Local Anaesthetics

Local anaesthetics produce reversible loss of function or sensation by preventing or diminishing the conduction of nerve impulses near to the site of their application or injection. Because their mode of action is to decrease permeability of the nerve cell membrane to sodium ions, they also have a membrane stabilising effect.

Clinically useful local anaesthetics have the same general chemical configuration of an amine portion joined to an aromatic residue by an ester or amide link. The type of linkage is important in determining the properties of the drug.

For a classification of local anaesthetics, see Table 1, below.

Table 1. Classification of local anaesthetics.

Amide type	Ester type
Articaine	*Esters of benzoic acid*
Bupivacaine	Amylocaine
Cinchocaine	Cocaine
Ethyl parapiperidino-acetylaminobenzoate	Propanocaine
Etidocaine	*Esters of meta-aminobenzoic acid*
Levobupivacaine	Proxymetacaine
Lignocaine [lidocaine]	*Esters of para-aminobenzoic acid*
Mepivacaine	Amethocaine [tetracaine]
Oxetacaine	Benzocaine
Prilocaine	Butacaine
Ropivacaine	Butoxycaine
Tolycaine	Butyl aminobenzoate
Trimecaine	Chloroprocaine
Miscellaneous	Oxybuprocaine
Diperodon	Parethoxycaine
Dyclonine	Procaine
Ethyl chloride	Propoxycaine
Ketocaine	Tricaine
Myrtecaine	
Octacaine	
Pramocaine	
Propipocaine	
Quinisocaine	

Adverse Effects

Adverse effects apparent after local anaesthesia may be caused by the anaesthetic or errors in technique, or may be the result of blockade of the sympathetic nervous system. Local anaesthetics may produce systemic adverse effects as a result of raised plasma concentrations that occur when the rate of uptake into the circulation exceeds the rate of breakdown, for example, following

- accidental intravascular injection
- excessive dosage or rate of administration
- absorption of large amounts through mucous membranes or damaged skin
- absorption of large amounts from inflamed or highly vascular areas.

The systemic toxicity of local anaesthetics mainly involves the CNS and the cardiovascular system. Excitation of the CNS may be manifested by restlessness, excitement, nervousness, paraesthesias, dizziness, tinnitus, blurred vision, nausea and vomiting, muscle twitching and tremors, and convulsions. Numbness of the tongue and perioral region, and lightheadedness followed by sedation may appear as early signs of systemic toxicity. Excitation when it occurs may be transient and followed by depression with drowsiness, respiratory failure, and coma. There may be effects on the cardiovascular system with myocardial depression and peripheral vasodilatation resulting in hypotension and bradycardia; arrhythmias and cardiac arrest may occur. Hypotension often accompanies spinal and epidural anaesthesia; inappropriate positioning of the patient may be a contributory factor for women in labour.

Hypersensitivity reactions are rare and generally limited to local anaesthetics of the ester type. There appears to be no cross-sensitivity between ester- and amide-type local anaesthetics. Idiosyncrasy to local anaesthetics has been reported. Hypersensitivity reactions to preservatives in local anaesthetic preparations have also occurred.

Some local anaesthetics cause methaemoglobinaemia.

Fetal intoxication has occurred following the use of local anaesthetics in labour, either as a result of transplacental diffusion or after accidental injection of the fetus.

Prolonged use of topical anaesthetics in the eye causes corneal damage.

Adverse effects may also be caused by concomitantly administered vasoconstrictors.

◊ Reviews.

1. McCaughey W. Adverse effects of local anaesthetics. *Drug Safety* 1992; **7:** 178–189.
2. Berde CB. Toxicity of local anesthetics in infants and children. *J Pediatr* 1993; **122** (suppl): S14–S20.
3. Naguib M, *et al.* Adverse effects and drug interactions associated with local and regional anaesthesia. *Drug Safety* 1998; **18:** 221–50.
4. Dalens BJ, Mazoit J-X. Adverse effects of regional anaesthesia in children. *Drug Safety* 1998; **19:** 251–68.

Adverse effects of central block. Central nerve block (see Local Anaesthetic Techniques, below), comprising spinal or epidural block, is very widely used and certain adverse effects are particularly associated with the technique. Systemic effects (see Adverse Effects, above) are more likely with epidural than with spinal block, because of the larger doses used.

Total spinal anaesthesia from extreme spread of a block or accidental penetration of the dura during an epidural block produces unconsciousness, hypotension, and respiratory arrest. Less extensive spread to the cervical region is usually associated with nausea, agitation, and hypotension.

Hypotension (associated with venodilatation and decreased cardiac output secondary to sympathetic block) is the **cardiovascular** effect most often associated with the technique, and may be especially problematic in pregnancy. Other cardiovascular complications may include bradycardia or heart block; cardiac arrest has also been reported unexpectedly after spinal anaesthesia.

Post-dural puncture headache (see Treatment of Adverse Effects, below) is probably the most common **neurological complication** related to these procedures and may be accompanied by tinnitus or photophobia. Headache following spinal block may rarely be caused by meningitis. Backache is a frequent postoperative complication following epidural, spinal, or general anaesthesia. Cranial nerve lesions and reversible loss of hearing in the low frequency range, usually affecting both ears, have been reported rarely following spinal block. Neurological complications associated with these blocks may also rarely include paraplegia caused by arachnoiditis, or trauma or compression of the spinal cord following development of a haematoma or abscess. Transient radicular irritation involving the lower back, buttocks, and thighs may develop within 24 hours of spinal block; recovery is usually within 1 week. Cauda equina syndrome, the symptoms of which include urinary retention, loss of perineal sensation, loss of sexual function, and faecal incontinence, is also a rare complication which can present many months after spinal block.

Perioperative shivering has been associated with epidural block.

References.

1. Kalmanovitch DVA, Simmons P. Post-anaesthetic complications in the home. *Prescribers' J* 1988; **28:** 124–31.
2. Wildsmith JAW, Lee JA. Neurological sequelae of spinal anaesthesia. *Br J Anaesth* 1989; **63:** 505–7.
3. Parnass SM, Schmidt KJ. Adverse effects of spinal and epidural anaesthesia. *Drug Safety* 1990; **5:** 179–94.
4. Anonymous. Perioperative shivering. *Lancet* 1991; **338:** 547–8.
5. Broome IJ. Hearing loss and dural puncture. *Lancet* 1993; **341:** 667–8.
6. Russell R, *et al.* Assessing long term backache after childbirth. *BMJ* 1993; **306:** 1299–1303.
7. Harding SA, *et al.* Meningitis after combined spinal-extradural anaesthesia in obstetrics. *Br J Anaesth* 1994; **73:** 545–7.
8. Gielen M. Spinal anaesthesia: hearing loss, failure, transient radicular irritation. *Anaesthesia* 1998; **53** (suppl 2): 23–5.
9. Horlocker TT, Wedel DJ. Neurologic complications of spinal and epidural anesthesia. *Reg Anesth Pain Med* 2000; **25:** 88–98.

Effects on the ears. Symptoms such as vertigo, nausea, and nystagmus, which have been reported following the use of local anaesthetics in the external[1] or middle ear,[2] may result from penetration of the local anaesthetic into the inner ear. For reference to hearing loss associated with spinal block, see under Adverse Effects of Central Block, above.

1. Raine NMN, Whittet HB. Emla cream and induced vertigo. *Br J Hosp Med* 1994; **51:** 614–15.
2. Blair Simmons F, *et al.* Lidocaine in the middle ear: a unique cause of vertigo. *Arch Otolaryngol* 1973; **98:** 42–3.

Hypersensitivity. Local anaesthetics may provoke types I and IV hypersensitivity reactions. Type I reactions (e.g. anaphylaxis) to local anaesthetics are generally rare. They occur more frequently with the ester-type than with the amide-type drugs, probably because of the metabolism of the former to para-aminobenzoic acid (PABA). Nevertheless, severe or fatal reactions have been associated not only with ester-type local anaesthetics such as amethocaine [tetracaine][1] and procaine[2] but also with the amide-type local anaesthetics lignocaine [lidocaine][3-7] and prilocaine.[3] Intolerance may also have been the cause of death in a patient who received mepivacaine for paracervical anaesthesia.[8] Hypotension encountered during dental anaesthesia is usually a vasovagal response unrelated to the type of local anaesthetic used and may be prevented by the use of diazepam. Patients sensitised by topical application may subsequently develop anaphylactic reactions when treated systemically.[9] The use of drugs such as benzocaine or amethocaine [tetracaine] in lozenges or throat sprays may also sensitise patients.[10]

Some patients diagnosed as being hypersensitive to local anaesthetics may have reacted to preservatives in the preparations.[11] Cross-hypersensitivity reactions may also occur between some ester-type local anaesthetics and topical preparations, such as sunscreens, that contain PABA or related compounds.[12]

Skin testing may be of benefit in patients who will require future local anaesthesia and when a patient's history does not rule out a possible allergic reaction. However, testing itself can cause severe or anaphylactic reactions.[9,13]

Type IV reactions (i.e. delayed reactions) to local anaesthetics have also been reported, albeit rarely.[14-16]

For reports of the incidence of allergy to local anaesthetics determined by patch testing, see under individual monographs.

1. Moriwaki K, *et al.* A case report of anaphylactic shock induced by tetracaine used for spinal anesthesia. *Masui* 1986; **35:** 1279–84.
2. MacLachlan D, Forrest AL. Procaine and malignant hyperthermia. *Lancet* 1974; **i:** 355.
3. Fisher MM, Pennington JC. Allergy to local anaesthesia. *Br J Anaesth* 1982; **54:** 893–4.
4. Howard JJ, *et al.* Adult respiratory distress syndrome following administration of lidocaine. *Chest* 1982; **81:** 644–5.
5. Promisloff RA, DuPont DC. Death from ARDS and cardiovascular collapse following lidocaine administration. *Chest* 1983; **83:** 585.
6. Ruffles SP, Ayres JG. Fatal bronchospasm after topical lignocaine before bronchoscopy. *BMJ* 1987; **294:** 1658–9.
7. Ball IA. Allergic reactions to lignocaine. *Br Dent J* 1999; **186:** 224–6.
8. Grimes DA, Cates W. Deaths from paracervical anesthesia used for first-trimester abortion, 1972–1975. *N Engl J Med* 1976; **295:** 1397–9.
9. Mulvey PM. Allergy to local anaesthetics. *Med J Aust* 1980; **1:** 386.
10. Verbov J. Drug eruptions. *Practitioner* 1979; **222:** 400–9.
11. Wildsmith JAW, *et al.* Alleged allergy to local anaesthetic drugs. *Br Dent J* 1998; **184:** 507–10.
12. Parnass SM, Schmidt KJ. Adverse effects of spinal and epidural anesthesia. *Drug Safety* 1990; **5:** 179–94.
13. Brown DT, *et al.* Allergic reaction to an amide local anaesthetic. *Br J Anaesth* 1981; **53:** 435–7.
14. Klein CE, Gall H. Type IV allergy to amide-type local anesthetics. *Contact Dermatitis* 1991; **25:** 45–8.
15. Craft DV, Good RP. Delayed hypersensitivity reaction of the knee after injection of arthroscopy portals with bupivacaine (Marcaine). *Arthroscopy* 1994; **10:** 305–8.
16. Bircher AJ, *et al.* Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests. *Contact Dermatitis* 1996; **34:** 387–9.

Methaemoglobinaemia. Methaemoglobinaemia has been reported following the use of several local anaesthetics including amethocaine [tetracaine],[1] benzocaine,[1-3] and lignocaine [lidocaine][1] but is more commonly associated with the use of prilocaine.[4-6] It may occur following local injection or topical administration. It has been suggested that the effect is due to the presence of an aniline group in the structure or, in the case of lignocaine [lidocaine] and prilocaine, metabolism to an aniline-like structure. Methaemoglobinaemia may result from the use of usual doses as well as exposure to toxic concentrations of local anaesthetic;[1,6] with prilocaine doses of 8 mg per kg body-weight or more [above recommended maxima] usually produce symptoms.[7]

Methaemoglobinaemia has occurred following the topical application of a eutectic preparation of prilocaine and lignocaine [lidocaine].[5] Although increases in methaemoglobin concentrations are generally small following the use of this mixture in infants[8,9] and children,[10] some infants may be particularly susceptible to induced methaemoglobinaemia during the first few months of life probably due to their limited enzyme capacity. In consequence the use of eutectic prilocaine/lignocaine [lidocaine] cream is not recommended in the UK below 1 year of age, although in some countries such preparations are licensed for limited use in neonates (see also Surface Anaesthesia, under Lignocaine p.1316).

Concomitant administration of other drugs such as sulfonamides[5] or antimalarials[7] may predispose to methaemoglobinaemia. Patients with haemoglobinopathies or glucose-

phosphate dehydrogenase deficiency may also be at greater risk.[1]

1. Olson ML, McEvoy GK. Methemoglobinemia induced by local anesthetics. *Am J Hosp Pharm* 1981; **38:** 89–93.
2. Rodriguez LF, *et al.* Benzocaine-induced methemoglobinemia: report of a severe reaction and review of the literature. *Ann Pharmacother* 1994; **28:** 643–9.
3. Tush GM, Kuhn RJ. Methemoglobinemia induced by an over-the-counter medication. *Ann Pharmacother* 1996; **30:** 1251–4.
4. Mandel S. Methemoglobinemia following neonatal circumcision. *JAMA* 1989; **261:** 702.
5. Jakobson B, Nilsson A. Methemoglobinemia associated with a prilocaine-lidocaine cream and trimetoprim-sulphamethoxazole: a case report. *Acta Anaesthesiol Scand* 1985; **29:** 453–5.
6. Knobeloch L, *et al.* Prilocaine-induced methemoglobinemia—Wisconsin, 1993. *JAMA* 1994; **272:** 1403–4.
7. Reynolds F. Adverse effects of local anaesthetics. *Br J Anaesth* 1987; **59:** 78–95.
8. Nilsson A, *et al.* Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy. *Br J Anaesth* 1990; **64:** 72–6.
9. Brisman M, *et al.* Methaemoglobin formation after the use of EMLA cream in term neonates. *Acta Paediatr* 1998; **87:** 1191–4.
10. Frayling IM, *et al.* Methaemoglobinaemia in children treated with prilocaine-lignocaine cream. *BMJ* 1990; **301:** 153–4.

Pregnancy. As mentioned under Adverse Effects of Central Block, above, hypotension may be particularly problematic for patients receiving epidural or spinal block for analgesia during labour. In addition it has been suggested that patients receiving epidural analgesia during labour may have an increased risk of pyrexia, which can lead to fetal compromise.[1] See also under Labour Pain on p.6.

For adverse effects on the fetus associated with paracervical block, see Peripheral Nerve Block under Local Anaesthetic Techniques, below.

1. Fusi L, *et al.* Maternal pyrexia associated with the use of epidural analgesia in labour. *Lancet* 1989; **i:** 1250–2.

Treatment of Adverse Effects

At the first signs of local anaesthetic toxicity due to parenteral administration, the injection should be stopped; in some cases it may also be possible to apply a tourniquet to limit further systemic absorption. Subsequent management, regardless of route of administration, is supportive. In the event of systemic reactions developing steps should be taken to maintain the circulation and respiration and to control convulsions. A patent airway must be established and oxygen given, together with assisted ventilation if necessary. The circulation should be maintained with infusions of intravenous fluids. Vasopressors have been suggested in the treatment of marked hypotension although their use is accompanied by a risk of CNS excitation. Ephedrine is preferred for the management of hypotension associated with spinal or epidural block, particularly in pregnancy. Vasopressors should not be given to patients receiving oxytocic drugs. Convulsions may be controlled by the intravenous administration of benzodiazepines such as diazepam although these drugs may also depress respiration and the circulation. Intravenous phenobarbital is used for persistent convulsions.

Methaemoglobinaemia may be treated by the intravenous administration of methylene blue [methylthioninium chloride].

Post-dural puncture headache. Headache following puncture of the dura mater (post-dural puncture headache) during procedures such as lumbar puncture or central nerve blocks is thought to be caused by subsequent leakage of CSF. The incidence of such headache is significantly reduced by the use of small, blunt needles which produce a smaller hole in the dura and separate its fibres rather than cutting them.

When treatment is necessary conservative therapy such as analgesics and hydration will relieve symptoms in the majority of patients with mild post-dural puncture headache within 1 to 2 days. Bed rest does not reduce the incidence but once headache develops the patient may feel some relief when recumbent. If the headache persists for a further 24 hours measures such as epidural saline or dextran or the use of intravenous caffeine and sodium benzoate may be effective; oral caffeine has also been shown to be of benefit. If such measures are unsuccessful then the epidural injection of autologous blood to form a blood patch over the dural puncture is extremely effective. There have been anecdotal reports of success using corticotropin or tetracosactide.

References.

1. Choi A, *et al.* Pharmacologic management of postdural puncture headache. *Ann Pharmacother* 1996; **30:** 831–9.
2. Broadley SA, Fuller GN. Lumbar puncture needn't be a headache. *BMJ* 1997; **315:** 1324–5.
3. Serpell MG, *et al.* Prevention of headache after lumbar puncture: questionnaire survey of neurologists and neurosurgeons in United Kingdom. *BMJ* 1998; **316:** 1709–10.

Precautions

As with any drug local anaesthetics are contra-indicated in patients with known hypersensitivity. However, it might be possible to avoid reactions by using a local anaesthetic of the alternative chemical type. Facilities for resuscitation should be available when local anaesthetics are administered parenterally.

Local anaesthetics should not be used in patients with complete heart block. They should be given cautiously to the elderly, to the debilitated, to children, and to patients with epilepsy, impaired cardiac conduction or respiratory function, shock, or hepatic impairment; patients with myasthenia gravis are particularly susceptible to the effects of local anaesthetics. Ester-type local anaesthetics are contra-indicated in patients with low plasma-cholinesterase concentrations. Techniques such as epidural or spinal block should not be employed in patients with cerebrospinal diseases, cardiogenic or hypovolaemic shock, or altered coagulation status. Because of the risk of transmitting infection into the CNS these techniques should not be employed where there is pyogenic infection of the skin at or adjacent to the injection site.

Because of the risk of systemic adverse effects when local anaesthetics are absorbed too rapidly, they should not be injected into or applied to inflamed or infected tissues or to damaged skin or mucosa. For similar reasons, the rate of injection should not be too rapid and great care must be taken to avoid inadvertent intravascular injection. The risk of adverse effects from the uptake of local anaesthetics into the circulation may be reduced by the inclusion of adrenaline [epinephrine] to produce vasoconstriction, but the lowest effective concentration of adrenaline [epinephrine] should be used. Solutions containing adrenaline [epinephrine] should not, however, be used for producing anaesthesia in appendages such as digits, because the profound ischaemia that follows may lead to gangrene. Mepivacaine and prilocaine tend to produce less vasodilatation at low concentrations than other local anaesthetics and may be useful where the addition of vasoconstrictors is contra-indicated (but see also under Action, below).

When used in the mouth or throat, local anaesthetics may impair swallowing and increase the risk of aspiration. Patients who have received local anaesthetics for procedures such as laryngoscopy or tracheoscopy should be cautioned not to eat or drink for at least 3 to 4 hours after the anaesthetic.

The cornea may be damaged by prolonged topical application of local anaesthetics, particularly cocaine. Patients should be warned not to rub or touch the eye while anaesthesia persists and the anaesthetised eye should be protected from dust and bacterial contamination.

Local anaesthetics may be ototoxic and should not be instilled into the middle ear.

The application of local anaesthetics to the skin for prolonged periods or to extensive areas should be avoided.

Precautions for central block. Epidural or spinal block may rarely result in paraplegia caused by an induced haematoma or abscess producing arachnoiditis, trauma, or compression of the spinal cord. These blocks have therefore in general been considered to be unsuitable for use in patients with pre-existing neurological disease, infection at the puncture site, or blood disorders or in those receiving aspirin or full-dose anticoagulant therapy. Such therapy may be discontinued at an appropriate time before surgery if central block is planned. It is necessary to balance the risk of withholding anticoagulation against the risk of bleeding in the individual patient. Epidural or spinal block in patients receiving low-dose anticoagulant therapy to prevent postoperative deep-vein thrombosis is still controversial. For further discussion and recommendations on concomitant use see p.903.

A study in the USA[1] involving 891 patients found that low-dose aspirin during pregnancy did not increase the risk of bleeding complications during epidural anaesthesia compared with placebo; it was considered that the recommendation to stop aspirin 7 to 10 days before delivery was unjustified.

1. Sibai BM, *et al.* Low-dose aspirin in correlation between bleeding time and maternal-neonatal bleeding complications. *Am J Obstet Gynecol* 1995; **172:** 1553–7.

Pregnancy. For discussions covering the precautions associated with the use of epidural or spinal blocks during labour, see under Labour Pain, p.6.

Tachyphylaxis. The effect of successive epidural injections of 2% solutions of lignocaine [lidocaine], mepivacaine, or prilocaine was reduced by 25 to 30% with each injection when the interval between the disappearance of analgesia and re-injection was more than 10 minutes but anaesthesia was augmented if this interval was less than 10 minutes.[1] Such tachyphylaxis, associated with the prolonged epidural administration of all local anaesthetics, has been reviewed more recently.[2]

1. Bromage PR, *et al.* Tachyphylaxis in epidural analgesia 1: augmentation and decay of local anesthesia. *J Clin Pharmacol* 1969; **9:** 30–8.
2. Mogensen T. Tachyphylaxis to epidural local anaesthetics. *Dan Med Bull* 1995; **42:** 141–6.

