the appropriate line (but see below).
- Patients receiving enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, rifampicin, and St John's wort, or those with malnutrition or a history of alcohol abuse, are considered at high risk, and should receive an antidote even if their plasma-paracetamol concentrations are up to 50% below the standard reference line.
- Plasma-paracetamol concentrations measured more than 15 hours after ingestion are not reliable indicators of hepatic toxicity. Furthermore, the nomogram may not be suitable for use when patients have taken modified-release preparations of paracetamol.[16-18] Some suggestions for modified strategies for the use of the Rumack-Matthew nomogram in the face of overdosage with modified-release preparations have been made.[19-21]
- Plasma-paracetamol concentrations and the Rumack-Matthew nomogram are also of little value in patients who have taken repeated supratherapeutic doses or multiple overdoses of paracetamol over a short period of time: such patients should be considered at serious risk and given antidote treatment.
- Deaths from liver failure have occurred in patients presenting with plasma-paracetamol concentrations below the treatment line: suggested explanations include inadequate patient histories and a need for a lower treatment threshold.[22]
- If there is any doubt about timing or the need to treat, then a patient **should** be treated with an antidote. In some centres, patients who have ingested 150 mg/kg or more of paracetamol are treated regardless of plasma-paracetamol concentrations.[23]
- Antidote treatment should be started as soon as possible after suspected paracetamol ingestion and should not be delayed while awaiting the results of plasma assays. Once the results become available, treatment may be stopped if the initial concentration was below the nomogram reference line. However, if the initial concentration is above the reference line, the full course of antidote must be given and should not be stopped when subsequent plasma concentrations fall below the reference line.

Choice of antidote. Acetylcysteine (p.1548) is usually the antidote of choice but the route of administration varies, and the best protocol has yet to be determined.[6,24] Intravenous use has been associated with anaphylactic reactions but is the preferred route in the UK because of fears that oral absorption might be reduced by vomiting or activated charcoal. However, in the USA the oral route is also used, and is clearly effective. The use of methionine (p.1450) by mouth is licensed in the UK, despite the same risks of impaired absorption due to vomiting or activated charcoal. It is cheaper and easier to give than intravenous acetylcysteine and may be used in situations where a patient cannot be transferred to hospital, provided it is given within 10 to 12 hours of the overdose and the patient is not vomiting.

Acetylcysteine is most effective when given during the first 8 hours after taking the overdose and the effect diminishes progressively thereafter. It used to be believed that starting treatment more than 15 hours after overdosage was of no benefit and might aggravate the risk of hepatic encephalopathy. However, late treatment was subsequently shown to be safe,[25] and studies of patients treated up to 36 hours after ingestion suggest that benefit may be obtained up to and possibly beyond 24 hours.[26,27] Furthermore, giving intravenous acetylcysteine to patients who had already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.[28]

- An initial dose of 150 mg/kg of acetylcysteine in 200 mL of glucose 5% is given intravenously over 15 minutes in the UK, or over 60 minutes in the USA. This is followed by an intravenous infusion of 50 mg/kg in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg in one litre over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable. The volume of intravenous fluids should be modified for children. If an anaphylactoid reaction develops, the infusion should be stopped and an antihistamine given; it may be possible to continue the acetylcysteine infusion at a slower rate.