Test dose. A test dose is recommended in epidural block to check for accidental intravenous or intrathecal injection but negative results should be treated with caution.[1] Accidental intravenous placement of the needle is notoriously more difficult to detect than inadvertent subarachnoid placement. Adrenaline [epinephrine] has been added to the test solution to aid detection of intravenous injection but is considered by some to be of little value.[2,3]

1. Scott DB. Test doses in extradural block. *Br J Anaesth* 1988; **61:** 129–30.
2. Thornburn J. Limitations of adrenaline test doses in obstetric patients undergoing extradural anaesthesia. *Br J Anaesth* 1989; **62:** 578–81.
3. Narchi P, *et al.* Heart rate response to an iv test dose of adrenaline and lignocaine with and without atropine pretreatment. *Br J Anaesth* 1991; **66:** 583–6.

Interactions

The metabolism of ester-type local anaesthetics may be inhibited by anticholinesterases thus increasing the risk of systemic toxicity.

Ester derivatives such as amethocaine [tetracaine], benzocaine, or procaine that are hydrolysed to para-aminobenzoic acid may antagonise the activity of aminosalicylic acid or sulfonamides. Ester-type local anaesthetics such as procaine and cocaine that are hydrolysed by plasma cholinesterase may competitively enhance the neuromuscular blocking activity of suxamethonium; the amide local anaesthetic, lignocaine [lidocaine] may have a similar effect.

There is an increased risk of myocardial depression when amide-type local anaesthetics such as bupivacaine, lignocaine [lidocaine], or ropivacaine are administered concomitantly with antiarrhythmics.

If local anaesthetics containing adrenaline [epinephrine] are given for epidural or paracervical block during labour the use of an oxytocic drug post partum may lead to severe hypertension. Although there is no clinical evidence of dangerous interactions between adrenaline [epinephrine]-containing local anaesthetics and MAOIs or tricyclic antidepressants, great care should nevertheless be taken to avoid inadvertent intravenous administration of the local anaesthetic preparation.

For further details of interactions between local anaesthetics and other drugs, see under individual monographs.

Pharmacokinetics

Most local anaesthetics are readily absorbed through mucous membranes, and through damaged skin. Local anaesthetics are weak bases and at tissue pH can diffuse through connective tissue and cellular membranes to reach the nerve fibre where ionisation can occur.

Anaesthetics of the ester type are hydrolysed by esterases in the plasma and, to a lesser extent, in the liver. The effect of spinal anaesthetics lasts until the drug is taken up into the blood circulation since there is little esterase in the spinal fluid.

Amide-type anaesthetics are metabolised in the liver and, in some cases, the kidneys. While there is little protein binding with most ester-type anaesthetics, the amide types are considerably bound.

◊ References.

1. Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; **58:** 717–31.
2. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; **16:** 283–311.
3. Smith C. Pharmacology of local anaesthetic agents. *Br J Hosp Med* 1994; **52:** 455–60.

Uses and Administration

Local anaesthetics act by preventing the generation and transmission of impulses along nerve fibres and at nerve endings; depolarisation and ion-exchange are inhibited. The effects are reversible. They are used for the local relief of painful conditions, and to prevent pain and discomfort of various medical and surgical procedure (see below). In general, loss of pain (analgesia) occurs before loss of sensory and autonomic function (anaesthesia) and loss of motor function (paralysis), but this may depend on the drug used and the site of administration.

Local anaesthetics vary in their potency and speed of onset and duration of action. The anaesthetic must penetrate the lipoprotein nerve sheath in its unionised form before it can act and therefore drugs with high lipid-solubility tend to have a greater potency and duration of action and a faster onset than drugs with low lipid-solubility. The most protein-bound drugs tend to have the longest duration of action.

The potency of local anaesthetics is traditionally compared against that of procaine, which is low; chloroprocaine, lignocaine [lidocaine], mepivacaine, prilocaine are similar or somewhat more potent; ocaine is of intermediate potency, bupivacaine and ropivacaine highly potent, and amethocaine [tetracaine] extremely potent.

Speed of onset and duration of action also depend on the technique employed (see below), the type of block, and the site of administration.

The speed of onset and duration of action of local anaesthetics may be increased by the addition of a vasoconstrictor, which has the effect of reducing the uptake of the local anaesthetic into the circulation from the injection site. Solutions containing adrenaline [epinephrine] 1 in 200 000 are generally advocated, although higher concentrations such as 1 in 80 000 may be used in dentistry where the total dose is small. The total amount of adrenaline [epinephrine] injected should not exceed 500 µg although the amount of adrenaline [epinephrine] absorbed varies considerably with the site of administration; some consider that the maximum dose should be 200 µg. Other vasoconstrictors including noradrenaline [norepinephrine] are also used, but authorities in the UK consider that noradrenaline [norepinephrine] should not be used since it presents no advantages and when administered at relatively high concentrations has occasionally been associated with severe hypertensive episodes. Vasotrictors should not be used when producing a ... .e block in an appendage such as a digit, as gangrene may occur. Vasoconstrictors have been added to injections for spinal block, but their use is not recommended because of the danger of reducing the blood supply to the spinal cord.

Local anaesthetics are generally administered as acidic solutions of the water-soluble hydrochloride salts; alkalinisation of these solutions or formulation as a carbonated base may increase the speed of onset (see under Administration, below).

The dosage of individual local anaesthetics depends on the injection site and the procedure used. The smallest effective dose and the lowest effective concentration should be used. Smaller doses are usually needed in the elderly, in children, in debilitated patients, and in cardiac disease. Doses should also be reduced in the presence of hepatic disease. Meticulous attention to technique is essential particularly in nerve block and spinal procedures. Injections for central nerve blocks, such as epidural (including caudal block) and spinal block should not contain preservatives.

Action. The intrinsic vasoactivity of a local anaesthetic can influence its rate of removal from the site of action and therefore its duration of action. Ester-type local anaesthetics such as amethocaine [tetracaine] and procaine are more likely to produce vasodilatation than amide-type local anaesthetics such as cinchocaine, lignocaine [lidocaine], mepivacaine, and prilocaine following intradermal administration.[1] However, cocaine differs from other ester-type local anaesthetics in that it produces vasoconstriction. The amide-type local anaesthetics can produce vasoconstriction but, apart from prilocaine, their vasoconstrictor activity has generally been found to decline with increasing concentration,[1,2] and, in one study, lignocaine [lidocaine] and bupivacaine produced more vasodilatation than vasoconstriction at the higher concentrations tested.[2] Mepivacaine has produced greater and more consistent vasoconstriction than lignocaine [lidocaine], cinchocaine, or prilocaine following intradermal injection[1] but this greater vasoactivity is not always evident.[3]

1. Willatts DG, Reynolds F. Comparison of the vasoactivity of amide and ester local anaesthetics: an intradermal study. *Br J Anaesth* 1985; **57:** 1006–11.
2. Aps C, Reynolds F. The effect of concentration on vasoactivity of bupivacaine and lignocaine. *Br J Anaesth* 1976; **48:** 1171–4.
3. Goebel WM, *et al.* Comparative circulatory levels of 2 per cent mepivacaine and 2 per cent lignocaine. *Br Dent J* 1980; **148:** 261–4.

Administration. Systemic toxic effects of local anaesthetics are related to blood concentrations and, as absorption varies considerably according to the site of injection, it has been suggested[1,2] that recommendation of a single maximum dose without regard to the site of the procedure is meaningless. If a plasma-lignocaine [lidocaine] concentration of 5 µg per mL were required for toxicity then this would be achieved by injection of 300 mg in the intercostal area, 500 mg epidurally, 600 mg in the region of the brachial plexus, or 1000 mg subcutaneously. The reduction of peak concentrations obtained by the addition of adrenaline [epinephrine] was also dependent on the site of injection. Furthermore, most cases of severe toxicity did not result from overdosage but from inadvertent intravascular injection or too rapid injection.

1. Scott DB. "Maximum recommended doses" of local anaesthetic drugs. *Br J Anaesth* 1989; **63:** 373–4.
2. Scott DB. Safe use of lignocaine. *BMJ* 1989; **299:** 56.

CARBONATED SOLUTIONS. The use of carbonated solutions of local anaesthetics instead of the usual hydrochloride salts has been discussed in several reviews.[1-3] Although some early studies indicated that carbonated solutions of bupivacaine, lignocaine [lidocaine], or prilocaine produced earlier onset of anaesthesia and improved the quality of epidural or brachial plexus blocks not all subsequent studies have confirmed these results. A method for preparing carbonated solutions has been published[4] but proprietary preparations of such solutions of bupivacaine or lignocaine [lidocaine] may be available in some countries.

1. Covino BG. Pharmacology of local anaesthetic agents. *Br J Anaesth* 1986; **58:** 701–16.
2. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; **16:** 283–311.
3. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia. *Br J Anaesth* 1990; **65:** 225–33.
4. Bromage PR. Improved conduction blockade in surgery and obstetrics: carbonated local anesthetics. *Can Med Assoc J* 1967; **97:** 1377–84.

PH OF SOLUTIONS. The pain associated with infiltration of local anaesthetics can be reduced by buffering the solution to physiological pH with sodium bicarbonate.[1,2] Although buffering itself does not appear to compromise the efficacy of anaesthesia,[2] alkalinisation of the solution may reduce the solubility of the local anaesthetic and cause precipitation.[2-4] To enhance stability local anaesthetic solutions are usually prepared to have an acidic pH and it is therefore recommended that if solutions are buffered they should be used immediately.[2] (Solutions containing adrenaline [epinephrine] require an acidic pH.)

Similar pH adjustments for solutions for intravenous regional anaesthesia have been reported to reduce the amount of local venous irritation and thrombophlebitis[5] and to increase the speed of onset and the duration of the block.[6] However, it has been noted that at alkaline pH lignocaine [lidocaine] can lower surface tension, thereby altering drop size and potentially resulting in a decreased dose if such solutions are infused via a drop counting device rather than a volume pump.[7] Alkalinisation of a solution used for epidural block for caesarean section has been reported to result in a more rapid onset of action and denser block.[8]

Alkalinisation has also been used to hasten the onset of peripheral nerve block[9] by increasing the proportion of the lipid-soluble nonionised free base but the effect in epidural block has been inconsistent.[10,11]

1. McKay W, *et al.* Sodium bicarbonate attenuates pain on skin infiltration with lidocaine, with or without epinephrine. *Anesth Analg* 1987; **66:** 572–4.
2. Cristoph RA, *et al.* Pain reduction in local anesthetic administration through pH buffering. *Ann Emerg Med* 1988; **17:** 117–20.
3. Bourget P, *et al.* Factors influencing precipitation of pH-adjusted bupivacaine solutions. *J Clin Pharm Ther* 1990; **15:** 197–204.
4. Nakano NI. Temperature-dependent aqueous solubilities of lidocaine, mepivacaine, and bupivacaine. *J Pharm Sci* 1979; **68:** 667–8.
5. Yudenfreund SM, *et al.* pH-Buffered 2-chloroprocaine for intravenous regional anesthesia. *DICP Ann Pharmacother* 1989; **23:** 614–15.
6. Armstrong P, *et al.* Effect of alkalinization of prilocaine on IV regional anaesthesia. *Br J Anaesth* 1989; **63:** 625P–626P.
7. Leor R, *et al.* The influence of pH on the intravenous delivery of lidocaine solutions. *Eur J Clin Pharmacol* 1990; **39:** 521–3.
8. Fernando R, Jones HM. Comparison of plain and alkalinized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural caesarean section. *Br J Anaesth* 1991; **67:** 699–703.
9. Coventry DM, Todd JG. Alkalinization of bupivacaine for sciatic nerve blockade. *Br J Anaesth* 1989; **62:** 227P.
10. Burm AGL. Clinical pharmacokinetics of epidural and spinal anaesthesia. *Clin Pharmacokinet* 1989; **16:** 283–311.
11. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia. *Br J Anaesth* 1990; **65:** 225–33.

Anorectal disorders. See under Surface Anaesthesia, below.

Cough. Drugs such as lignocaine [lidocaine] or bupivacaine have been given by inhalation in severe intractable cough (p.1082), including cough caused by malignant neoplasms.[1-4] Cough suppression is produced by an indirect peripheral action on sensory receptors, but as all protective pulmonary reflexes may be lost and bronchospasm may be induced, nebulised local anaesthetics should be used in controlled circumstances only; there may also be temporary loss of the swallowing reflex.

1. Howard P, *et al.* Lignocaine aerosol and persistent cough. *Br J Dis Chest* 1977; **71:** 19–24.
2. Stewart CJ, Coady TJ. Suppression of intractable cough. *BMJ* 1977; **i:** 1660–1.
3. Sanders RV, Kirkpatrick MB. Prolonged suppression of cough after inhalation of lidocaine in a patient with sarcoid. *JAMA* 1984; **252:** 2456–7.
4. Brown RC, Turton CWG. Cough and angiotensin converting enzyme inhibition. *BMJ* 1988; **296:** 1741.

Endoscopy. Local anaesthetics such as lignocaine [lidocaine] are sometimes used before endoscopy to improve patient comfort and facilitate passage of the endoscope. As mentioned in the discussion on drugs used in endoscopy (see p.652) some consider that the use of local anaesthetics for procedures such as gastrointestinal endoscopy should probably be reserved for those patients who prefer not to be sedated as their use in addition to premedication with opioids or benzodiazepines appears to serve little purpose.

References.

1. Chuah SY, *et al.* Topical anaesthesia in upper gastrointestinal endoscopy. *BMJ* 1991; **303:** 695.
2. Jameson JS, *et al.* Topical anaesthesia improves toleration for upper gastrointestinal endoscopy. *Gut* 1992; **33** (suppl): S51.
3. Randell T, *et al.* Topical anaesthesia of the nasal mucosa for fibreoptic airway endoscopy. *Br J Anaesth* 1992; **68:** 164–7.

Mouth ulceration. For the role of local anaesthetics in the management of mouth ulceration, see p.1206.

Pain. Pain and its general management are discussed on p.2. Local anaesthetics are used in a variety of situations for the management of pain. They are usually given by local injection or applied topically but are sometimes used intravenously in techniques such as intravenous regional anaesthesia, which involves the continuous infusion of local anaesthetics such as lignocaine [lidocaine] to produce general analgesia. However, the technique is potentially dangerous and seldom employed.

CANCER PAIN. For the role of local anaesthetics in the management of cancer pain, see p.5.

INTRAOPERATIVE AND POSTOPERATIVE PAIN. Local anaesthetic techniques can be used to prevent intraoperative pain and discomfort, see below. For details of the use of local anaesthetics in postoperative analgesia, see p.4 and also under Choice of Analgesics in Children, p.3.

LABOUR PAIN. For the role of epidural analgesia with local anaesthetics in the relief of labour pain, see p.6.

LOW BACK PAIN. For the role of local anaesthetics in the management of low back pain, see p.6.

Postherpetic neuralgia. For the role of local anaesthetics in the management of postherpetic neuralgia, see p.7.

Soft-tissue rheumatism. For the adjunctive use of local anaesthetics in the management of soft-tissue rheumatism, see p.10.

Spasticity. The management of spasticity (p.1322) involves physiotherapy together with the use of antispastic drugs. Other approaches to treatment include nerve blocks with local anaesthetics; these can improve spasticity but should generally only be used when further muscle relaxation would not increase disability.

Local Anaesthetic Techniques

Local anaesthetics are employed in several techniques. In order of increasing level of anaesthesia they are: surface or topical anaesthesia; infiltration anaesthesia; and regional nerve block, including peripheral nerve block, sympathetic nerve block, and central nerve block which includes epidural and spinal (intrathecal or subarachnoid) block. Local anaesthetics may also be given intravenously for regional anaesthesia in the extremities.

Surface anaesthesia

Surface or topical anaesthesia blocks the sensory nerve endings in the skin or mucous membranes. Many local anaesthetics are effective surface anaesthetics, a notable exception being procaine. Penetration of intact skin by most local anaesthetics is poor whereas absorption through mucous membranes may be rapid. However reliable percutaneous anaesthesia can be achieved by application of a eutectic mixture of lignocaine [lidocaine] and prilocaine to intact skin (see under Surface Anaesthesia in Lignocaine, p.1316). Eutectic mixtures may be of value in providing surface anaesthesia for a number of minor medical or surgical procedures. Amethocaine [tetracaine] also

provides reliable percutaneous anaesthesia. Other methods of dermal delivery of local anaesthetics include a transdermal patch of lignocaine [lidocaine], and an iontophoretic drug delivery system incorporating lignocaine [lidocaine] and adrenaline [epinephrine]. Anaesthesia of the skin and subcutaneous tissues is also discussed under Infiltration Anaesthesia, below.

There are a number of special uses of topical anaesthesia including anaesthetising the cornea during ophthalmological procedures and the throat and larynx before intubation and bronchoscopy. Absorption from the respiratory tract is rapid and care is essential to avoid administering a toxic dose. Great care is also necessary when employing local anaesthetics to anaesthetise the urethra; if trauma has occurred, rapid absorption of the drug may occur and give rise to serious adverse effects.

Local anaesthetics have been included in topical preparations to relieve the pain of haemorrhoids (p.1205) but good evidence of their efficacy is lacking. Similar uses include pain relief in pruritus ani and anal fissure. Excessive application of local anaesthetics to the rectal mucosa should be avoided as absorption can occur; use for periods of no longer than a few days is recommended to prevent sensitisation of the anal skin. Local anaesthetics are sometimes included in topical preparations for the relief of pruritus (p.1106). However, they are only marginally effective and can very occasionally cause sensitisation. The use of local anaesthetics in rubefacient and topical analgesic preparations is discussed on p.4.

Infiltration anaesthesia

Infiltration anaesthesia is produced by injection of a local anaesthetic such as lignocaine [lidocaine] or bupivacaine directly into and around the field of operation without attempting to identify individual nerves. The drug used should not be absorbed too rapidly otherwise the anaesthesia will wear off too quickly for practical use; some local anaesthetics require the addition of a vasoconstrictor in low concentrations, which can increase the duration of infiltration anaesthesia and reduce peak plasma concentrations of the local anaesthetic. Infiltration anaesthesia is extensively used in dentistry.

Anaesthesia of small areas by infiltration techniques requires a relatively large amount of local anaesthetic, which is not a problem for minor surgery but would be for more extensive areas that required anaesthesia. The amount of local anaesthetic used can be reduced and the duration of anaesthesia increased by blocking specific nerves that innervate the area. This may be carried out at several levels. In *field block* anaesthesia subcutaneous injection of a local anaesthetic close to the nerves around the area to be anaesthetised blocks sensory nerve paths. This is a form of infiltration anaesthesia, but the technique requires less drug for a given area to be anaesthetised.

Regional nerve block

Regional nerve block anaesthesia involves specific blocks at the levels of major nerves or spinal roots, and may include peripheral nerve block, sympathetic nerve block, and central nerve block including epidural and spinal block. For a discussion of the use of nerve blocks in the management of pain, see p.3.

Peripheral nerve block. Peripheral nerve block anaesthesia involves injection into or around a peripheral nerve or plexus supplying the part to be anaesthetised; motor fibres may be blocked as well as sensory fibres. *Brachial plexus block* is widely used for procedures involving the arm; lower limb blocks are less simple although *sciatic* and *femoral blocks* may be combined to permit surgery below the knee. Other peripheral nerve blocks such as those for the head and neck, or *intercostal* or *paravertebral blocks* for local anaesthesia of the trunk, are mostly highly specialised techniques. Lignocaine [lidocaine], prilocaine, bupivacaine or ropivacaine have all been widely employed for peripheral nerve blocks. Adrenaline [epinephrine] is often added as a vasoconstrictor.

Pudendal block (usually with prilocaine) may be useful in obstetrics before forceps delivery, but as mentioned under Labour Pain on p.6, the technique of *paracervical local anaesthetic block* has largely fallen out of favour because of the high incidence of serious adverse effects on the fetus.

Sympathetic nerve block. Sympathetic nerve block such as *stellate ganglion blockade* and *lumbar sympathectomy* is used in the management of a range of painful conditions and vascular diseases (see under Sympathetic Pain Syndromes on p.8). Temporary block is obtained using local anaesthetics such as lignocaine [lidocaine] or bupivacaine but permanent block may be produced with use of neurolytic agents such as phenol (see Pain, p.1153) or alcohol (see Pain, p.1132).

Central nerve block. Central nerve block includes epidural and spinal block.

Epidural block (also referred to as *extradural* or *peridural block*) is widely used to provide analgesia or anaesthesia in surgical and obstetric procedures. It involves injecting a local anaesthetic such as lignocaine [lidocaine], bupivacaine, or ropivacaine, alone or with a small dose of an opioid analgesic into the epidural space in the lumbar, sacral (*caudal block*), thoracic, or cervical regions. Introduction of a cannula into the epidural space enables prolonged analgesia or anaesthesia (epidural anaesthesia) to be provided through the use of 'top-up' doses or continuous infusion of the drugs. A vasoconstrictor is sometimes added to reduce systemic exposure to the local anaesthetic. A test dose at the intended injection site is recommended before starting epidural anaesthesia to ensure that the main dose is not accidentally injected intravascularly or into the subarachnoid space.

Spinal block (also referred to as *subarachnoid* or *intrathecal block*) is produced by injecting a solution of a suitable drug such as bupivacaine within the spinal subarachnoid space, causing temporary paralysis of the nerves with which it comes into contact. It may be used, for example, to produce spinal anaesthesia in surgical procedures on the lower body. Vasoconstrictors have been added to prolong the duration of the block but the effect is not always clinically useful and there is a danger of restricting the blood supply to the spinal cord; therefore this practice is not recommended. The somatic level at which anaesthesia occurs depends on many factors including the specific gravity or baricity of the anaesthetic solution used and the positioning of the patient.

For the adverse effects of and precautions for central block, see above.

Intravenous regional anaesthesia

Intravenous regional anaesthesia (Bier's block) involves injection of a dilute solution of local anaesthetic into a suitable limb vein after exsanguination and application of a tourniquet, in order to produce anaesthesia distal to it. Arterial flow must remain occluded for at least 20 minutes after injection and adrenaline [epinephrine] should not be used. Intravenous regional anaesthesia may be used for short procedures where postoperative pain is not marked, such as manipulation of fractures and minor surgical procedures to the limbs. Although a safe procedure when performed correctly, complications have arisen; there have been fatalities associated with the use of bupivacaine and prilocaine is the drug of choice. Facilities for resuscitation should be available.

Amethocaine (7603-v)

Amethocaine *(BAN)*.

Tetracaine *(BAN, rINN)*. 2-Dimethylaminoethyl 4-butylaminobenzoate.

$C_{15}H_{24}N_2O_2$ = 264.4.

CAS — 94-24-6.

ATC — *C05AD02; D04AB06; N01BA03; S01HA03.*

Pharmacopoeias. In *Chin.* and *US.*

Pharmacopoeial description

USP 25: A white or light yellow waxy solid. M.p. 41° to 46°. Very slightly soluble in water; soluble 1 in 5 of alcohol and 1 in 2 of chloroform or of ether; soluble in benzene. Store in airtight containers. Protect from light.

Amethocaine Hydrochloride (7604-g)

Amethocaine Hydrochloride *(BANM)*.

Tetracaine Hydrochloride *(BANM, rINNM)*; Dicainum; Tetracaini Hydrochloridum; Tetracainii Chloridum.

$C_{15}H_{24}N_2O_2$,HCl = 300.8.

CAS — *136-47-0.*

NOTE. AME and TET are codes approved by the BP 2001 for use on single unit doses of eye drops containing amethocaine [tetracaine] hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vi), *Int.*, *Jpn*, *Pol.*, and *US.*

Pharmacopoeial description

Ph. Eur.: A white, slightly hygroscopic, polymorphic, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 4.5 to 6.5. Protect from light.

USP 25: A fine, white, odourless, hygroscopic, polymorphic, crystalline powder. Very soluble in water; soluble in alcohol; insoluble in ether and in benzene. Its solutions are neutral to litmus. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p.1302.

Amethocaine [tetracaine] has high systemic toxicity. Absorption of amethocaine [tetracaine] from mucous membranes is rapid and adverse reactions can occur abruptly without the appearance of prodromal signs or convulsions; fatalities have occurred.

A stinging sensation may occur when amethocaine [tetracaine] is used in the eye. Mild erythema at the site of application is frequently seen with topical administration; slight oedema or pruritus occur less commonly. Blistering of the skin may occur.

Urethral stricture. There has been a report[1] of a sudden increase in the incidence of urethral stricture following transurethral surgery, which may have been due to an increase in the concentration of amethocaine [tetracaine] hydrochloride in the lubricant gel from 0.1 to 3%.

1. Pansadoro V. Role of local anaesthetics in urethral strictures after transurethral surgery. *Lancet* 1990; **336**: 64.

Precautions

As for Local Anaesthetics in general, p.1303.

Amethocaine [tetracaine] should not be applied to inflamed, traumatised, or highly vascular surfaces. It should not be used to provide anaesthesia for bronchoscopy or cystoscopy, as lignocaine [lidocaine] is a safer alternative.

Interactions

For interactions associated with local anaesthetics, see p.1303.

Pharmacokinetics

See under Local Anaesthetics, p.1303. Amethocaine [tetracaine] is reported to be about 15% bioavailable following application of a 4% gel to intact skin, with a mean absorption and elimination half-life of about 75 minutes.

Uses and Administration

Amethocaine [tetracaine], a para-aminobenzoic acid ester, is a potent local anaesthetic with actions and uses similar to those described on p.1304. It is used for surface anaesthesia and spinal block; its use in other local anaesthetic techniques is restricted by its systemic toxicity.

Amethocaine [tetracaine] is generally used as the hydrochloride in solutions and creams, and as the base in gels or ointments.

For *anaesthesia of the eye*, solutions containing 0.5 to 1% amethocaine [tetracaine] hydrochloride and ointments containing 0.5% amethocaine [tetracaine] have been used. Instillation of a 0.5% solution produces anaesthesia within 25 seconds that lasts for 15 minutes or longer and is suitable for use before minor surgical procedures.

For *topical anaesthesia*, a 1% cream or a 0.5% ointment has been used. These preparations have been used for painful conditions of the *anus or rectum*. A 4% gel is used as a *percutaneous local anaesthetic* before *venepuncture or venous cannulation*. The gel is applied to the centre of the area to be anaesthetised and covered with an occlusive dressing. Gel and dressing are removed after 30 minutes for venepuncture and after 45 minutes for venous cannulation. A single application generally provides anaesthesia for 4 to 6 hours. This method is not suitable for premature infants or those less than 1 month of age.

Amethocaine [tetracaine] hydrochloride has also been used in the *mouth* in sprays and lozenges.

Amethocaine [tetracaine] hydrochloride has also been used for *spinal block* usually as a 0.5% solution.

Action. For a comparison of the vasoactivity of amethocaine [tetracaine] with some other local anaesthetics, see p.1304.

Spinal block. A study[1] in 40 patients indicated that for patients undergoing caesarean section with spinal anaesthesia (see Central Nerve Block, p.1305) doses of 12 or 14 mg of amethocaine [tetracaine] provided better intraoperative analgesia than doses of 8 or 10 mg without leading to excessive spread of the block.

1. Hirabayashi Y, *et al.* Visceral pain during Caesarean section: effect of varying dose of spinal amethocaine. *Br J Anaesth* 1995; **75**: 266–8.

Surface anaesthesia. A topical gel formulation of amethocaine [tetracaine] 4% appears to provide more rapid and prolonged surface anaesthesia (see p.1304) than a eutectic mixture of lignocaine [lidocaine] and prilocaine.[1,2] In a double-blind placebo-controlled study[3] the amethocaine [tetracaine] gel formulation was significantly better than the eutectic mixture in reducing pain caused by laser treatment of portwine stains. Similar findings were also seen in a comparative study in children requiring venous cannulation.[4] The same formulation appears to be equally effective when incorporated into a transdermal patch.[5]

There have been reports of seizures and death in children following the use of a mixture of amethocaine [tetracaine], adrenaline [epinephrine], and cocaine on mucosal surfaces;[6] application of preparations of amethocaine [tetracaine] to highly vascular surfaces is contra-indicated. A gel containing a mixture of lignocaine [lidocaine], adrenaline [epinephrine], and amethocaine [tetracaine] has been found to be an effective alternative to the cocaine-containing preparation.[7]

Amethocaine [tetracaine] has also been incorporated into a mucosa-adhesive polymer film to relieve the pain of oral lesions resulting from radiation and antineoplastic therapy.[8] Lipo-

some-encapsulated amethocaine [tetracaine] has also been shown to provide adequate surface anaesthesia.[9]

1. McCafferty DF, *et al.* In vivo assessment of percutaneous local anaesthetic preparations. *Br J Anaesth* 1989; **62:** 17–21.
2. Rømsing J, *et al.* Tetracaine gel vs EMLA cream for percutaneous anaesthesia in children. *Br J Anaesth* 1999; **82:** 637–8.
3. McCafferty DF, *et al.* Effect of percutaneous local anaesthetics on pain reduction during pulse dye laser treatment of portwine stains. *Br J Anaesth* 1997; **78:** 286–9.
4. Arrowsmith J, Campbell C. A comparison of local anaesthetics for venepuncture. *Arch Dis Child* 2000; **82:** 309–10.
5. McCafferty DF, Woolfson AD. New patch delivery system for percutaneous local anaesthesia. *Br J Anaesth* 1993; **71:** 370–4.
6. Wong S, Hart LL. Tetracaine/adrenaline/cocaine for local anesthesia. *DICP Ann Pharmacother* 1990; **24:** 1181–3.
7. Ernst AA, *et al.* Lidocaine adrenaline tetracaine gel versus tetracaine adrenaline cocaine gel for topical anesthesia in linear scalp and facial lacerations in children aged 5 to 17 years. *Pediatrics* 1995; **95:** 255–8.
8. Yotsuyanagi T, *et al.* Mucosa-adhesive film containing local analgesic. *Lancet* 1985; **ii:** 613.
9. Fisher R, *et al.* Topical anaesthesia of intact skin: liposome-encapsulated tetracaine vs EMLA. *Br J Anaesth* 1998; **81:** 972–3.

Preparations

BP 2001: Tetracaine Eye Drops;
USP 25: Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution; Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Tetracaine and Menthol Ointment; Tetracaine Hydrochloride Cream; Tetracaine Hydrochloride for Injection; Tetracaine Hydrochloride in Dextrose Injection; Tetracaine Hydrochloride Injection; Tetracaine Hydrochloride Ophthalmic Solution; Tetracaine Hydrochloride Topical Solution; Tetracaine Ointment; Tetracaine Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)
Braz.: Anestesico; *Canad.:* Ametop; Cepacol Viractin; Pontocaine; Supracaine†; *Ger.:* Oto-Flexiole N†; *Israel:* Pontocaine; *NZ:* Ametop; *Port.:* Anestesico; *S.Afr.:* Ametop; Anethaine; Covostet; *Spain:* Anest Compuesto†; Anestesia Topi Braun C/A; Anestesico; Hemonet; *UK:* Ametop; Anethaine; *USA:* Ak-T-Caine†; Cepacol Viractin Cold Sore Treatment; Pontocaine.

Multi-ingredient: *Aust.:* Dynexan; Herviros; Neocones; Tonexol†; *Belg.:* Anesthesique Double†; *Braz.:* Anesdente do Bebe; Anestesiol; Anevrase; Hexomedine; Osmogenol; Oto Betnovate; Oto-Biotic; UM Instante; *Canad.:* Endospray; Panocaine†; *Fr.:* Amygdospray†; Aphtoral; Broncorinol maux de gorge; Cantalene; Codetricine vitamine C; Drill; Eludril; Hexomedine; Lysofon; Oromedine; Oroseptol Lysozyme; Oroseptol†; Otylol; Solutricine Maux de Gorge; Solutricine Tetracaine; Tyrcine; *Ger.:* Acoin; Gingicain D; Herviros; Ophtocain; *Hong Kong:* Herviros; Norgotin; *Israel:* Anaesthetic Ear Drops; Otidin; *Ital.:* Corizzina; Donalg; Lasoproct†; Odongi; Recto-Reparil; Ruscoroid; *Port.:* Anucet; Davicaina†; Drill; Hemofissural; Xilonibsa; *S.Afr.:* Dynexan; *Spain:* Anesti Doble; Anestina Braun†; Blastoestimulina; Carbocaina; Dentikrisos; Neocones; Otogen Calmante; Resorborina; Topicaina; Vinciseptil Otico; *Switz.:* Adrectal†; Angidine; Dynexan; Eludril; Tonex; Tyrothricine + Gramicidine; *UK:* Eludril; *USA:* Cetacaine; Stypto-Caine.

Amylocaine Hydrochloride (7605-q)

Amylocaine Hydrochloride *(BANM).*

Amylenii Chloridum; Amylocain. Hydrochlor.; Chlorhydrate d'Amyléine. 1-(Dimethylaminomethyl)-1-methylpropyl benzoate hydrochloride.

$C_{14}H_{21}NO_2.HCl = 271.8$.
CAS — 532-59-2 (amylocaine hydrochloride); 644-26-8 (amylocaine hydrochloride).
Pharmacopoeias. In *Belg.*

Profile

Amylocaine, a benzoic acid ester, is a local anaesthetic (p.1302) used mainly as the hydrochloride in a range of preparations for application to the skin or mucous membranes. It has also been used in preparations for the relief of painful anorectal conditions and has been included in oral mixtures for the relief of coughs.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Belg.:* Babygencal; Dentophar; Dequalinium†; Rectovasol; *Braz.:* Fonergin; *Canad.:* Pommade Midy; Rhino-Mex; *Fr.:* Amygdol; Artralgon†; Avenoc†; Bronchodermine; Campho-Pneumine; Collustan; Dolodent; Elenol; Frazoline; Glottyl; Parkipan; Pholcones†; Pulmoll; Sedaplaie; *Ital.:* Dentinale; Proctosedyl; *Spain:* Eucalyptospirine Lact†; Hemodren Compuesto; *Thai.:* Lobacin; Mybacin.

Articaine Hydrochloride (7614-p)

Articaine Hydrochloride *(BANM, USAN, rINNM).*

40045; Articaini Hydrochloridum; Carticaine Hydrochloride; Hoe-045. Methyl 4-methyl-3-(2-propylaminopropionamido)thiophene-2-carboxylate hydrochloride.

$C_{13}H_{20}N_2O_3S.HCl = 320.8$.
CAS — 23964-58-1 (articaine); 23964-57-0 (articaine hydrochloride).
Pharmacopoeias. In *Eur.* (see p.vi).

Pharmacopoeial description

Ph. Eur.: A white or almost white crystalline powder. Freely soluble in water and in alcohol. A 1% solution in water has a pH of 4.2 to 5.2. Protect from light.

Profile

Articaine hydrochloride is an amide local anaesthetic (p.1302). It has been used as a 1 or 2% solution with or without adrenaline [epinephrine] for infiltration and regional anaesthesia. A 4% solution of articaine hydrochloride with adrenaline [epinephrine] is used similarly in dentistry. A 5% hyperbaric solution of articaine hydrochloride with glucose has been used for spinal block.

Porphyria. Articaine hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Ubistesin; Ultracain Dental; *Canad.:* Astracaine; Ultracaine D-S; *Fin.:* Ultracain D-Suprarenin; *Fr.:* Alphacaine; Predesic; *Ger.:* Ubistesin; Ultracain; Ultracain D-S; Ultracain hyperbar; Ultracain-Suprarenin; *Ital.:* Cartidont; Citocartin; Septanest; Ubistesin; Ultracain D-S; *Neth.:* Ultracain D-S; Ultracain Hyperbaar; *Spain:* Ultracain; *Switz.:* Rudocaine; Septanest; Ubistesin; Ultracaine D-S; *UK:* Septanest; *USA:* Septocaine.

Benzocaine (7608-w)

Benzocaine *(BAN, rINN).*

Anaesthesinum; Anesthamine; Benzocainum; Ethoform; Éthoforme; Ethyl Aminobenzoate; Ethylis Aminobenzoas. Ethyl 4-aminobenzoate.

$C_9H_{11}NO_2 = 165.2$.
CAS — 94-09-7.
ATC — C05AD03; D04AB04; N01BA05; R02AD01.
Pharmacopoeias. In *Chin., Eur.* (see p.vi), *Int., Jpn, Pol.,* and *US.*

Pharmacopoeial description

Ph. Eur.: Colourless crystals or a white crystalline powder. M.p. 89° to 92°. Very slightly soluble in water; freely soluble in alcohol and in ether. Protect from light.

USP 25: Small, white crystals or a white odourless crystalline powder. M.p. 88° to 92°. Soluble 1 in 2500 of water, 1 in 5 of alcohol, 1 in 2 of chloroform, 1 in 4 of ether, and 1 in 30 to 50 of almond oil or olive oil; dissolves in dilute acids.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p.1302.

Hypersensitivity. The incidence of positive reactions in patients patch tested with benzocaine has ranged from 3.3 to 5.9%.[1,2] Patch testing with benzocaine has been recommended by The International Contact Dermatitis Research Group as an indicator of contact hypersensitivity to local anaesthetics. However, it was found that of 40 patients who had had positive reactions to benzocaine with amethocaine [tetracaine] and cinchocaine 21 were not allergic to benzocaine alone.[3]

1. Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; **83:** 543–5.
2. Bandmann H-J, *et al.* Dermatitis from applied medicaments. *Arch Dermatol* 1972; **106:** 335–7.
3. Beck MH, Holden A. Benzocaine—an unsatisfactory indicator of topical local anaesthetic sensitization for the UK. *Br J Dermatol* 1988; **118:** 91–4.

Precautions

As for Local Anaesthetics in general, p.1303.

Interactions

For interactions associated with local anaesthetics, see p.1303.

Pharmacokinetics

See under Local Anaesthetics, p.1303.

Uses and Administration

Benzocaine, a para-aminobenzoic acid ester, is a local anaesthetic used for surface anaesthesia (p.1304); it has low potency and systemic toxicity. It is used, often in combination with other drugs such as analgesics, antiseptics, antibacterials, antifungals, and antipruritics, for the temporary local relief of pain associated with dental conditions, oropharyngeal disorders, haemorrhoids, anal pruritus, and ear pain.

Lozenges containing benzocaine in usual doses of up to 10 mg are used for the relief of sore throat. Gels, pastes, solutions, and sprays containing benzocaine in concentrations of up to 20% have been used for surface anaesthesia of the mouth and throat.

Benzocaine is used in ear drops, creams, ointments, lotions, solutions, sprays, gels, and suppositories in concentrations up to 20% for topical analgesia and anaesthesia.

Benzocaine has also been used as the hydrochloride.

Obesity. It has been reported[1] that despite the inclusion of benzocaine in some over-the-counter appetite suppressants there is no good evidence of its value in obesity (p.1505).

1. Anonymous. A nasal decongestant and a local anesthetic for weight control? *Med Lett Drugs Ther* 1979; **21:** 65–6.

Preparations

USP 25: Antipyrine and Benzocaine Otic Solution; Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution; Benzocaine and Menthol Topical Aerosol; Benzocaine Cream; Benzocaine Gel; Benzocaine Lozenges; Benzocaine Ointment; Benzocaine Otic Solution; Benzocaine Topical Aerosol; Benzocaine Topical Solution; Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution.

Proprietary Preparations (details are given in Part 3)
Aust.: Anaestherit; *AustraL.:* Applicaine; Topicaine†; *Canad.:* Anbesol Baby; Baby Orajel; Johnson & Johnson Burn Cream; Orajel; Outgro; Sirop Dentition; Topicaine†; Zilactin Baby; Zilactin-B; *Ger.:* Anaesthesin; Flavamed Halstabletten; Subcutin N; Zahnerol N; *Israel:* Anadent; Baby Gel; Lanacane; Maintain; *Ital.:* Gengivarium†; *Mex.:* Auralyt; *NZ:* Applicaine; *Port.:* Dentispray; *Spain:* Dentispray; Gartricin; Hurricaine; Lanacane; *Switz.:* Orajel†; *UK:* AAA; Burneze; Lanacane; Ultracare; Vicks Ultra Chloraseptic; *USA:* 3 in 1 Toothache Relief; Americaine; Americaine Anesthetic; Americaine Otic; Baby Anbesol; Baby Orajel; BanSmoke†; Benzodent; Chigger-Tox; Dent's Extra Strength Toothache Gum; Dent's Lotion-Jel; Dent's Maximum Strength Toothache Drops; Dermoplast; Detane; Diet Ayds†; Hurricaine; Lanacane; Mycinettes; Numzident; Orabase Baby; Orabase Gel; Orabase-B; Orajel; Otocain; Red Cross Canker Sore Medication†; SensoGARD; Slim Mint†; Spec-T; Trocaine; Vicks Children's Chloraseptic; Zilactin-B Medicated; ZilaDent†.

Multi-ingredient: numerous preparations are listed in Part 3.

Bupivacaine Hydrochloride (7609-e)

Bupivacaine Hydrochloride *(BANM, USAN, rINNM).*

AH-2250; Bupivacaini Hydrochloridum; LAC-43; Win-11318. (±)-(1-Butyl-2-piperidyl)formo-2′,6′-xylidide hydrochloride monohydrate.

$C_{18}H_{28}N_2O.HCl.H_2O = 342.9$.
CAS — 2180-92-9 (bupivacaine); 18010-40-7 (anhydrous bupivacaine hydrochloride); 14252-80-3 (bupivacaine hydrochloride monohydrate).
Pharmacopoeias. In *Chin., Eur.* (see p.vi), *Int., Pol.,* and *US.*

Pharmacopoeial description

Ph. Eur.: A white crystalline powder or colourless crystals. Soluble in water; freely soluble in alcohol. Protect from light.

USP 25: A white, odourless, crystalline powder. Freely soluble in water and in alcohol; slightly soluble in acetone and in chloroform. A 1% solution in water has a pH of 4.5 to 6.0.

Stability of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1304.

For reference to the stability of admixtures of bupivacaine and fentanyl in solution, with or without adrenaline [epinephrine], see under Fentanyl, p.37.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p.1302.

Bupivacaine appears to be more cardiotoxic than other local anaesthetics. Cardiac arrest due to bupivacaine can be resistant to electrical defibrillation and a successful outcome may require prolonged resuscitative efforts.

◊ For reference to the toxic threshold for bupivacaine plasma concentrations, see Absorption under Pharmacokinetics, below.

Effects on the cardiovascular system. Bupivacaine[1,2] and etidocaine[2] appear to be more cardiotoxic than most other commonly used local anaesthetics and marked cardiovascular depression may occur at plasma concentrations only slightly above those for CNS toxicity.[2] Fatalities have occurred. Simultaneous seizures and cardiovascular collapse may develop rapidly following inadvertent intravascular injection and even prompt oxygenation and blood pressure support might not prevent cardiac arrest.[2] Ventricular fibrillation which is very resistant to normal methods of defibrillation may develop. Since lignocaine [lidocaine] and the other local anaesthetics have additive effects on the CNS bretylium may be preferable to lignocaine [lidocaine] for the treatment of induced arrhythmias.[1] Fatal cardiotoxicity has occurred following the use of bupivacaine in intravenous regional anaesthesia, possibly due to leakage past the tourniquet, and the use of bupivacaine in this technique should be avoided.[1] Fatalities have also been associated with the use of 0.75% solutions for epidural anaesthesia in obstetric patients and this strength is no longer recommended for obstetric anaesthesia. See also Labour Pain under Uses and Administration, below.

1. Anonymous. Cardiotoxicity of local anaesthetic drugs. *Lancet* 1986; **ii:** 1192–4.
2. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; **51:** 285–7.

Effects on the eyes. Bilateral retinal haemorrhages developed in a 47-year-old woman[1] after receiving a caudal block with bupivacaine 0.5%. The haemorrhages cleared and her visual vision returned by 3 months.

1. Ling C, *et al.* Bilateral retinal haemorrhages following epidural injection. *Br J Ophthalmol* 1993; **77:** 316–17.

Prolonged block. Reports of prolonged block following the use of bupivacaine in regional anaesthesia.[1,2]

1. Pathy GV, Rosen M. Prolonged block with recovery after extradural analgesia for labour. *Br J Anaesth* 1975; **47:** 520–2.
2. Brockway MS, *et al.* Prolonged brachial plexus block with 0.42% bupivacaine. *Br J Anaesth* 1989; **63:** 604–5.

Precautions

As for Local Anaesthetics in general, p.1303.

Bupivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics. The 0.75% solution is contra-indicated for epidural block in obstetrics.

Renal impairment. Spinal block after the administration of 3 mL bupivacaine 0.75% was reported to be more rapid in onset and of shorter duration in patients with chronic renal failure when compared with control patients.[1]

1. Orko R, *et al.* Subarachnoid anaesthesia with 0.75% bupivacaine in patients with chronic renal failure. *Br J Anaesth* 1986; **58:** 605–9.

Interactions

For interactions associated with local anaesthetics, see p.1303.

Antiarrhythmics. There is an increased risk of myocardial depression when bupivacaine and antiarrhythmics are administered concomitantly.

Beta blockers. *Propranolol* reduced the clearance of bupivacaine by 35% in 6 healthy subjects.[1] There is therefore the risk of increased bupivacaine toxicity if these drugs are administered concomitantly.

1. Bowdle TA, *et al.* Propranolol reduces bupivacaine clearance. *Anesthesiology* 1987; **66:** 36–8.

Histamine H_2-antagonists. Studies of the effect of H_2-antagonists on the pharmacokinetics of bupivacaine have yielded variable results. While one group of workers[1] found that pretreatment with *cimetidine* decreased the clearance of bupivacaine, others have failed to find any significant pharmacokinetic effects.[2,3] Similarly, pretreatment with *ranitidine* has either increased plasma concentrations of bupivacaine[4] or had no significant effect.[3]

1. Noble DW, *et al.* Effects of H-2 antagonists on the elimination of bupivacaine. *Br J Anaesth* 1987; **59:** 735–7.
2. Pihlajamäki KK. Lack of effect of cimetidine on the pharmacokinetics of bupivacaine in healthy subjects. *Br J Clin Pharmacol* 1988; **26:** 403–6.
3. Flynn RJ, *et al.* Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? *Br J Anaesth* 1989; **62:** 87–91.
4. Wilson CM. Plasma bupivacaine concentrations associated with extradural anaesthesia for caesarean section: influence of pretreatment with ranitidine. *Br J Anaesth* 1986; **58:** 1330P–1331P.

Local anaesthetics. For reference to the effect of bupivacaine on the protein binding of lignocaine [lidocaine] and mepivacaine, see p.1314 and p.1317, respectively.

Pharmacokinetics

Bupivacaine is about 95% bound to plasma proteins. Reported half-lives are from 1.5 to 5.5 hours in adults and about 8 hours in neonates. It is metabolised in the liver and is excreted in the urine principally as metabolites with only 5 to 6% as unchanged drug.

Bupivacaine is distributed into breast milk in small quantities. It crosses the placenta but the ratio of fetal concentrations to maternal concentrations is relatively low. Bupivacaine also diffuses into the CSF.

See also under Local Anaesthetics, p.1303.

Absorption. The toxic threshold for bupivacaine plasma concentrations is considered by some[1] to lie in the range of 2 to 4 µg per mL and in the UK the maximum single recommended dose for anhydrous bupivacaine hydrochloride is 150 mg (equivalent to approximately 2 mg per kg body-weight). Administration of bupivacaine for regional anaesthesia of the head and neck in a mean total dose of 3.4 mg per kg body-weight has produced mean peak plasma concentrations of 3.56 and 4.95 µg per mL when administered with or without adrenaline [epinephrine] respectively, without producing toxicity.[2] Similarly, intrapleural administration of bupivacaine 0.5% in a dose of 2.5 mg per kg has produced mean peak plasma concentrations of 2.57 and 3.22 µg per mL when given with or without adrenaline [epinephrine] respectively, without producing toxicity.[3] A further study[4] in which a 72-hour interpleural infusion of bupivacaine hydrochloride with adrenaline [epinephrine] was administered to cholecystectomy patients showed appreciable interpatient variability in steady-state plasma drug concentrations (range 1.3 to 3.2 µg per mL; mean 2.1 µg per mL); no patient suffered any adverse effects. Bilateral intercostal nerve blocks using bupivacaine 2 mg per kg have also produced concentrations within the presumed toxic range without adverse effects but the use of adrenaline [epinephrine] with this block did not reliably reduce peak plasma-bupivacaine concentrations.[5]

Stellate ganglion block with bupivacaine 0.25% has produced a mean peak plasma concentration of 0.34 and 0.47 µg per mL after doses of 10 or 20 mL respectively.[6] Administration of bupivacaine 0.5% in a dose of 3 mg per kg with or without adrenaline [epinephrine] for sciatic and femoral nerve block produced mean peak plasma concentrations below 0.8 µg per mL.[7]

Bupivacaine is rapidly absorbed from the synovial membrane of the knee during arthroscopy but plasma concentrations did not exceed 0.35 µg per mL after controlled pressure-irrigation with isotonic solutions containing up to 200 mg.[8] Although one group of workers found that the maximum plasma concentrations of bupivacaine after intra-articular injection of 30 mL of a 0.5% solution for arthroscopy was 0.875 µg per mL they suggested that adrenaline [epinephrine] should probably be added to minimise absorption.[9]

1. Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; **58:** 717–31.
2. Neill RS, Watson R. Plasma bupivacaine concentrations during combined regional and general anaesthesia for resection and reconstruction of head and neck carcinomata. *Br J Anaesth* 1984; **56:** 485–92.
3. Gin T, *et al.* Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration. *Br J Anaesth* 1990; **64:** 662–6.
4. Kastrissios H, *et al.* The disposition of bupivacaine following a 72h interpleural infusion in cholecystectomy patients. *Br J Clin Pharmacol* 1991; **32:** 251–4.
5. Bodenham A, Park GR. Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation. *Br J Anaesth* 1990; **64:** 436–41.
6. Hardy PAJ, Williams NE. Plasma concentrations of bupivacaine after stellate ganglion block using two volumes of 0.25% bupivacaine plain solution. *Br J Anaesth* 1990; **65:** 243–4.
7. Misra U, *et al.* Plasma concentrations of bupivacaine following combined sciatic and femoral 3 in 1 nerve blocks in open knee surgery. *Br J Anaesth* 1991; **66:** 310–13.
8. Debruyne D, *et al.* Monitoring serum bupivacaine levels during arthroscopy. *Eur J Clin Pharmacol* 1985; **27:** 733–5.
9. Butterworth JF, *et al.* Effect of adrenaline on plasma concentrations of bupivacaine following intra-articular injection of bupivacaine for knee arthroscopy. *Br J Anaesth* 1990; **65:** 537–9.

SURFACE ANAESTHESIA. Studies of the absorption of bupivacaine following surface application.

1. McBurney A, *et al.* Absorption of lignocaine and bupivacaine from the respiratory tract during fibreoptic bronchoscopy. *Br J Clin Pharmacol* 1984; **17:** 61–6.

Pregnancy. Bupivacaine crosses the placenta to a lesser degree than lignocaine [lidocaine] or mepivacaine following maternal injection. Values of 0.2 to 0.4 have been reported[1,2] for the ratio of fetal to maternal concentrations for bupivacaine compared with values of 0.5 to 0.7 quoted[2,3] for lignocaine [lidocaine] and mepivacaine. The greater degree of protein-binding of bupivacaine compared with these other drugs not only limits the amount of bupivacaine available to cross the placenta but also reduces the relative amount of free drug in the fetal circulation[2] (see also under Protein Binding, below). Addition of adrenaline [epinephrine] to the injection does not appear to affect the placental transfer rate of bupivacaine.[4] Measurement of a beta-phase half-life of 25 hours in the neonate compared with 1.25 hours in mothers suggests that the neonate is less able to metabolise bupivacaine.[5]

1. Denson DD, *et al.* Serum bupivacaine concentrations in term parturients following continuous epidural analgesia for labor and delivery. *Ther Drug Monit* 1984; **6:** 393–8.
2. Blogg CE, Simpson BR. Obstetric analgesia and the newborn baby. *Lancet* 1974; **i:** 1283.
3. Poppers PJ. Evaluation of local anaesthetic agents for regional anaesthesia in obstetrics. *Br J Anaesth* 1975; **47:** 322–7.
4. Reynolds F, *et al.* Effect of time and adrenaline on the feto-maternal distribution of bupivacaine. *Br J Anaesth* 1989; **62:** 509–14.
5. Caldwell J, *et al.* Pharmacokinetics of bupivacaine administered epidurally during childbirth. *Br J Clin Pharmacol* 1976; **3:** 956P–957P.

Protein binding. The two major binding proteins for bupivacaine in the blood are α-1-acid glycoprotein, the influence of which is predominant at low concentrations, and albumin, which plays the major role at high concentrations. Reduction in pH from 7.4 to 7.0 decreases the affinity of the α_1-acid glycoprotein for bupivacaine but has no effect on albumin affinity.[1] Binding of bupivacaine is reduced during pregnancy but it is considered that the increase in free bupivacaine concentrations is unlikely to cause a clinically significant increase in the risk of CNS or cardiovascular toxicity.[2]

As fetal plasma contains little α_1-acid glycoprotein the binding capacity for bupivacaine is reduced and this may contribute to the difference between maternal and fetal plasma concentration at delivery[3] (see also under Pregnancy, above).

Ageing, uncomplicated by disease, does not affect the protein binding of bupivacaine.[4]

1. Denson D, *et al.* Alpha$_1$-acid glycoprotein and albumin in human serum bupivacaine binding. *Clin Pharmacol Ther* 1984; **35:** 409–15.
2. Denson DD, *et al.* Bupivacaine protein binding in the term parturient: effects of lactic acidosis. *Clin Pharmacol Ther* 1984; **35:** 702–9.
3. Petersen MC, *et al.* Relationship between the transplacental gradients of bupivacaine and α_1-acid glycoprotein. *Br J Clin Pharmacol* 1981; **12:** 859–62.
4. Veering BT, *et al.* Age does not influence the serum protein binding of bupivacaine. *Br J Clin Pharmacol* 1991; **32:** 501–3.

Uses and Administration

Bupivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p.1304. It has a slow onset and a long duration of action. The speed of onset and duration of action are increased by the addition of a vasoconstrictor, and absorption into the circulation from the site of injection is reduced. Slow accumulation occurs with repeated doses. It is used mainly for infiltration anaesthesia and regional nerve blocks, particularly epidural block, but is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). The 0.75% solution is contra-indicated for epidural block in obstetrics. (Local anaesthetic techniques are discussed on p.1304.)

Bupivacaine is a racemic mixture but the *S*(−)-isomer levobupivacaine (see p.1312) is also used. The carbonated solution of bupivacaine is also available for injection in some countries (see p.1304).

In recommended doses bupivacaine produces complete sensory blockade but the concentration of bupivacaine solution used affects the extent of motor blockade achieved. A 0.25% solution generally produces incomplete motor block, a 0.5% solution will usually produce motor block and some muscle relaxation, and complete motor block and muscle relaxation can be achieved with a 0.75% solution.

The dosage of bupivacaine used depends on the site of injection and the procedure used, as well as the status of the patient. Doses of bupivacaine are expressed in terms of the anhydrous hydrochloride. In the UK the suggested general **maximum single dose** of bupivacaine hydrochloride is 150 mg with or without adrenaline [epinephrine] followed if necessary by doses of up to 50 mg every 2 hours. In the USA the recommended maximum single dose is 175 mg of the plain preparation or 225 mg when given with adrenaline [epinephrine]; doses may be repeated at intervals of not less than 3 hours but the total daily dose should not exceed 400 mg. The dose should be reduced in the elderly, in children, in debilitated patients, and in cardiac or hepatic disease.

A test dose of bupivacaine, preferably with adrenaline [epinephrine], should be given before commencing epidural block to detect inadvertent intravascular administration. Subsequent doses should be given in small increments.

Solutions with or without adrenaline [epinephrine] may be used for most **local anaesthetic techniques** and procedures apart from dental infiltration, when adrenaline [epinephrine] is added to the solution (see below).

For *infiltration anaesthesia* bupivacaine hydrochloride is typically used as a 0.25% solution in doses up to the recommended maximum (see above). When a longer duration of anaesthesia is required, as in dental or surgical procedures of the maxillary and mandibular area, a 0.5% solution with adrenaline [epinephrine] 1 in 200 000 has been used but a total dose of 90 mg (18 mL) should not be exceeded over a single dental sitting. For *peripheral nerve block* the usual dose is 12.5 mg (5 mL) as a 0.25% solution or 25 mg (5 mL) as a 0.5% solution, although doses up to the recommended maximum single dose (see above) may also be given. For *sympathetic nerve block* 50 to 125 mg (20 to 50 mL) as a 0.25% solution is recommended. A 0.75% solution has been used for *retrobulbar block* in ophthalmic surgery in a dose of 15 to 30 mg (2 to 4 mL).

For *lumbar epidural block* in surgery a 0.25% solution of bupivacaine hydrochloride may be used in a dose of 25 to 50 mg (10 to 20 mL) or as a 0.5% solution in a dose of 50 to 100 mg (10 to 20 mL). Lower doses of 15 to 30 mg (6 to 12 mL) as the 0.25% solution or 30 to 60 mg (6 to 12 mL) as the 0.5% solution have been recommended for analgesia during labour. A 0.75% solution is also used for induction of lumbar epidural block in non-obstetric surgery in a single dose of 75 to 150 mg (10 to 20 mL). For *caudal block* in surgery 37.5 to 75 mg (15 to 30 mL) as a 0.25%

solution or 75 to 150 mg (15 to 30 mL) as a 0.5% solution may be used. For analgesia during labour a dose of 25 to 50 mg (10 to 20 mL) as a 0.25% solution or 50 to 100 mg (10 to 20 mL) as a 0.5% solution has been recommended.

Hyperbaric solutions of bupivacaine hydrochloride without adrenaline [epinephrine] may be used for *spinal block*. Preparations containing 0.5% are available and are given in doses of 10 to 20 mg (2 to 4 mL).

Action. Addition of potassium chloride 0.2 mmol to 40 mL of bupivacaine 0.25% solution resulted in a more rapid onset of sensory loss than the same dose of plain bupivacaine in patients undergoing brachial plexus block for forearm or hand surgery.[1]

Hyaluronidase did not increase the speed of onset of brachial plexus block produced by bupivacaine 0.5%, with or without adrenaline [epinephrine], but did reduce the duration of anaesthesia.[2]

Administration of bupivacaine encapsulated in liposomes can prolong postsurgical analgesic action without motor block.[3,4]

For a comparison of the vasoactivity of bupivacaine and some other local anaesthetics, see p.1304.

1. Parris MR, Chambers WA. Effects of the addition of potassium to prilocaine or bupivacaine: studies on brachial plexus blockade. *Br J Anaesth* 1986; **58:** 297–300.
2. Keeler JF, *et al.* Effect of addition of hyaluronidase to bupivacaine during axillary brachial plexus block. *Br J Anaesth* 1992; **69:** 68–71.
   oogaerts S, *et al.* Epidural administration of liposomal bupivacaine for the management of postsurgical pain. *Br J Anaesth* 1993; **70:** (suppl 1): 104.
4. Boogaerts JG, *et al.* Pharmacokinetic-pharmacodynamic specific behaviour of liposome-associated bupivacaine in humans. *Br J Anaesth* 1995; **74** (suppl 1): 74.

Administration in children. Bupivacaine 0.25% injected intra-operatively up to a maximum dose of 1.5 mg per kg bodyweight with adrenaline [epinephrine] has been used in infants for the control of postoperative pain due to pyloromyotomy and appears to attenuate some of the cardiac and respiratory effects associated with the use of general anaesthesia alone.[1] Doses of 2.5 mg of bupivacaine per year of age administered as a 0.5% solution have been used for ilio-inguinal nerve block in children undergoing herniotomy.[2] A study[3] in infants undergoing abdominal surgery found that an epidural infusion of bupivacaine produced comparable analgesia to an intravenous infusion of morphine. It was considered that bupivacaine might be preferable to morphine in neonates and young infants who are particularly prone to respiratory depression, but older children might require additional sedation or analgesia to prevent postoperative restlessness.

1. McNicol LR, *et al.* Peroperative bupivacaine for pyloromyotomy pain. *Lancet* 1990; **335:** 54–5.
2. Smith BAC, Jones SEF. Analgesia after herniotomy in a paediatric day unit. *BMJ* 1982; **285:** 1466.
3. Wolf AR, Hughes D. Pain relief for infants undergoing abdominal surgery: comparison of infusions of IV morphine and extradural bupivacaine. *Br J Anaesth* 1993; **70:** 10–16.

Labour pain. For a discussion of the management of labour pain, including mention of the use of local anaesthetics, see p.6.

' / experience in nearly 1000 patients suggested that 8 mL 0.5% solution of bupivacaine with adrenaline [epinephrine] was the optimum dose for epidural block during labour;[1] pain relief lasted for about 2 hours. Decreasing the concentration of the final dose to 0.25% reduced the persistence of sensory and motor nerve block after delivery. Others[2] found that bupivacaine 0.375% was the most suitable concentration for epidural analgesia when using a regimen of regular 'top-up' doses of 0.5 mg per kg body-weight about every 90 minutes. However, the use of low doses of bupivacaine 0.25% for epidural analgesia in primiparous women was associated with a lower incidence of forceps delivery and oxytocin augmentation.[3] Although an even lower concentration of bupivacaine (0.0625%) used in combination with sufentanil[4] produced analgesia similar to that with 0.125% bupivacaine used alone, the duration of the second stage of labour and the incidence of instrumental and surgical delivery were not reduced. Similar results were obtained using bupivacaine 0.0625% with diamorphine 0.005%; in addition pruritus and drowsiness produced by diamorphine were considered to be troublesome in many patients.[5]

Intrathecal injections of bupivacaine with or without an opioid are sometimes used[6,7] with epidural injections to achieve a faster onset of analgesia and a reduced degree of motor block in the management of labour pain. Intrathecal injections containing bupivacaine have also been given alone[8,9] for the management of labour pain but the use of this route alone is usually associated with anaesthesia and management of postoperative pain in caesarean section. Bupivacaine has also been tried with lignocaine [lidocaine] for epidural anaesthesia in caesarean section in order to reduce the dose of bupivacaine and minimise cardiotoxicity.[10]

1. Crawford JS. Lumbar epidural block in labour: a clinical analysis. *Br J Anaesth* 1972; **44:** 66–74.
2. Purdy G, *et al.* Continuous extradural analgesia in labour: comparison between "on demand" and regular "top-up" injections. *Br J Anaesth* 1987; **59:** 319–24.
3. Turner MJ, *et al.* Primiparous women using epidural analgesia. *BMJ* 1990; **300:** 123.
4. Auroy Y, Benhamou D. Extradural analgesia for labour: 0.125% bupivacaine vs 0.0625% bupivacaine with 0.2 μg mL^{-1} sufentanil. *Br J Anaesth* 1995; **74** (suppl 1): 105–6.
5. Bailey CR, *et al.* Diamorphine-bupivacaine mixture compared with plain bupivacaine for analgesia. *Br J Anaesth* 1994; **72:** 58–61.
6. Stacey RGW, *et al.* Single space combined spinal-extradural technique for analgesia in labour. *Br J Anaesth* 1993; **71:** 499–502.
7. Collis RE, *et al.* Randomised comparison of combined spinal-epidural and standard epidural analgesia in labour. *Lancet* 1995; **345:** 1413–16.
8. Kestin IG, *et al.* Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *Br J Anaesth* 1992; **68:** 244–7.
9. McHale S, *et al.* Continuous subarachnoid infusion of 0.125% bupivacaine for analgesia during labour. *Br J Anaesth* 1992; **69:** 634–6.
10. Howell P, *et al.* Comparison of four local extradural anaesthetic solutions for elective Caesarean section. *Br J Anaesth* 1990; **65:** 648–53.

Preparations

BP 2001: Bupivacaine and Adrenaline Injection; Bupivacaine Injection;
USP 25: Bupivacaine Hydrochloride in Dextrose Injection; Bupivacaine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Aust.: Bucain; Carboneural†; Carbostesin; ***Austral.:*** Marcain; ***Belg.:*** Marcaine; ***Braz.:*** Marcaina; Neocaina; ***Canad.:*** Marcaine; Sensorcaine; ***Denm.:*** Marcain; ***Fin.:*** Bicain; Marcain; ***Fr.:*** Marcaine; ***Ger.:*** Bucain; Carbostesin; Dolanaest; ***Hong Kong:*** Marcaine; ***Irl.:*** Marcain; ***Israel:*** Kamacaine; Marcaine; ***Ital.:*** Bupiforan; Bupyl; Marcaina; ***Mex.:*** Buvacaina; ***Neth.:*** Marcaine; ***Norw.:*** Marcain; ***NZ:*** Marcain; ***Port.:*** Marcaina†; ***S.Afr.:*** Macaine; Regibloc†; ***Singapore:*** Marcain; ***Spain:*** Svedocain Sin Vasoconstr; ***Swed.:*** Marcain; ***Switz.:*** Carbostesin; Duracain; ***Thai.:*** Marcaine; ***UK:*** Marcain; ***USA:*** Marcaine; Sensorcaine.

Multi-ingredient: ***Austral.:*** Marcain with Fentanyl; Marcain with Pethidine; ***Fin.:*** Solomet c bupivacain hydrochlorid; ***NZ:*** Marcain with Fentanyl; Marcain with Pethidine.

Butacaine Sulfate (7610-b)

Butacaine Sulfate *(rINNM)*.

Butacain. Sulph.; Butacaine Sulphate *(BANM)*. 3-Dibutylaminopropyl 4-aminobenzoate sulphate.

$(C_{18}H_{30}N_2O_2)_2.H_2SO_4 = 711.0$.

CAS — 149-16-6 (butacaine); 149-15-5 (butacaine sulfate).

Profile

Butacaine, a para-aminobenzoic acid ester, is a local anaesthetic (p.1302) used for surface anaesthesia. It has been used topically, as the sulfate, in solutions for dental pain and in ear and nasal drops.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Relaxoddi†; ***Spain:*** Topicaina.

Butoxycaine Hydrochloride (11333-y)

Butoxycaini Hydrochloridum. 2-Diethylaminoethyl-(*p*-butoxybenzoate) hydrochloride.

$C_{17}H_{27}NO_3.HCl = 329.9$.

CAS — 3772-43-8 (butoxycaine); 2350-32-5 (butoxycaine hydrochloride).

Profile

Butoxycaine, a para-aminobenzoic acid ester, is a local anaesthetic (p.1302) that has been used as the base or hydrochloride for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Braz.:*** Nene Dent; ***Ger.:*** Bismolan; Hamo-ratiopharm.

Butyl Aminobenzoate (7613-q)

Butamben *(USAN)*; Butoforme. Butyl 4-aminobenzoate.

$C_{11}H_{15}NO_2 = 193.2$.

CAS — 94-25-7.

Pharmacopoeias. In *Fr.* and *US.*

Pharmacopoeial description

USP 25: A white, odourless, crystalline powder. M.p. 57° to 59°. Soluble 1 in 7000 of water; soluble in alcohol, in ether, in chloroform, in fixed oils, and in dilute acids. It slowly hydrolyses when boiled with water.

Butyl Aminobenzoate Picrate (9857-x)

Abbott-34842; Butamben Picrate *(USAN)*.

$(C_{11}H_{15}NO_2)_2.C_6H_3N_3O_7 = 615.6$.

CAS — 577-48-0.

Profile

Butyl aminobenzoate, a para-aminobenzoic acid ester, is a local anaesthetic (p.1302) that has been used for surface anaesthesia of the skin and mucous membranes. It has also been used for relief of pain and pruritus associated with anorectal disorders. A suspension of butyl aminobenzoate 5 or 10% has been given epidurally.

Butyl aminobenzoate picrate is applied to the skin as a 1% ointment.

◊ References.

1. Korsten HH, *et al.* Long-lasting epidural sensory blockade by n-butyl-p-aminobenzoate in the terminally ill intractable cancer pain patient. *Anesthesiology* 1991; **75:** 950–60.
2. Armstrong DG, Kanat IO. Analgesic efficacy of topical butamben picrate. *J Am Podiatr Med Assoc* 1995; **85:** 738–40.
3. Shulman M, *et al.* Nerve blocks with 5% butamben suspension for the treatment of chronic pain syndromes. *Reg Anesth Pain Med* 1998; **23:** 395–401.

Preparations

USP 25: Benzocaine, Butamben, and Tetracaine Hydrochloride Gel; Benzocaine, Butamben, and Tetracaine Hydrochloride Ointment; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol; Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution; Erythromycin Ethylsuccinate Injection.

Proprietary Preparations (details are given in Part 3)
USA: Butesin Picrate.

Multi-ingredient: ***Austral.:*** Butesin Picrate; ***Braz.:*** Nestosyl; Predmicin; ***Fr.:*** Ginkor Procto†; Nestosyl; Preparation H; Tyrothricine Lafran†; ***Spain:*** Alvogil; Topicaina; ***Switz.:*** Alvogyl; ***USA:*** Cetacaine.

Chloroprocaine Hydrochloride (7615-s)

Chloroprocaine Hydrochloride *(rINNM)*.

2-Diethylaminoethyl 4-amino-2-chlorobenzoate hydrochloride.

$C_{13}H_{19}ClN_2O_2.HCl = 307.2$.

CAS — 133-16-4 (chloroprocaine); 3858-89-7 (chloroprocaine hydrochloride).

Pharmacopoeias. In *US.*

Pharmacopoeial description

USP 25: A white odourless crystalline powder. Soluble 1 in 20 of water and 1 in 100 of alcohol; very slightly soluble in chloroform; practically insoluble in ether. Solutions are acid to litmus.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1304.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1302. Chloroprocaine is said to be unsuitable for intravenous regional anaesthesia (Bier's block) because of a high incidence of thrombophlebitis associated with such use. It is also contra-indicated in spinal anaesthesia due to potential neurotoxicity.

Interactions

For interactions associated with local anaesthetics, see p.1303.

Pharmacokinetics

Chloroprocaine is hydrolysed rapidly in the circulation by plasma cholinesterase. It has a half-life of 19 to 26 seconds in adults. It is excreted in the urine mainly as metabolites.

See also under Local Anaesthetics, p.1303.

Uses and Administration

Chloroprocaine, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p.1304. It has properties similar to those of procaine (p.1319). It has a rapid onset (6 to 12 minutes) and short duration (one hour) of action.

Chloroprocaine is used as the hydrochloride for infiltration, peripheral nerve block, and central nerve block including lumbar and caudal epidural blocks. It may be given, if necessary, with adrenaline [epinephrine] 1 in 200 000 to delay absorption and reduce toxicity. Chloroprocaine is not an effective surface anaesthetic. It should not be used for spinal anaesthesia. (Local anaesthetic techniques are discussed on p.1304.)

The dosage of chloroprocaine used depends on the site of injection and the procedure used. In adults the maximum single dose of chloroprocaine hydrochloride without adrenaline [epinephrine] should not exceed 800 mg; when given with adrenaline [epinephrine] 1 in 200 000 the maximum single dose should not exceed 1 g.

For *mandibular nerve block* a 2% solution is used in a dose of 40 to 60 mg (2 to 3 mL) and for *infra-orbital nerve block* a dose of 10 to 20 mg (0.5 to 1 mL) as a 2% solution is used. A 2% solution is also used for *brachial plexus block* in a dose of 600 to 800 mg (30 to 40 mL). For *digital nerve block* a 1% solution without adrenaline [epinephrine] is used in a dose of 30 to 40 mg (3 to 4 mL). In obstetrics a dose of 200 mg (10 mL) per side as a 2% solution is suggested for *pudendal block*, and for a *paracervical block* a 1% solution in a dose of 30 mg (3 mL) at each of 4 sites. For *lumbar epidural block* 40 to 50 mg (2 to 2.5 mL) as a 2% solution or 60 to 75 mg (2 to 2.5 mL) as a 3% solution is used for each segment to be anaesthetised, the usual total dose being 300 to 750 mg with smaller repeat doses being given at intervals of 40 to 50 minutes. For *caudal block* a dose of 300 to 500 mg (15 to 25 mL) as a 2% solution or 450 to 750 mg (15 to 25 mL) as a 3% solution may be given and repeated at intervals of 40 to 60 minutes.

Dosages should be reduced in children, elderly or debilitated patients, and those with cardiac or liver disease. For children

concentrations of 0.5 to 1.0% are suggested for infiltration and 1.0 to 1.5% for nerve block procedures.

Preparations

USP 25: Chloroprocaine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Canad.: Nesacaine; *Switz.:* Ivracain; Nesacain; *USA:* Nesacaine.

Cinchocaine (7616-w)

Cinchocaine *(BAN, rINN).*

Cincainum; Dibucaine. 2-Butoxy-*N*-(2-diethylaminoethyl)cinchoninamide; 2-Butoxy-*N*-(2-diethylaminoethyl)quinoline-4-carboxamide.

$C_{20}H_{29}N_3O_2$ = 343.5.

CAS — 85-79-0.

ATC — C05AD04; D04AB02; N01BB06; S01HA06.

Pharmacopoeias. In *US.*

Pharmacopoeial description

USP 25: A white to off-white powder, with a slight characteristic odour. M.p. 62.5° to 66°. Soluble 1 in 4600 of water, 1 in 0.7 of alcohol, 1 in 0.5 of chloroform, and 1 in 1.4 of ether; soluble in 1N hydrochloric acid. It darkens on exposure to light. Store in airtight containers. Protect from light.

Cinchocaine Hydrochloride (7617-e)

Cinchocaine Hydrochloride *(BANM, rINNM).*

Cincaini Chloridum; Cinchocaini Hydrochloridum; Dibucaine Hydrochloride; Dibucainium Chloride; Percainum; Sovcainum.

$C_{20}H_{29}N_3O_2$,HCl = 379.9.

CAS — 61-12-1.

NOTE. This compound was originally marketed under the name Percaine, but accidents occurred owing to the confusion of this name with procaine.

Pharmacopoeias. In *Eur.* (see p.vi), *Jpn,* and *US.*

Pharmacopoeial description

Ph. Eur.: A white or almost white, crystalline powder or colourless crystals; it is hygroscopic. It agglomerates very easily. Very soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane. A 2% solution in water has a pH of 5.0 to 6.0. Store in airtight containers. Protect from light.

USP 25: Colourless or white to off-white crystals or white to off-white, crystalline powder. It is odourless, somewhat hygroscopic, and darkens on exposure to light. Freely soluble in water, in alcohol, in acetone, and in chloroform. Its solutions have a pH of about 5.5. Store in airtight containers. Protect from light.

Profile

Cinchocaine is an amide local anaesthetic (p.1302) that is now generally only used for surface anaesthesia. It is one of the most potent and toxic of the long-acting local anaesthetics and its parenteral use was restricted to spinal anaesthesia.

For surface anaesthesia cinchocaine has been used, as the base or hydrochloride, in creams and ointments containing up to 1% and in suppositories for the temporary relief of pain and itching associated with skin and anorectal conditions. Cinchocaine benzoate has also been used topically.

Action. For a comparison of the vasoactivity of cinchocaine and some other local anaesthetics, see p.1304.

Plasma cholinesterase deficiency. For mention of the use of cinchocaine in the determination of plasma cholinesterase activity, see under Precautions of Suxamethonium Chloride, p.1341.

Preparations

USP 25: Dibucaine Cream; Dibucaine Hydrochloride Injection; Dibucaine Ointment.

Proprietary Preparations (details are given in Part 3)
Austral.: Nupercaine Heavy; *Braz.:* Nupercainal; *Canad.:* Nupercainal; *Denm.:* Cincain; *Ger.:* DoloPosterine N; *Swed.:* Cincain; *Switz.:* Nupercainal†; *UK:* Nupercainal; *USA:* Nupercainal.

Multi-ingredient: *Aust.:* Ciloprin cum Anaesthetico; Scheriproct; Ultraproct; *Austral.:* Proctosedyl; Rectinol HC; Scheriproct; Ultraproct; *Belg.:* Hemosedan; Scheriproct; Trihistalex; Ultraproct; *Braz.:* Proctil; Senol; Ultraproct; *Canad.:* Nupercainal; Proctosedyl; Proctosone; *Denm.:* Proctosedyl; *Fin.:* Ciloprin cum Anaesthetico; Faktu; Proctosedyl; Scheriproct; *Fr.:* Anti-Hemorroidaires†; Deliproct; Ultraproct; *Ger.:* Anumedin; Faktu; Otobacid N; Procto-Kaban; Proctospre; Scheriproct; Ultraproct; *Hong Kong:* Borraginol-N; Decatylen; Faktu; Proctosedyl; Proctosone; Protozone; Ultraproct; *Irl.:* Proctosedyl; Scheriproct; Ultraproct; *Israel:* Proctosedyl; *Ital.:* Ultraproct; *Mex.:* Proctoacid; Scheriproct; Ultraproct; *Neth.:* Proctosedyl; Ultraproct†; *Norw.:* Proctosedyl; Scheriproct; *NZ:* Proctosedyl; Ultraproct; *Port.:* Faktu; Scheriproct; *S.Afr.:* Cepacaine; Proctosedyl; Scheriproct; *Singapore:* Decatylen; Faktu; Proctosedyl; *Spain:* Anestesia Loc Braun S/A; Ruscus; Scheriproct; *Swed.:* Proctosedyl; Scheriproct N; *Switz.:* Ciloprine ca; Decatylene Neo; Faktu; Locaseptil-Neo; Proctospre; Scheriproct; Ultraproct†; *Thai.:* Faktu; Proctosedyl; Scheriproct; *UAE:* Supraproct-S; *UK:* Proctosedyl; Scheriproct; Ultraproct; Uniroid-HC; Uniroid†; *USA:* Corticaine.

Used as an adjunct in: Aust.: Butazolidin; Delta-Tomanol†; *Ger.:* Butazolidin; *Switz.:* Butazolidine†.

Coca (7618-l)

Coca Leaves; Hoja de Coca.

The dried leaves of *Erythroxylum coca* (Bolivian or Huanuco leaf) or of *E. truxillense* (Peruvian or Truxillo leaf) (Erythroxylaceae), indigenous to Bolivia and Peru and cultivated in Colombia and Indonesia.

Coca leaves contain about 0.7 to 1.5% of total alkaloids, of which cocaine, cinnamyl-cocaine, and α-truxilline are the most important.

Profile

Coca was formerly used for its stimulant action and for the relief of gastric pain, nausea, and vomiting, but it has no place in modern medicine. The practice of coca leaf chewing still continues in South America.

Cocaine (7619-y)

Cocaine *(BAN).*

Cocaina; Methyl Benzoylecgonine. (1*R*,2*R*,3*S*,5*S*)-2-Methoxycarbonyltropan-3-yl benzoate.

$C_{17}H_{21}NO_4$ = 303.4.

CAS — 50-36-2.

ATC — N01BC01; R02AD03; S01HA01; S02DA02.

NOTE. The following names have also been used to describe various forms of cocaine: basuco, bazooka, bernice, blow, C, charlie, coke, crack, flake, freebase, girl, gold dust, her, lady, leaf, nose candy, pasta, rock, she, snow, space dust, toot, white girl, white lady.

Pharmacopoeias. In *Br., It.,* and *US.*

Pharmacopoeial description

BP 2001: It may be obtained from the leaves of *Erythroxylum coca* and other spp. of *Erythroxylum,* or by synthesis. Colourless crystals or a white, crystalline powder. It is slightly volatile. M.p. 96° to 98°. Practically insoluble in water; freely soluble in alcohol and in ether; very soluble in chloroform; soluble in arachis oil; slightly soluble in liquid paraffin.

USP 25: Colourless to white crystals or white, crystalline powder. M.p. 96° to 98°. Soluble 1 in 600 of water, 1 in 7 of alcohol, 1 in 1 of chloroform, 1 in 3.5 of ether, 1 in 12 of olive oil, and 1 in 80 to 100 of liquid paraffin. A saturated solution in water is alkaline to litmus. Protect from light.

Cocaine Hydrochloride (7620-g)

Cocaine Hydrochloride *(BANM).*

Chloridrato de Cocaína; Cocaine Hydrochlor.; Cocaini Hydrochloridum; Cocainium Chloratum.

$C_{17}H_{21}NO_4$,HCl = 339.8.

CAS — 53-21-4.

NOTE. CCN is a code approved by the BP 2001 for use on single unit doses of eye drops containing cocaine hydrochloride where the individual containers may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p.vi), *Jpn, Pol.,* and *US.*

Cocaine hydrochloride 1.12 g is approximately equivalent to 1 g of cocaine. Solutions are adversely affected by alkalis.

Pharmacopoeial description

Ph. Eur.: Hygroscopic, colourless crystals or a white crystalline powder. M.p. about 197° with decomposition. Very soluble in water; freely soluble in alcohol; practically insoluble in ether. Protect from moisture and light.

USP 25: Colourless crystals or white, crystalline powder. Soluble 1 in 0.5 of water, 1 in 3.5 of alcohol, and 1 in 15 of chloroform; soluble in glycerol; insoluble in ether. Protect from light.

Stability of solutions. A stability study[1] was conducted in response to queries over conflicting data on the incompatibility of cocaine hydrochloride solutions and phenol. Some pharmacists had reported that cocaine hydrochloride eye drops preserved with phenol had shown no sign of physical incompatibility. The BPC 1973 states that cocaine hydrochloride is incompatible with phenol but suggests that cocaine hydrochloride solutions may be preserved with chlorocresol. The study found that there was no sign of physical incompatibility in aqueous solutions containing cocaine hydrochloride 5% and phenol 0.5% stored for a year at temperatures of 0° to 37° but there was a fall in pH, greatest at the higher temperatures, which was suggestive of chemical change. It was recommended that such solutions should be stored in a cool place.

1. *PSGB Lab Report P/75/14* 1975.

Adverse Effects

Because the therapeutic use of cocaine is now very restricted many reports of adverse effects occur in the context of abuse. However, both systemic and local effects have followed its use as a surface anaesthetic. Although some effects are similar to those of other local anaesthetics (p.1302), cocaine differs in that it acts as a potent indirect-acting sympathomimetic. It stimulates the CNS causing agitation, dilated pupils, tachycardia, hypertension, hallucinations, hypertonia, and hyperreflexia. Convulsions, coma, and metabolic acidosis may develop. Symptoms of CNS stimulation and sympathetic overactivity are very marked in overdosage with cocaine. A single oral dose of 1.2 g or less may be fatal, but some persons have a cocaine idiosyncrasy and severe toxicity may occur after doses of only 10 mg intravenously. Systemic absorption of small doses may slow the heart, but with increasing doses tachycardia, hypertension, and ventricular fibrillation occur.

High concentrations of cocaine should not be used topically as, in addition to risks of systemic toxicity following absorption, lasting local damage may occur.

Topical application of cocaine to the cornea can cause corneal damage with clouding, pitting, sloughing, and occasionally ulceration. Topical application to the nose or mouth has been reported to cause loss of smell and taste respectively.

Prolonged use of cocaine by nasal inhalation may cause mucosal damage or perforation of the nasal septum.

Abuse. Cocaine abuse and its effects have been discussed in a number of reviews.[1-5]

Cocaine abuse was once only in the form of chewing of Coca leaves containing small amounts of cocaine but processing of the leaves has led to abuse with a variety of more dangerous preparations containing higher concentrations of cocaine.[6] Coca paste, produced by maceration of the leaves with petrol and sulfuric acid, contains about 40 to 90% of cocaine sulfate and is smoked with tobacco or cannabis. Treatment of coca paste with hydrochloric acid produces cocaine hydrochloride, which is abused by intravenous injection, either alone or with diamorphine, or by sniffing to achieve nasal absorption. Alkaloidal cocaine (cocaine base; 'freebase'), which is abused by smoking, is produced by treating cocaine hydrochloride with alkali, followed either by heating (to form 'crack' cocaine) or by extracting the base from ether or another organic solvent. The route of administration of cocaine determines the rate and extent of its absorption, although once absorbed, the pharmacokinetics are independent of route. The route of administration rather than the form of cocaine used is important in determining the abuse potential; intravenous cocaine hydrochloride and smoked cocaine base have a greater potential for abuse than intranasal cocaine hydrochloride because of their greater rapidity and intensity of effects.

The psychological effects of cocaine abuse may be described by a cycle of initial euphoria followed by dysphoria and finally schizophreniform psychosis.[6,7] Euphoria may be accompanied by other symptoms of stimulation such as sexual arousal, anorexia, insomnia, hyperexcitability, loquacity, and grandiosity, and users may appear manic. After a short time these feelings are replaced by symptoms of dysphoria including considerable anxiety, fear, depression, apathy, irritability, suspiciousness. Dysphoria may be ameliorated by repeated administration, so the user develops the need to take the drug continuously to feel relatively well, but repeated administration appears to diminish the intensity of the effects.[6] During euphoria and dysphoria users may experience a wide range of physical symptoms including palpitations, headache, dizziness, gastrointestinal effects, hyperhidrosis, tremors, tachycardia, hypertension, fever, and myoclonic jerks. Seizures can also occur following repeated use. In chronic abusers psychological deterioration may eventually occur, resulting in loss of mental function, compulsive disorders, suicidal ideation, psychopathic disorders, and ultimately a psychosis resembling acute paranoid schizophrenia similar to that seen with amfetamines.[6,7] Symptoms may include paranoia, stereotyped behaviour, delusions, loss of impulse control, violence, and visual, olfactory, auditory, gustatory, and tactile hallucinations. Overdosage can result in death due to status epilepticus, hyperthermia, ventricular tachycardia, and cardiac or respiratory arrest.[6]

For further details of the adverse effects of cocaine abuse, including effects due to use during pregnancy, see below.

1. Johanson C-E, Fischman MW. The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 1989; **41:** 3–52.
2. Warner EA. Cocaine abuse. *Ann Intern Med* 1993: **119:** 226–35.
3. Strang J, *et al.* Cocaine in the UK—1991. *Br J Psychiatry* 1993; **162:** 1–13.
4. Das G. Cocaine abuse in North America: a milestone in history. *J Clin Pharmacol* 1993; **33:** 296–310.
5. Hatsukami DK, Fischman MW. Crack cocaine and cocaine hydrochloride: are the differences myth or reality? *JAMA* 1996; **276:** 1580–8.
6. Arif A, ed. *Adverse health consequences of cocaine abuse.* Geneva: WHO, 1987.
7. Leikin JB, *et al.* Clinical features and management of intoxication due to hallucinogenic drugs. *Med Toxicol Adverse Drug Exp* 1989; **4:** 324–50.

EFFECTS ON THE BLOOD. References.

1. Leissinger CA. Severe thrombocytopenia associated with cocaine use. *Ann Intern Med* 1990; **112:** 708–10.

† The symbol † denotes a preparation no longer actively marketed

EFFECTS ON THE CARDIOVASCULAR SYSTEM. There appears to be no relationship between underlying heart disease and the risk of cocaine-induced cardiac effects and cardiac events can occur regardless of the route of abuse.[1] Cardiovascular toxicity due to cocaine may be related to individual sensitivity and therefore may not be predictable or dose dependent.[2] Patients with plasma cholinesterase deficiency are particularly at risk for sudden death.[3] Other risk factors for cardiovascular disease, such as cigarette smoking, may exacerbate the cardiac toxicity of cocaine.[4,5] Cocaine blocks reuptake of catecholamines at adrenergic nerve endings and thus produces sympathetic stimulation of the cardiovascular system. Accumulation of catecholamines predisposes the myocardium to arrhythmias,[6] and sinus tachycardia, supraventricular or ventricular tachyarrhythmias, myocarditis, and sudden arrhythmic death may occur.[6-8] Severe hypertension can lead to cerebrovascular accidents and stroke has occurred even in young adults without other predisposing conditions.[9,10] Aortic dissection[11,12] and rupture of the aorta have also occurred.[3] Myocardial infarction and ischaemia have been associated with cocaine abuse[1,3,6] but self-limiting chest pain without signs of myocardial infarction also commonly occurs;[7] asymptomatic myocardial ischaemia manifesting as episodes of ST segment elevation has also been reported during withdrawal of cocaine.[13] The mechanism for these changes remains to be resolved but coronary vasospasm,[13] vasoconstriction,[14] coronary thrombosis,[15,16] and direct myocardiotoxicity[17] are among the suggested causes. Some workers[18] have found that the timing of the coronary vasoconstriction correlated with ...nd concentration of cocaine's active metabolites, benzoecgonine and ethyl methyl ecgonine.

Vasoconstriction due to cocaine may also produce ischaemia in the fingers, toes, spinal cord,[7] kidneys,[19] spleen,[20] and intestines.[21] Other reported cardiovascular effects include dilated cardiomyopathy.[22]

1. VanDette JM, Cornish LA. Medical complications of illicit cocaine use. *Clin Pharm* 1989; **8:** 401–11.
2. Thadani PV. Cardiovascular toxicity of cocaine: underlying mechanisms. *J Appl Cardiol* 1990; **5:** 317–20.
3. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med* 1986; **315:** 1495–1500.
4. Moliterno DJ, *et al.* Coronary-artery vasoconstriction induced by cocaine, cigarette smoking, or both. *N Engl J Med* 1994; **330:** 454–9.
5. Higgins ST, *et al.* Influence of cocaine use on cigarette smoking. *JAMA* 1994; **272:** 1724.
6. Loper KA. Clinical toxicology of cocaine. *Med Toxicol Adverse Drug Exp* 1989; **4:** 174–85.
7. Anonymous. Acute reactions to drugs of abuse. *Med Lett Drugs Ther* 1990; **32:** 92–4.
8. Bauman JL, *et al.* Cocaine-related sudden cardiac death: a hypothesis correlating basic science and clinical observations. *J Clin Pharmacol* 1994; **34:** 902–11.
9. Kaku DA, Lowenstein DH. Emergence of recreational drug abuse as a major risk factor for stroke in young adults. *Ann Intern Med* 1990; **113:** 821–7.
10. Levine SR, *et al.* Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine. *N Engl J Med* 1990; **323:** 699–704.
11. Edwards J, Rubin RN. Aortic dissection and cocaine abuse. *Ann Intern Med* 1987; **107:** 779–80.
12. Jaffe BD, *et al.* Cocaine-induced coronary-artery dissection. *N Engl J Med* 1994; **330:** 510–11.
13. Nademanee K, *et al.* Myocardial ischemia during cocaine withdrawal. *Ann Intern Med* 1989; **111:** 876–80.
14. ...nge RA, *et al.* Cocaine-induced coronary-artery vasoconstriction. *N Engl J Med* 1989; **321:** 1557–62.
15. Minor RL, *et al.* Cocaine-induced myocardial infarction in patients with normal coronary arteries. *Ann Intern Med* 1991; **115:** 797–806.
16. Kugelmass AD, Ware JA. Cocaine and coronary artery thrombosis. *Ann Intern Med* 1992; **116:** 776–7.
17. Peng S-K, *et al.* Direct cocaine cardiotoxicity demonstrated by endomyocardial biopsy. *Arch Pathol Lab Med* 1989; **113:** 842–5.
18. Brogan WC, *et al.* Recurrent coronary vasoconstriction caused by intranasal cocaine: possible role for metabolites. *Ann Intern Med* 1992; **116:** 556–61.
19. Sharff JA. Renal infarction associated with intravenous cocaine use. *Ann Emerg Med* 1984; **13:** 1145–7.
20. Novielli KD, Chambers CV. Splenic infarction after cocaine use. *Ann Intern Med* 1991; **114:** 251–2.
21. Freudenberger RS, *et al.* Intestinal infarction after intravenous cocaine administration. *Ann Intern Med* 1990; **113:** 715–16.
22. Chokshi SK, *et al.* Reversible cardiomyopathy associated with cocaine intoxication. *Ann Intern Med* 1989; **111:** 1039–40.

EFFECTS ON THE CNS. Severe CNS depression with deep coma has been seen in a few cocaine abusers after prolonged binges.[1]

1. Roberts JR, Greenberg MI. Cocaine washout syndrome. *Ann Intern Med* 2000; **132:** 679–80.

EFFECTS ON THE KIDNEYS. For reference to renal failure following rhabdomyolysis associated with cocaine abuse, see under Effects on the Muscles, below. There has been a report[1] of acute renal failure occurring in a 16-year-old girl secondary to cocaine abuse but without evidence of rhabdomyolysis.

For reference to renal ischaemia due to cocaine abuse, see under Effects on the Cardiovascular System, above.

1. Leblanc M, *et al.* Cocaine-induced acute renal failure without rhabdomyolysis. *Ann Intern Med* 1994; **121:** 721–2.

EFFECTS ON THE LUNGS. Smoking the free base has resulted in a range of pulmonary complications not previously encountered with other methods of abuse for cocaine. Associated adverse effects have included pulmonary oedema, hypersensitivity pneumonitis, pulmonary haemorrhage, obliterative bronchiolitis, abnormalities of pulmonary function, pneumomediastinum, and pneumothorax.[1] Severe or life-threatening exacerbations of asthma have also been reported.[2]

1. Ettinger NA, *et al.* A review of the respiratory effects of smoking cocaine. *Am J Med* 1989; **87:** 664–8.
2. Rubin RB, Neugarten J. Cocaine-associated asthma. *Am J Med* 1990; **88:** 438–9.

EFFECTS ON THE MOUTH. Gingival necrosis following the abuse of cocaine by local application to the gingivae has been reported.[1]

1. Parry J, *et al.* Mucosal lesions due to oral cocaine use. *Br Dent J* 1996; **180:** 462–4.

EFFECTS ON THE MUSCLES. Rhabdomyolysis, sometimes progressing to renal failure, has been associated with free-base smoking or injection of cocaine hydrochloride.[1-3]

1. Roth D, *et al.* Acute rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1988; **319:** 673–7.
2. Herzlich BC, *et al.* Rhabdomyolysis related to cocaine abuse. *Ann Intern Med* 1988; **109:** 335–6.
3. Pogue VA, Nurse HM. Cocaine-associated acute myoglobinuric renal failure. *Am J Med* 1989; **86:** 183–6.

EFFECTS ON SEXUAL FUNCTION. While the initial euphoria of cocaine abuse may be accompanied by sexual arousal, sexual dysfunction can occur[1] and male infertility has been reported.[2] Priapism associated with cocaine abuse has also occurred.[3]

1. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med* 1986; **315:** 1495–1500.
2. Bracken MB, *et al.* Association of cocaine use with sperm concentration, motility, and morphology. *Fertil Steril* 1990; **53:** 315–22.
3. Altman AL, *et al.* Cocaine associated priapism. *J Urol* 1999; **161:** 1817–18.

EFFECTS ON THE SKIN. Urticarial vasculitis occurred in a young man following intranasal abuse of cocaine.[1]

1. Hofbauer GFL, *et al.* Uritcarial vasculitis following cocaine use. *Br J Dermatol* 1999; **141:** 600–601.

OVERDOSAGE. References to fatal overdosage from cocaine abuse.

1. Mittleman RE, Wetli CV. Death caused by recreational cocaine use. *JAMA* 1984; **252:** 1889–93.
2. Cowart V. National concern about drug abuse brings athletes under unusual scrutiny. *JAMA* 1986; **256:** 2457–65.
3. Greenland VC, *et al.* Vaginally administered cocaine overdose in a pregnant woman. *Obstet Gynecol* 1989; **74:** 476–7.
4. Peretti FJ, *et al.* Cocaine fatality: an unexplained blood concentration in a fatal overdose. *Forensic Sci Int* 1990; **48:** 135–8.
5. Karch SB, *et al.* Relating cocaine blood concentrations to toxicity–an autopsy study of 99 cases. *J Forensic Sci* 1998; **43:** 41–5.

PREGNANCY AND BREAST FEEDING. The effects of cocaine abuse during pregnancy have been reviewed.[1-3] Women who abuse cocaine during pregnancy appear to have an increased risk of spontaneous abortion,[4] abruptio placentae[5,6] and associated still-births,[7] premature labour,[8-10] and other birth complications.[8-10] These effects may be due to vasoconstriction by cocaine increasing maternal blood pressure and reducing placental blood flow.[11] Uterine rupture[12] during pregnancy and rupture of ectopic pregnancies[13] have also been associated with cocaine. Neonates born to mothers abusing cocaine have an increased risk of intra-uterine growth retardation and may have lower birth-weight, smaller head size, and shorter length.[5,7-9,14-16] Cocaine is possibly teratogenic and congenital abnormalities associated with abuse include cardiovascular abnormalities,[8,17,18] limb reduction defects,[19] intestinal atresia or infarction,[19] skull defects,[7] and genito-urinary tract anomalies.[20] Neurobehavioural impairment[21] and signs of transient CNS irritability[22] may also occur. Some workers[23,24] have found effects on cognition and motor delays while others have found effects on arousal and attention regulation rather than cognitive processes.[25] Cocaine can increase neonatal cerebral blood flow[26] and cerebral infarction and associated seizures have occurred in neonates whose mothers took cocaine near to the onset of labour.[27] Evidence on the risk of intraventricular haemorrhage is conflicting.[6,23]

Acute intoxication has been reported in a breast-fed child whose mother was using cocaine intranasally.[28]

1. Slutsker L. Risks associated with cocaine use during pregnancy. *Obstet Gynecol* 1992; **79:** 778–89.
2. Volpe JJ. Effects of cocaine use on the fetus. *N Engl J Med* 1992; **327:** 399–407. Correction. *ibid.*; 1039.
3. Wiggins RC. Pharmacokinetics of cocaine in pregnancy and effects on fetal maturation. *Clin Pharmacokinet* 1992; **22:** 85–93.
4. Chasnoff IJ, *et al.* Cocaine use in pregnancy. *N Engl J Med* 1985; **313:** 666–9.
5. Dombrowski MP, *et al.* Cocaine abuse is associated with abruptio placentae and decreased birth weight, but not shorter labor. *Obstet Gynecol* 1991; **77:** 139–41.
6. Dusick AM, *et al.* Risk of intracranial hemorrhage and other adverse outcomes after cocaine exposure in a cohort of 323 very low birth weight infants. *J Pediatr* 1993; **122:** 438–45.
7. Bingol N, *et al.* Teratogenicity of cocaine in humans. *J Pediatr* 1987; **110:** 93–6.
8. Little BB, *et al.* Cocaine abuse during pregnancy: maternal and fetal implications. *Obstet Gynecol* 1989; **73:** 157–60.
9. Mastrogiannis DS, *et al.* Perinatal outcome after recent cocaine usage. *Obstet Gynecol* 1990; **76:** 8–11.
10. Spence MR, *et al.* The relationship between recent cocaine use and pregnancy outcome. *Obstet Gynecol* 1991; **78:** 326–9.
11. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115:** 665–75.
12. Gonsoulin W, *et al.* Rupture of unscarred uterus in primigravid woman in association with cocaine abuse. *Am J Obstet Gynecol* 1990; **163:** 526–7.
13. Thatcher SS, *et al.* Cocaine use and acute rupture of ectopic pregnancies. *Obstet Gynecol* 1989; **74:** 478–9.
14. Zuckerman B, *et al.* Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 1989; **320:** 762–8.
15. Chasnoff IJ, *et al.* Temporal patterns of cocaine use in pregnancy: perinatal outcome. *JAMA* 1989; **261:** 1741–4.
16. Little BB, Snell LM. Brain growth among fetuses exposed to cocaine in utero: asymmetrical growth retardation. *Obstet Gynecol* 1991; **77:** 361–4.
17. Lipshultz SE, *et al.* Cardiovascular abnormalities in infants prenatally exposed to cocaine. *J Pediatr* 1991; **118:** 44–51.
18. Shaw GM, *et al.* Maternal use of cocaine during pregnancy and congenital cardiac anomalies. *J Pediatr* 1991; **118:** 167–8.
19. Hoyme HE, *et al.* Prenatal cocaine exposure and fetal vascular disruption. *Pediatrics* 1990; **85:** 743–7.
20. Chávez GF, *et al.* Maternal cocaine use during early pregnancy as a risk factor for congenital urogenital anomalies. *JAMA* 1989; **262:** 795–8.
21. Singer LT, *et al.* Neurobehavioural sequelae of fetal cocaine exposure. *J Pediatr* 1991; **119:** 667–72.
22. Doberczak TM, *et al.* Neonatal neurologic and electroencephalographic effects of intrauterine cocaine exposure. *J Pediatr* 1988; **113:** 354–8.
23. Singer LT, *et al.* Increased incidence of intraventricular hemorrhage and developmental delay in cocaine-exposed, very low birth weight infants. *J Pediatr* 1994; **124:** 765–71.
24. Azuma SD, Chasnoff IJ. Outcome of children prenatally exposed to cocaine and other drugs: a path analysis of three-year data. *Pediatrics* 1993; **92:** 396–402.
25. Mayes LC, *et al.* Information processing and developmental assessments in 3-month-old infants exposed prenatally to cocaine. *Pediatrics* 1995; **95:** 539–45.
26. van der Bor M, *et al.* Increased cerebral blood flow velocity in infants of mothers who abuse cocaine. *Pediatrics* 1990; **85:** 733–6.
27. Chasnoff IJ, *et al.* Perinatal cerebral infarction and maternal cocaine use. *J Pediatr* 1986; **108:** 456–9.
28. Chasnoff IJ, *et al.* Cocaine intoxication in a breast-fed infant. *Pediatrics* 1987; **80:** 836–8.

Treatment of Adverse Effects

As for Local Anaesthetics in general, p.1303.

Cocaine overdosage. In the emergency management of overdosage with cocaine the general aims are to establish adequate ventilation and support the circulation. If oral ingestion of a large amount is suspected the stomach should be emptied and activated charcoal administered.[1] A tourniquet may be applied to limit absorption if the drug was injected. Patients who have swallowed packages containing cocaine for the purpose of smuggling, may be given laxatives but surgical intervention may be required if signs of toxicity appear.[2]

Sedation with intravenous diazepam may be sufficient to manage the symptoms of cocaine overdose. Sedation with benzodiazepines may also be appropriate initial therapy for hypertension or tachyarrhythmias since the excessive sympathetic tone is largely centrally mediated.[3] Severe life-threatening arrhythmias may require treatment with intravenous propranolol although, following a report of paradoxical hypertension presumably due to unopposed α-adrenergic stimulation, a beta blocker with both α- and β-adrenergic effects such as labetalol is preferred by some if hypertension is also present;[2,4] sodium nitroprusside[3,4] or phentolamine[3,5] may also be used. Although labetalol can reduce the hypertension it does not alleviate cocaine-induced coronary vasoconstriction;[6] it has therefore been suggested that glyceryl trinitrate would be preferable for patients with cocaine-induced chest pain.[5,6] Calcium-channel blockers such as verapamil may also be of use as an antagonist for coronary artery vasoconstriction induced by cocaine.[5] There is concern about the use of lignocaine [lidocaine] for the treatment of cocaine-induced arrhythmias as lignocaine [lidocaine] may enhance toxicity.[5] Diazepam should be used to manage seizures[1,4] but if they cannot be controlled phenytoin can be used as an adjunct.[1] Hyperthermia should be treated with physical cooling but the use of dantrolene may also be necessary.[1] Control of anxiety and agitation with benzodiazepines when combined with rapid cooling may also have the effect of decreasing heat production in hyperthermic patients.[3] Metabolic acidosis should be monitored and treated where necessary.[1,4] Short-acting barbiturates or benzodiazepines may be used for dysphoric agitation but drugs that lower the seizure threshold or aggravate hyperthermia such as phenothiazines or haloperidol should be avoided.[1]

1. Loper KA. Clinical toxicology of cocaine. *Med Toxicol Adverse Drug Exp* 1989; **4:** 174–85.
2. Ramrakha P, Barton I. Drug smuggler's delirium. *BMJ* 1993; **306:** 470–1.
3. Anonymous. Acute reactions to drugs of abuse. *Med Lett Drugs Ther* 1996; **38:** 43–6.
4. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115:** 665–75.
5. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995; **333:** 1267–72.
6. Boehrer JD, *et al.* Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. *Am J Med* 1993; **94:** 608–10.

Withdrawal. Cocaine can produce psychological dependence but does not produce a major physical withdrawal syndrome. The management of cocaine abuse and dependence has been reviewed.[1-3] There is no advantage to gradual withdrawal and it is best for the patient to discontinue the drug abruptly.[1,4] The three major psychiatric complications associated with cocaine withdrawal are dysphoric agitation, severe depression, and psychotic symptoms.[1] Such complications are initially managed with psychosocial treatments. However patients with more severe dependence or those who fail to respond to psychosocial treatments should be considered for drug therapies. Dysphoric agitation is best treated with diazepam; propranolol may also be used in more persistent cases. Depressive symptoms during the acute post-cocaine phase are usually transient and require no treatment other than close observation. Desipramine has

been used with equivocal results; it appears to be of most benefit in patients who have antecedent or consequent symptoms of severe depression.[3] Trazodone and imipramine have also been tried but had more adverse effects than desipramine.[3] Antipsychotics such as chlorpromazine, haloperidol, and promazine have been used successfully to manage patients with psychotic symptoms associated with cocaine dependence.[1]

Several drugs have been tried in the maintenance of abstinence from cocaine.[1] Lithium may be useful in patients with bipolar disorder or cyclothymic personality. Methylphenidate may be helpful in patients with attention deficit disorders but has potential for abuse itself. Phenothiazine derivatives have been tried in the control of impulsive behaviour and to decrease cocaine craving, although adverse effects may limit their acceptability. Carbamazepine has been reported to suppress the craving for cocaine although this has not been supported by subsequent trials.[3] Buprenorphine has been investigated to suppress cocaine and opioid use in patients dependent on both drugs.[3] Anxiolytics or antidepressants are considered unlikely to be of benefit in maintaining abstinence.[3] MAOIs such as phenelzine have been used in a manner analogous to the use of disulfiram in alcohol abuse to provoke unpleasant reactions if patients relapse.[5]

There is evidence to suggest that cocaine use affects the dopaminergic modulation of CNS function, and several drugs that interact with the dopamine system have been tried in the treatment of cocaine abuse and dependence, but with mixed results.[3]

1. Arif A, ed. *Adverse health consequences of cocaine abuse.* Geneva: WHO, 1987.
2. Kleber HD. Pharmacotherapy, current and potential, for the treatment of cocaine dependence. *Clin Neuropharmacol* 1995; **18** (suppl 1): S96–S109.
3. Mendelson JH, Mello NK. Management of cocaine abuse and dependence. *N Engl J Med* 1996; **334:** 965–72.
4. DoH. *Drug misuse and dependence: guidelines on clinical management.* London: HMSO, 1999.
5. Brewer C. Cocaine and crakk. *BMJ* 1989; **299:** 792.

Precautions

As for Local Anaesthetics in general, p.1303.

Since some patients have a marked sensitivity to cocaine the administration of a test dose before use on mucous membranes has been suggested. Cocaine should not be applied to damaged mucosa because of the risk of systemic toxicity from enhanced absorption. Ophthalmic preparations of cocaine should not be applied to the eyes for prolonged periods as damage to the cornea may occur not only from the local action of cocaine, but also from loss of the protective eyelid reflexes. As with other mydriatics, there is also a risk of cocaine precipitating angle-closure glaucoma in patients predisposed to the condition. Patients receiving cocaine for surface anaesthesia should be monitored for possible cardiovascular effects. Cocaine should be used with great caution in patients with hypertension, cardiovascular disease, or thyrotoxicosis. It is not recommended for use during pregnancy or breast feeding.

Abuse. Cocaine is subject to abuse. See under Adverse Effects, above.

Gilles de la Tourette's syndrome. Gilles de la Tourette's syndrome, which had been well controlled for 10 years by haloperidol, was precipitated in a 27-year-old man following intranasal use of cocaine on one occasion.[1]

1. Mesulam M-M. Cocaine and Tourette's syndrome. *N Engl J Med* 1986; **315:** 398.

Myasthenia gravis. Report of a patient in whom cocaine abuse first unmasked and then exacerbated myasthenia gravis.[1]

1. Berciano J, *et al.* Myasthenia gravis unmasked by cocaine abuse. *N Engl J Med* 1991; **325:** 892.

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

Interactions

For interactions associated with local anaesthetics, see p.1303.

Cocaine and adrenaline [epinephrine] enhance each other's sympathomimetic effects and should preferably not be used in association. Caution is needed if cocaine is used with other drugs that may also potentiate the action of catecholamines such as guanethidine or MAOIs.

Adrenaline [epinephrine]. In a report[1] of 3 cases of arrhythmias associated with the use of a paste containing cocaine 25% and adrenaline [epinephrine] 0.18% for local anaesthesia of the nasal mucosa, the amount of cocaine applied to the nasal mucosa ranged from about 2.5 to 4.5 mg per kg body-weight. The maximum recommended dose of cocaine alone in healthy adults is 1.5 mg per kg.

1. Nicholson KEA, Rogers JEG. Cocaine and adrenaline paste: a fatal combination? *BMJ* 1995; **311:** 250–1.

Alcohol. In the presence of alcohol, cocaine is metabolised to its ethyl homologue cocaethylene.[1] Cocaethylene appears to have the same stimulant effects as cocaine but it has a longer half-life and *animal* studies suggest that it is more toxic than the parent drug.

1. Randall T. Cocaine, alcohol mix in body to form even longer lasting, more lethal drug. *JAMA* 1992; **267:** 1043–4.

Beta blockers. *Propranolol* potentiated cocaine-induced coronary vasoconstriction following intranasal administration of cocaine in a placebo-controlled study.[1] Because of a possible risk of paradoxical hypertension associated with the use of propranolol to manage arrhythmias associated with cocaine overdosage some prefer the use of labetalol for this indication (see under Treatment of Adverse Effects, above).

1. Lange RA, *et al.* Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. *Ann Intern Med* 1990; **112:** 897–903.

Haloperidol. For the effect of cocaine on haloperidol, see under Chlorpromazine, p.665.

Pharmacokinetics

Cocaine may be slowly absorbed from some sites because of the vasoconstriction it produces, but absorption occurs from all sites of application, including mucous membranes and the gastrointestinal tract, and may be enhanced when there is inflammation. Cocaine is rapidly absorbed when smoked.

Cocaine is rapidly metabolised by plasma esterases and hepatic esterases to ecgonine methyl ester. Benzoylecgonine, another major metabolite of cocaine, may be produced by spontaneous hydrolysis. Cocaine is also demethylated to the active metabolite norcocaine which is not excreted but undergoes further metabolism. There is considerable interindividual variation in the plasma half-life of cocaine possibly due to differences in esterase activity.

Cocaine and its metabolites are excreted in the urine, approximately 10% appearing as unchanged drug; they may be detectable in urine for several days or even weeks after administration. Cocaine crosses the blood-brain barrier and accumulates within the CNS. It does not appear to undergo rapid metabolism within the brain and concentrations in the CNS following acute intoxication may greatly exceed those in plasma.

Cocaine crosses the placenta and the presence of its metabolites in neonatal hair has been used to indicate intra-uterine exposure. Cocaine is distributed into breast milk.

See also under Local Anaesthetics, p.1303.

◊ References.

1. Busto U, *et al.* Clinical pharmacokinetics of non-opiate abused drugs. *Clin Pharmacokinet* 1989; **16:** 1–26.
2. Graham K, *et al.* Determination of gestational cocaine exposure by hair analysis. *JAMA* 1989; **262:** 3328–30.
3. Burke WM, Ravi NV. Urinary excretion of cocaine. *Ann Intern Med* 1990; **112:** 548–9.
4. Ravi NV, Burke WM. Cocaine and traffic accident fatalities in New York City. *JAMA* 1990; **263:** 2887.
5. Schenker S, *et al.* The transfer of cocaine and its metabolites across the term human placenta. *Clin Pharmacol Ther* 1993; **53:** 329–39.

Absorption. Cocaine is rapidly absorbed from the pulmonary vasculature when smoked and the speed of onset of its effects is similar to that obtained after intravenous injection.[1] Absorption from mucous membranes is delayed by vasoconstriction and peak plasma concentrations of up to 474 nanograms per mL have been obtained 15 to 120 minutes after application of doses of 1.5 to 2 mg per kg body-weight to the nasal mucosa as a 10% cocaine hydrochloride solution;[2,3] cocaine may still be detectable in the nose several hours later and this may result in prolonged systemic absorption.[2] In one study it was estimated that only 5% of the total dose of cocaine hydrochloride used prior to nasal surgery was absorbed from the nasal mucosa following application of 500 mg of cocaine hydrochloride as a 25% paste with adrenaline [epinephrine] or 200 mg as a 10% solution with adrenaline [epinephrine] (Moffett's solution) and blood concentrations were well below those associated with toxicity[4] (but see also Adrenaline [epinephrine], under Interactions, above). Peak serum concentrations of cocaine have been obtained after 50 to 90 minutes following oral administration and are similar to those obtained after nasal application.[3]

1. Farrar HC, Kearns GL. Cocaine: clinical pharmacology and toxicology. *J Pediatr* 1989; **115:** 665–75.
2. Van Dyke C, *et al.* Cocaine: plasma concentrations after intranasal application in man. *Science* 1976; **191:** 859–61.
3. Van Dyke C, *et al.* Oral cocaine: plasma concentrations and central effects. *Science* 1978; **200:** 211–13.
4. Quiney RE. Intranasal topical cocaine: Moffett's method or topical cocaine paste? *J Laryngol Otol* 1986; **100:** 279–83.

Uses and Administration

Cocaine, a benzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p.1304. It is used as a surface anaesthetic but, because of systemic adverse effects and its abuse potential, its use is now almost entirely restricted to surgery of the ear, nose, and throat. It has been largely replaced by other drugs in ophthalmology because of its corneal toxicity, although it may still be useful in removal or debridement of the corneal epithelium. Cocaine also blocks the uptake of catecholamines at adrenergic nerve endings and potentiates the action of catecholamines. Its sympathomimetic actions cause tachycardia, peripheral vasoconstriction, a rise in blood pressure, and mydriasis. The use of cocaine in association with drugs such as adrenaline [epinephrine] increases the risk of cardiac arrhythmias. Despite this hazard some use this combination in otolaryngology to improve the operative field and reduce absorption.

When applied to mucous membranes, surface anaesthesia develops rapidly and persists for 30 minutes or longer depending on the concentration of cocaine used, the dose, and on the vascularity of the tissue.

Cocaine hydrochloride is used for the administration of cocaine in aqueous solutions. Solutions containing up to 4% have been used in ophthalmology (but see Precautions, above).

Solutions containing up to 10% of cocaine are applied to the nasal mucosa in otolaryngological procedures. Pastes containing up to 25% of cocaine have also been applied.

In order to avoid systemic effects, the usual maximum total dose recommended for application to the nasal mucosa in healthy adults is 1.5 mg per kg bodyweight. It should be used only by those skilled in the precautions needed to minimise absorption and the consequent risk of arrhythmias.

Cocaine was used in conjunction with diamorphine or morphine for the relief of severe pain, especially in terminal illness, but this use is now obsolete.

Cocaine solutions should *never* be administered by injection; other local anaesthetics are equally effective and much safer.

◊ References.

1. Middleton RM, Kirkpatrick MB. Clinical use of cocaine: a review of the risks and benefits. *Drug Safety* 1993; **9:** 212–17.
2. Latorre F, Klimek L. Does cocaine still have a role in nasal surgery? *Drug Safety* 1999; **20:** 9–13.

Preparations

USP 25: Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Cocaine Hydrochloride Tablets for Topical Solution.

Diperodon Hydrochloride (7624-w)

Diperodon Hydrochloride (*BANM, rINNM*).

Diperocaine Hydrochloride. 3-Piperidinopropylene bis(phenylcarbamate) hydrochloride.

$C_{22}H_{27}N_3O_4.HCl = 433.9$.

CAS — 101-08-6 (anhydrous diperodon); 51552-99-9 (diperodon monohydrate); 537-12-2 (diperodon hydrochloride).

Profile

Diperodon is a local anaesthetic (p.1302) that has been used as the base or the hydrochloride for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: *USA:* A-Caine†; Bactine First Aid Antibiotic Plus Anesthetic†.

Dyclonine Hydrochloride (7625-e)

Dyclonine Hydrochloride (*BANM, rINNM*).

Dyclocaine Hydrochloride; Dyclocaini Chloridum. 4′-Butoxy-3-piperidinopropiophenone hydrochloride.

$C_{18}H_{27}NO_2.HCl = 325.9$.

CAS — 586-60-7 (dyclonine); 536-43-6 (dyclonine hydrochloride).

Pharmacopoeias. In *US.*

Pharmacopoeial description

USP 25: White crystals or white crystalline powder, with a slight odour. Soluble 1 in 60 of water, 1 in 24 of alcohol, and 1 in 2.3 of chloroform; soluble in acetone; practically insoluble in ether and in hexane. A 1% solution in water has a pH of 4.0 to 7.0. Store in airtight containers. Protect from light.

Profile

Dyclonine hydrochloride is a local anaesthetic (p.1302) used topically for surface anaesthesia of the skin and mucous membranes in concentrations of 0.5 or 1%. Single doses in excess of 200 mg should generally not be used. Lozenges containing up to 3 mg have been used for the temporary relief of pain associated with sore throats or mouth irritation. It may cause irritation at the site of application and should not be given by injection or used in the eyes.

Preparations

USP 25: Dyclonine Hydrochloride Gel; Dyclonine Hydrochloride Topical Solution.

Proprietary Preparations (details are given in Part 3)
Canad.: Sucrets; Sucrets for Kids; *Israel:* Childrens Cherry Sucrets; Sucrets Children's Formula; Sucrets Maximum Strength; *USA:* Dyclone; Sucrets.

Multi-ingredient: *Canad.:* Skin Shield†; Tanac; *USA:* Cepacol Maximum Strength Sore Throat; Skin Shield; Tanac.

Ethyl Chloride (3108-b)

hylium Chloratum; Chlorethyl; Cloruro de Etilo; Ethylis ..loridum; Hydrochloric Ether; Monochlorethane. Chloroethane.

C_2H_5Cl = 64.51.
CAS — 75-00-3.
ATC — N01BX01.
Pharmacopoeias. In *Aust., Belg., Br., Pol.,* and *US.*

Pharmacopoeial description

BP 2001: Gaseous at ambient temperatures and pressures, but usually compressed to a colourless, mobile, flammable, and very volatile liquid, with an ethereal odour. If prepared from Industrial Methylated Spirit it may contain a small variable proportion of methyl chloride. Distillation range 12° to 12.5°. Slightly soluble in water; miscible with alcohol and with ether. The residual liquid from a solution in water after the ethyl chloride has evaporated is neutral to litmus. Store at a temperature not exceeding 20°. Protect from light.

USP 25: A colourless, mobile, very volatile liquid at low temperatures or under pressure, with a characteristic ethereal odour. B.p. 12° to 13°. Slightly soluble in water; freely soluble in alcohol and in ether. Store in airtight containers, preferably hermetically sealed.

◊ CAUTION. Ethyl chloride is highly flammable and mixtures of the gas with 5 to 15% of air are explosive.

Adverse Effects and Precautions

As for Chloroform, p.1257.

Cutaneous sensitisation can occur rarely. Thawing of frozen tissue following surgery may be painful and prolonged spraying onto the skin can cause chemical frostbite. Freezing may distort the histological structure of biopsy specimens. ..l chloride should not be applied to broken skin or mucous membranes.

Uses and Administration

Owing to its low boiling-point and the intense cold produced by evaporation, ethyl chloride has been used as a local anaesthetic in minor surgery but such use is not generally recommended. It has also been used topically for the relief of pain. Ethyl chloride was formerly used as an inhalational anaesthetic but has no place in modern anaesthetic practice.

Preparations

Proprietary Preparations (details are given in Part 3)
Denm.: Kloraetyl; *Ger.:* Chloraethyl "Dr Henning"; Holsten aktiv†; WariActiv; *Hong Kong:* WariActiv; *Mex.:* Traumazol; *Spain:* Cloretilo Chemirosa; *Switz.:* Chlorethyl; *UK:* Cryogesic.

Multi-ingredient: *Ger.:* Olbas; *Spain:* Talgo Odontalgico†; *USA:* Fluro-Ethyl.

Ethyl *p*-Piperidinoacetylaminobenzoate

(8638-n)

EPAB; SA-7. 4-[(1-Piperidinylacetyl)amino]benzoic acid ethyl ester.

$C_{16}H_{22}N_2O_3$ = 290.4.
CAS — 41653-21-8.

Profile

Ethyl *p*-piperidinoacetylaminobenzoate is an amide local anaesthetic (p.1302) that has been given by mouth for the symptomatic relief of gastritis.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Sulcain.

Multi-ingredient: *Hong Kong:* Sulcain; *Singapore:* Sulcain; *Thai.:* Sulcain.

Etidocaine Hydrochloride (7626-l)

Etidocaine Hydrochloride *(BANM, rINNM).*
W-19053. (±)-2-(*N*-Ethylpropylamino)butyro-2',6'-xylidide hydrochloride.
$C_{17}H_{28}N_2O,HCl$ = 312.9.
CAS — 36637-18-0 (etidocaine); 36637-19-1 (etidocaine hydrochloride).

NOTE. Etidocaine is *USAN.*

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1302.

Effects on the cardiovascular system. For a discussion of the cardiotoxicity of etidocaine, see under the Adverse Effects of Bupivacaine Hydrochloride, p.1306.

Porphyria. Etidocaine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals.*

Interactions

For interactions associated with local anaesthetics, see p.1303.

Pharmacokinetics

Etidocaine is rapidly absorbed into the circulation after parenteral injection and is about 95% bound to plasma proteins. It crosses the placenta but the ratio of fetal to maternal concentrations is relatively low. It also diffuses across the blood-brain barrier. Etidocaine is metabolised in the liver and its numerous metabolites are excreted in the urine; less than 10% of the drug is excreted unchanged. The plasma elimination half-life of etidocaine is 2 to 3 hours in adults.

See also under Local Anaesthetics, p.1303.

Pregnancy. Following maternal injection etidocaine rapidly crosses the placenta[1] but the degree of transfer is less than for other local anaesthetics including bupivacaine.[2] The ratio of fetal to maternal concentrations of etidocaine varies but values up to about 0.35 are usual.[1,2] Some metabolites appear to be transferred to a greater degree than the parent compound[1]. Etidocaine is highly protein bound but the fraction of unbound drug in plasma increases in pregnant women during delivery.[1] Protein binding of etidocaine is also reduced in fetal plasma.[3] Although neonates are able to metabolise etidocaine it appears that they are less able to do so than adults; a mean elimination half-life of 6.42 hours has been reported in neonates.[3]

1. Morgan DJ, *et al.* Disposition and placental transfer of etidocaine in pregnancy. *Eur J Clin Pharmacol* 1977; **12:** 359–65.
2. Poppers PJ. Evaluation of local anaesthetic agents for regional anaesthesia in obstetrics. *Br J Anaesth* 1975; **47:** 322–7.
3. Morgan D, *et al.* Pharmacokinetics and metabolism of the anilide local anaesthetics in neonates: 11: etidocaine. *Eur J Clin Pharmacol* 1978; **13:** 365–71.

Uses and Administration

Etidocaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p.1304. It has a rapid onset and a long duration of action. Etidocaine is used for infiltration anaesthesia, peripheral nerve block, and epidural block, usually with adrenaline [epinephrine] 1 in 200 000. (Local anaesthetic techniques are discussed on p.1304.)

The dose of etidocaine hydrochloride varies with the site of injection and the **local anaesthetic technique** being used. The **maximum single dose** should not generally exceed 300 mg when given without adrenaline [epinephrine], or 400 mg when given with adrenaline [epinephrine]. Generally, additional incremental doses may be administered every 2 to 3 hours.

For *infiltration anaesthesia* a 0.5% solution of etidocaine hydrochloride may be used in a dose of 5 to 400 mg (1 to 80 mL). For dentistry a dose of 15 to 75 mg (1 to 5 mL) may be given as a 1.5% solution. For *peripheral nerve blocks* a 0.5% solution may be used in a dose of 25 to 400 mg (5 to 80 mL) or a 1% solution in a dose of 50 to 400 mg (5 to 40 mL). For *retrobulbar block* a 1% solution may be used in a dose of 20 to 40 mg (2 to 4 mL) or a 1.5% solution in a dose of 30 to 60 mg (2 to 4 mL).

When given by *epidural injection* etidocaine hydrochloride produces a profound degree of motor blockade and although the degree of abdominal muscle relaxation produced may be desirable in some obstetrical procedures it makes this drug unsuitable for use in vaginal deliveries. A dose of 100 to 300 mg (10 to 30 mL) may be injected as a 1% solution or 150 to 300 mg (10 to 20 mL) as a 1.5% solution for *lumbar epidural block* prior to surgery, including caesarean section. Lower doses of 50 to 150 mg (10 to 30 mL) as a 0.5% solution or 50 to 200 mg (5 to 20 mL) as a 1% solution are suggested for gynaecological procedures. For *caudal anaesthesia* 50 to 150 mg (10 to 30 mL) as a 0.5% solution or 100 to 300 mg (10 to 30 mL) as a 1% solution may be given.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Duranest†; *Fr.:* Duranest; *Ger.:* Duranest†; *USA:* Duranest.

Ketocaine Hydrochloride (12882-b)

Ketocaine Hydrochloride *(rINNM).*
Chetocaina Cloridrata. 2'-(2-Di-isopropylaminoethoxy)butyrophenone hydrochloride.
$C_{18}H_{29}NO_2,HCl$ = 327.9.
CAS — 1092-46-2 (ketocaine); 1092-47-3 (ketocaine hydrochloride).

Profile

Ketocaine hydrochloride is a local anaesthetic (p.1302) that has been used as a surface anaesthetic in suppositories or ointments for anorectal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Ital.:* Proctolyn.

Levobupivacaine (17525-d)

Levobupivacaine *(BAN, rINN).*
S(−)-Bupivacaine; Levobupivacaina; Lévobupivacaïne. (*S*)-1-Butyl-2-piperidylformo-2',6'-xylidide.
$C_{18}H_{28}N_2O$ = 288.4.
CAS — 27262-47-1.
ATC — N01BB10.

Levobupivacaine Hydrochloride (675-e)

Levobupivacaine Hydrochloride *(BANM, USAN, rINNM).*
$C_{18}H_{28}N_2O,HCl$ = 324.9.
CAS — 27262-48-2.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1302.

Levobupivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics. The 0.75% solution is contra-indicated for epidural block in obstetrics.

Effects on the cardiovascular system. It has been suggested[1] that levobupivacaine may have a lower risk of causing cardiotoxicity than bupivacaine (for the effects of bupivacaine on the cardiovascular system see p.1306).

1. Mather LE, Chang DH. Cardiotoxicity with modern local anaesthetics: is there a safer choice? *Drugs* 2001; **61:** 333–42.

Interactions

For interactions associated with local anaesthetics, see p.1303. Plasma concentrations of levobupivacaine may be reduced by enzyme-inducing drugs such as rifampicin. Levobupivacaine is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP1A2 and there is a theoretical possibility that substrates for or inhibitors of these isoenzymes may adversely alter plasma concentrations of levobupivacaine.

Pharmacokinetics

The pharmacokinetics of levobupivacaine are similar to those of the racemic form, bupivacaine (p.1307). Levobupivacaine is at least 97% bound to plasma proteins. After intravenous administration the mean half-life is about 80 minutes. Levobupivacaine is extensively metabolised and excreted as its metabolites mainly in the urine, with smaller amounts appearing in the faeces. 3-Hydroxylevobupivacaine is a major metabolite and its formation is mediated by the cytochrome P450 isoenzyme CYP1A2; CYP3A4 is also involved in the metabolism of levobupivacaine.

Uses and Administration

Levobupivacaine is a local anaesthetic of the amide type with actions and uses similar to those described on p.1304. It is the S-enantiomer of bupivacaine (p.1306). Levobupivacaine is given as the hydrochloride for infiltration anaesthesia and regional nerve blocks including epidural block; however it is contra-indicated for obstetric paracervical block and for use in intravenous regional anaesthesia (Bier's block). The 0.75% solution is contra-indicated for epidural blocks in obstetrics. (Local anaesthetic techniques are discussed on p.1304.)

Levobupivacaine hydrochloride is available in solutions containing the equivalent of 0.25 to 0.75% of levobupivacaine. The dosage depends on the site of injection and the procedure used as well as the status of the patient. The recommended **maximum single** dose is 150 mg. The total daily dose should not exceed 400 mg. A test dose of a suitable local anaesthetic, preferably with adrenaline [epinephrine], should be given before commencing epidural block with levobupivacaine to detect inadvertent intravascular administration. Subsequent doses of levobupivacaine should be given in small increments.

For **surgical anaesthesia** doses of levobupivacaine for *epidural block* are 50 to 100 mg (10 to 20 mL) as a 0.5% solution, or 75 to 150 mg (10 to 20 mL) as a 0.75% solution; for caesarean section, doses are 75 to 150 mg (15 to 30 mL) as a 0.5% solution. The dose for *spinal block* is 15 mg (3 mL) as a 0.5% solution. For *peripheral nerve blocks*, doses are 2.5 to 150 mg as a 0.25 or 0.5% solution; a volume of 40 mL should not be exceeded. Alternatively doses for peripheral block may be expressed on the basis of body-weight: 1 to 2 mg per kg body-weight (0.4 mL per kg) as a 0.25 or 0.5% solution. For *infiltration anaesthesia* up to 150 mg (60 mL) as a 0.25% solution may be used. For peribulbar block in *ophthalmic* procedures 37.5 to 112.5 mg (5 to 15 mL) as a 0.75% solution may be given. For ilioinguinal or iliohypogastric blocks in **children** under 12 years of age, doses of levobupivacaine are 1.25 to 2.5 mg per kg (0.25 to 0.5 mL per kg) as a 0.25 or 0.5% solution.

In the management of **acute pain** it may be given as an epidural bolus or by continuous infusion. For pain relief during *labour* 15 to 50 mg (6 to 20 mL) as a 0.25% solution is given as a bolus. Alternatively a 0.125% solution may be given as an infusion in a dose of 5 to 12.5 mg (4 to 10 mL) per hour. For *postoperative pain* 10 to 25 mg (4 to 10 mL) per hour as a 0.25% solution or 12.5 to 18.75 mg (10 to 15 mL) per hour as a 0.125% solution may be given as an epidural infusion. When necessary, dilutions should be made with sodium chloride 0.9%.

◊ Reviews

1. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. *Drugs* 2000; **59:** 551–79.

Action. A comparison[1] of epidural bupivacaine with levobupivacaine in women in labour found that levobupivacaine had 98% of the potency of the racemate, a clinically insignificant difference. However it was pointed out that whereas the concentration of bupivacaine solutions was expressed in terms of the hydrochloride, solutions of levobupivacaine had their strength expressed in terms of the free base. When calculations were made in terms of molar equivalents levobupivacaine appeared to be 13% less potent then racemic bupivacaine. The difference in expression should be borne in mind when evaluating comparative studies.

1. Lyons G, *et al.* Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. *Br J Anaesth* 1998; **81:** 899–901.

Preparations

Proprietary Preparations (details are given in Part 3)

Neth.: Chirocaine; *Swed.:* Chirocaine; *UK:* Chirocaine; *USA:* Chirocaine.

Lignocaine (7602-b)

Lignocaine *(BAN)*.

Lidocaine *(BAN, rINN)*; Lidocainum. 2-Diethylaminoaceto-2',6'-xylidide.

$C_{14}H_{22}N_2O$ = 234.3.

CAS — 137-58-6.

ATC — C01BB01; C05AD01; D04AB01; N01BB02; R02AD02; S01HA07; S02DA01.

Pharmacopoeias. In *Eur.* (see p.vi), *Int.*, *Jpn*, and *US.*

Lignocaine [lidocaine] forms a mixture with prilocaine that has a melting-point lower than that of either ingredient. This eutectic mixture is used in the preparation of topical dosage forms.

Pharmacopoeial description

Ph. Eur.: A white or almost white, crystalline powder. M.p. 66° to 70°. Practically insoluble in water; very soluble in alcohol and in dichloromethane; freely soluble in ether.

USP 25: A white to slightly yellow crystalline powder with a characteristic odour. M.p. 66° to 69°. Practically insoluble in water; very soluble in alcohol and in chloroform; freely soluble in ether and in benzene; dissolves in oils.

Lignocaine Hydrochloride (7601-m)

Lignocaine Hydrochloride *(BANM)*.

Lidocaine Hydrochloride *(BANM, rINNM)*; Lidocaini Hydrochloridum; Lignoc. Hydrochlor.

$C_{14}H_{22}N_2O.HCl.H_2O$ = 288.8.

CAS — 73-78-9 (anhydrous lignocaine [lidocaine] hydrochloride); 6108-05-0 (lignocaine [lidocaine] hydrochloride monohydrate).

NOTE. LIDFLN is a code approved by the BP 2001 for use on single unit doses of eye drops containing lignocaine [lidocaine] hydrochloride and fluorescein sodium where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vi), *Int.*, *Pol.*, and *US.*

Lignocaine [lidocaine] hydrochloride monohydrate 1.23 g or anhydrous lignocaine [lidocaine] hydrochloride 1.16 g is approximately equivalent to 1 g of lignocaine [lidocaine].

Pharmacopoeial description

Ph. Eur.: A white crystalline powder. M.p. 74° to 79°. Very soluble in water; freely soluble in alcohol; practically insoluble in ether. A 0.5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 25: A white, odourless, crystalline powder. M.p. 74° to 79°. Very soluble in water and in alcohol; soluble in chloroform; insoluble in ether.

Incompatibility. Lignocaine [lidocaine] hydrochloride has been reported to be incompatible in solution with amphotericin B,[1] sulfadiazine sodium,[2] methohexital sodium,[2] cefazolin sodium,[3] or phenytoin sodium.[4]

Acid stable drugs such as adrenaline [epinephrine] hydrochloride, noradrenaline [norepinephrine] acid tartrate, or isoprenaline may begin to deteriorate within several hours of admixture with lignocaine [lidocaine] hydrochloride as lignocaine [lidocaine] solutions may raise the pH of the final solution above the maximum pH for their stability. Such extemporaneous mixtures should be used promptly after preparation.[5]

1. Whiting DA. Treatment of chromoblastomycosis with high local concentrations of amphotericin B. *Br J Dermatol* 1967; **79:** 345–51.
2. Riley BB. Incompatibilities in intravenous solutions. *J Hosp Pharm* 1970; **28:** 228–40.
3. Kleinberg ML, *et al.* Stability of antibiotics frozen and stored in disposable hypodermic syringes. *Am J Hosp Pharm* 1980; **37:** 1087–8.
4. Kirschenbaum HL, *et al.* Stability and compatibility of lidocaine hydrochloride with selected large-volume parenterals and drug additives. *Am J Hosp Pharm* 1982; **39:** 1013–15.
5. Parker EA. Xylocaine hydrochloride 2% injection. *Am J Hosp Pharm* 1971; **28:** 805.

pH of solutions. For the effect pH has on the surface tension and administration of lignocaine [lidocaine] solutions by infusion, see under Administration in Uses and Administration, p.1304. For its effect on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1304.

Stability. Although there was no decrease in the lignocaine [lidocaine] content of lignocaine [lidocaine] hydrochloride and adrenaline [epinephrine] injection during transport and storage under tropical conditions, the content of adrenaline [epinephrine] fell to almost zero in some samples after several months; supply of the injection as a dry powder and separate solvent should be considered for the tropics.[1]

The lignocaine [lidocaine] content of buffered cardioplegic solutions has been reported[2] to decrease when stored in PVC containers at ambient temperature, but not when stored at 4°. This loss appeared to result from pH-dependent sorption of lignocaine [lidocaine] onto the plastic and did not occur when lignocaine [lidocaine] solutions were stored in glass bottles.

1. Abu-Reid IO, *et al.* Stability of drugs in the tropics: a study in Sudan. *Int Pharm J* 1990; **4:** 6–10.
2. Lackner TE, *et al.* Lidocaine stability in cardioplegic solution stored in glass bottles and polyvinyl chloride bags. *Am J Hosp Pharm* 1983; **40:** 97–101.

Adverse Effects and Treatment

As for Local Anaesthetics in general, p.1302.

Effects on the CNS. A report[1] of suspected psychotic reactions associated with the use of lignocaine [lidocaine] in 6 patients given intravenous lignocaine [lidocaine] for the treatment of cardiac disorders.

1. Turner WM. Lidocaine and psychotic reactions. *Ann Intern Med* 1982; **97:** 149–50.

Effects on the skin. Erythema and pigmentation of the upper lip in a child following local dental infiltration of lignocaine [lidocaine] was attributed to a type of fixed drug eruption.[1] Erythema may also occur after topical administration of some lignocaine [lidocaine] formulations, such as transdermal patches, while transient blanching of the skin is frequent after application of eutectic lignocaine [lidocaine]/prilocaine mixtures to the skin.[2]

True hypersensitivity reactions, including dermatitis, are rare (see also p.1302) but can occur.[3]

1. Curley RK, *et al.* An unusual cutaneous reaction to lignocaine. *Br Dent J* 1987; **162:** 113–14.
2. Villada G, *et al.* Local blanching after epicutaneous application of EMLA cream: a double-blind randomized study among 50 healthy volunteers. *Dermatologica* 1990; **181:** 38–40.
3. Bircher AJ, *et al.* Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests. *Contact Dermatitis* 1996; **34:** 387–9.

Overdosage. The most serious effects of lignocaine [lidocaine] intoxication are on the CNS and cardiovascular system and overdosage can result in severe hypotension, asystole, bradycardia, apnoea, seizures, coma, cardiac arrest, respiratory arrest, and death. Intoxication with lignocaine [lidocaine] is relatively common and can occur as a result of acute overdosage following poor control of intravenous maintenance infusions or after accidental injection of concentrated solutions. However, it more commonly results from inadvertent intravascular administration during regional anaesthesia, or from too rapid injection of antiarrhythmic doses, particularly in patients with circulatory insufficiency, or when clearance is reduced due to heart failure, liver disease, old age, or through interaction with other drugs.[1] Seizures have also been reported after excessive doses administered subcutaneously.[2] Although the bioavailability of lignocaine [lidocaine] is low it may be sufficient to result in significant toxicity when swallowed[1] and there have been reports of CNS toxicity, seizures, and death in children[3-7] and adults[8-10] following the ingestion of topical solutions and after the use of viscous preparations in the mouth. Death has also ensued after gargling with a 4% lignocaine [lidocaine] solution.[11] Lignocaine [lidocaine] is absorbed from mucous membranes and serious toxicity has been reported after urethral[12] or rectal[13] instillation of lignocaine [lidocaine] preparations.

1. Denaro CP, Benowitz NL. Poisoning due to class 1B antiarrhythmic drugs: lignocaine, mexiletine and tocainide. *Med Toxicol Adverse Drug Exp* 1989; **4:** 412–28.
2. Pelter MA, *et al.* Seizure-like reaction associated with subcutaneous lidocaine injection. *Clin Pharm* 1989; **8:** 767–8.
3. Sakai RI, Lattin JE. Lidocaine ingestion. *Am J Dis Child* 1980; **134:** 323.
4. Rothstein P, *et al.* Prolonged seizures associated with the use of viscous lidocaine. *J Pediatr* 1982; **101:** 461–3.
5. Mofenson HC, *et al.* Lidocaine toxicity from topical mucosal application. *Clin Pediatr (Phila)* 1983; **22:** 190–2.
6. Giard MJ, *et al.* Seizures induced by oral viscous lidocaine. *Clin Pharm* 1983; **2:** 110.
7. Amitai Y, *et al.* Death following accidental lidocaine overdose in a child. *N Engl J Med* 1986; **314:** 182–3.
8. Parish RC, *et al.* Seizures following oral lidocaine for esophageal anesthesia. *Drug Intell Clin Pharm* 1985; **19:** 199–201.
9. Fruncillo RJ, *et al.* CNS toxicity after ingestion of topical lidocaine. *N Engl J Med* 1982; **306:** 426–7.
10. Geraets DR, *et al.* Toxicity potential of oral lidocaine in a patient receiving mexiletine. *Ann Pharmacother* 1992; **26:** 1380–1.
11. Zuberi BF, *et al.* Lidocaine toxicity in a student undergoing upper gastrointestinal endoscopy. *Gut* 2000; **46:** 435.
12. Dix VW, Tresidder GC. Collapse after use of lignocaine jelly for urethral anaesthesia. *Lancet* 1963; **i:** 890.
13. Pottage A, Scott DB. Safety of "topical" lignocaine. *Lancet* 1988; **i:** 1003.

Pregnancy. The overall effect of maternal epidural anaesthesia appears to be beneficial for the fetus (see under Labour Pain, p.6) but lignocaine [lidocaine] may have transient effects on the neonatal auditory system.[1]

1. Bozynski MEA, *et al.* Effect of prenatal lignocaine on auditory brain stem evoked response. *Arch Dis Child* 1989; **64:** 934–8.

Precautions

As for Local Anaesthetics in general, p.1303.

In general lignocaine [lidocaine] should not be given to patients with hypovolaemia, heart block or other conduction disturbances, and should be used with caution in patients with congestive heart failure, bradycardia, or respiratory depression. Lignocaine [lidocaine] is metabolised in the liver and must be given with caution to patients with hepatic insufficiency. The plasma half-life of lignocaine [lidocaine] may be prolonged in conditions that reduce hepatic blood flow such as cardiac and circulatory failure.

Metabolites of lignocaine [lidocaine] may accumulate in patients with renal impairment.

The intramuscular injection of lignocaine [lidocaine] may increase creatine phosphokinase concentrations that can interfere with the diagnosis of acute myocardial infarction.

Cerebrovascular disorders. Administration of lignocaine [lidocaine] 5 mg per kg body-weight by intravenous infusion over 30 minutes was associated with a 12% reduction in cerebral blood flow in healthy subjects although it returned to normal within 60 minutes.[1] Cerebral blood flow in patients with diabetes was lower than in healthy subjects, but was unaffected by lignocaine [lidocaine] infusion, indicating reduced cerebrovascular reactivity.

1. Kastrup J, *et al.* Intravenous lidocaine and cerebral blood flow: impaired microvascular reactivity in diabetic patients. *J Clin Pharmacol* 1990; **30:** 318–23.

Porphyria. Lignocaine [lidocaine] is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Renal impairment. The pharmacokinetics of lignocaine [lidocaine] and its metabolite monoethylglycinexylidide appear to be unaffected in patients with renal failure except that accumulation of the metabolite glycinexylidide may occur during infusions of 12 hours or more.[1] Data to predict the amount of lignocaine [lidocaine] and glycinexylidide removed during modialysis have been provided by several workers.[2,3] Lignocaine [lidocaine] does not appear to be removed during haemofiltration.[4]

1. Collinsworth KA, *et al.* Pharmacokinetics and metabolism of lidocaine in patients with renal failure. *Clin Pharmacol Ther* 1975; **18:** 59–64.
2. Gibson TP, Nelson HA. Drug kinetics and artificial kidneys. *Clin Pharmacokinet* 1977; **2:** 403–26.
3. Lee CC, Marbury TC. Drug therapy in patients undergoing haemodialysis: clinical pharmacokinetic considerations. *Clin Pharmacokinet* 1984; **9:** 42–66.
4. Saima S, *et al.* Negligible removal of lidocaine during arteriovenous hemofiltration. *Ther Drug Monit* 1990; **12:** 154–6.

Smoking. The effects of smoking on lignocaine [lidocaine] therapy are unclear. Studies in a limited number of patients have found reduced systemic bioavailability suggestive of induction of drug-metabolising activity[1] and an inconsistent effect on protein binding.[2,3]

1. Huet P-M, Lelorier J. Effects of smoking and chronic hepatitis B on lidocaine and indocyanine green kinetics. *Clin Pharmacol Ther* 1980; **28:** 208–15.
2. McNamara PJ, *et al.* Effect of smoking on binding of lidocaine to human serum proteins. *J Pharm Sci* 1980; **69:** 749–51.
3. Davis D, *et al.* The effects of age and smoking on the plasma protein binding of lignocaine and diazepam. *Br J Clin Pharmacol* 1985; **19:** 261–5.

Interactions

For interactions associated with local anaesthetics, see p.1303.

The clearance of lignocaine [lidocaine] may be reduced by propranolol and cimetidine (see below).

The cardiac depressant effects of lignocaine [lidocaine] are additive with those of beta blockers and of other antiarrhythmics including intravenous phenytoin; long-term administration of enzyme-inducers such as phenytoin may increase dosage requirements of lignocaine [lidocaine] (see below). Hypokalaemia produced by acetazolamide, loop diuretics, and thiazides antagonises the effect of lignocaine [lidocaine].

Antiarrhythmics. Lignocaine [lidocaine] toxicity, arising from the use of an oral preparation containing lignocaine [lidocaine], has been reported[1] in a patient who was receiving *mexiletine*. There are individual reports of seizures or heart failure and cardiac arrest in patients who received intravenous lignocaine [lidocaine] concomitantly with *ajmaline*,[2] *amiodarone*,[3,4] or *tocainide*.[5] Delirium has been reported in a patient who received lignocaine [lidocaine] together with *procainamide*.[6]

1. Geraets DR, *et al.* Toxicity potential of oral lidocaine in a patient receiving mexiletine. *Ann Pharmacother* 1992; **26:** 1380–1.
2. Bleifeld W. Side effects of antiarrhythmic drugs. *Naunyn Schmiedebergs Arch Pharmacol* 1971; **269:** 282–97.
3. Siegmund JB, *et al.* Amiodarone interaction with lidocaine. *J Cardiovasc Pharmacol* 1993; **21:** 513–15.
4. Keidar S, *et al.* Sinoatrial arrest due to lidocaine injection in sick sinus syndrome during amiodarone administration. *Am Heart J* 1982; **104:** 1384–5.
5. Forrence E, *et al.* A seizure induced by concurrent lidocaine-tocainide therapy—is it just a case of additive toxicity? *Drug Intell Clin Pharm* 1986; 20: 56–9.
6. Ilyas M, *et al.* Delirium induced by a combination of anti-arrhythmic drugs. *Lancet* 1969; **ii:** 1368–9.

Antiepileptics. Studies in healthy subjects and patients with epilepsy[1,2] suggest that long-term use of drugs such as *phenytoin* or *barbiturates* may increase dosage requirements for lignocaine [lidocaine] due to induction of drug-metabolising microsomal enzymes. Administration of phenytoin can also increase plasma concentrations of α_1-acid glycoprotein and thereby reduce the free fraction of lignocaine [lidocaine] in plasma.[3]

The cardiac depressant effects of lignocaine [lidocaine] may be dangerously enhanced by intravenous phenytoin.[4]

1. Heinonen J, *et al.* Plasma lidocaine levels in patients treated with potential inducers of microsomal enzymes. *Acta Anaesthesiol Scand* 1970; **14:** 89–95.
2. Perucca E, Richens A. Reduction of oral bioavailability of lignocaine by induction of first pass metabolism in epileptic patients. *Br J Clin Pharmacol* 1979; **8:** 21–31.
3. Routledge PA, *et al.* Lignocaine disposition in blood in epilepsy. *Br J Clin Pharmacol* 1981; **12:** 663–6.
4. Wood RA. Sinoatrial arrest: an interaction between phenytoin and lignocaine. *BMJ* 1971; **1:** 645.

Beta blockers. Significant increases in plasma-lignocaine [lidocaine] concentrations have occurred during concomitant therapy with *propranolol*[1–4] owing to a reduction in the clearance of lignocaine [lidocaine] from plasma. A similar interaction has been observed with *nadolol*[3] and *metoprolol*,[2] although in another study[5] metoprolol did not alter the pharmacokinetics of lignocaine [lidocaine]. The hepatic metabolism of lignocaine [lidocaine] may be reduced as a result of a fall in hepatic blood flow associated with reduced cardiac output or it may be caused by direct inhibition of hepatic microsomal enzymes.[6] Significant impairment of lignocaine [lidocaine] clearance would therefore be most likely to occur with those drugs that lack intrinsic sympathomimetic activity and have a greater effect on cardiac output or with the more lipid-soluble drugs that have greater effects on microsomal oxygenases. Results of one study[4] suggest that the reduction in clearance produced by propranolol is mainly by direct inhibition of metabolism rather than by lowering of hepatic blood flow.

1. Ochs HR, *et al.* Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. *N Engl J Med* 1980; **303:** 373–7.
2. Conrad KA, *et al.* Lidocaine elimination: effects of metoprolol and of propranolol. *Clin Pharmacol Ther* 1983; **33:** 133–8.
3. Schneck DW, *et al.* Effects of nadolol and propranolol on plasma lidocaine clearance. *Clin Pharmacol Ther* 1984; **36:** 584–7.
4. Bax NDS, *et al.* The impairment of lignocaine clearance by propranolol—major contribution from enzyme inhibition. *Br J Clin Pharmacol* 1985; **19:** 597–603.
5. Miners JO, *et al.* Failure of 'therapeutic' doses of β-adrenoceptor antagonists to alter the disposition of tolbutamide and lignocaine. *Br J Clin Pharmacol* 1984; **18:** 853–60.
6. Tucker GT, *et al.* Effects of β-adrenoceptor antagonists on the pharmacokinetics of lignocaine. *Br J Clin Pharmacol* 1984; **17:** 21S–28S.

H_2-antagonists. There have been numerous studies[1–4] of the interaction between *cimetidine* and lignocaine [lidocaine] but differences between the studies makes interpretation of the overall clinical significance of the results difficult. Cimetidine appears to reduce the hepatic metabolism of lignocaine [lidocaine]; it may also reduce its clearance by decreasing hepatic blood flow. Significant increases in plasma-lignocaine [lidocaine] concentrations have been reported. Changes in protein binding are not generally important but patients with myocardial infarction who have increased levels of α_1-acid glycoprotein may be partially protected from increases in concentrations of free lignocaine [lidocaine].[5] Since it is not possible to identify those patients at risk all patients receiving these drugs concurrently should be closely monitored for signs of toxicity. The use of other H_2-antagonists may be preferable. In studies in healthy subjects *ranitidine* either had no effect on lignocaine [lidocaine] kinetics[6] or produced changes consistent with small reductions in hepatic blood flow.[7]

1. Feely J, *et al.* Increased toxicity and reduced clearance of lidocaine by cimetidine. *Ann Intern Med* 1982; **96:** 592–4.
2. Knapp AB, *et al.* The cimetidine-lidocaine interaction. *Ann Intern Med* 1983; **98:** 174–7.
3. Patterson JH, *et al.* Influence of a continuous cimetidine infusion on lidocaine plasma concentrations in patients. *J Clin Pharmacol* 1985; **25:** 607–9.
4. Bauer LA, *et al.* Cimetidine-induced decrease in lidocaine metabolism. *Am Heart J* 1984; **108:** 413–15.
5. Berk SI, *et al.* The effect of oral cimetidine on total and unbound serum lidocaine concentrations in patients with suspected myocardial infarction. *Int J Cardiol* 1987; **14:** 91–4.
6. Feely J, Guy E. Lack of effect of ranitidine on the disposition of lignocaine. *Br J Clin Pharmacol* 1983; **15:** 378–9.
7. Robson RA, *et al.* The effect of ranitidine on the disposition of lignocaine. *Br J Clin Pharmacol* 1985; **20:** 170–3.

Local anaesthetics. Although a number of drugs were shown to reduce the amount of lignocaine [lidocaine] bound to α_1-acid glycoprotein only the displacement produced by *bupivacaine* was considered to be of possible clinical significance.[1]

There is concern about the use of lignocaine [lidocaine] to treat *cocaine*-induced arrhythmias as lignocaine [lidocaine] may enhance toxicity.[2]

1. Goolkasian DL, *et al.* Displacement of lidocaine from serum α_1-acid glycoprotein binding sites by basic drugs. *Eur J Clin Pharmacol* 1983; **25:** 413–17.
2. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995; **333:** 1267–72.

Neuromuscular blockers. The possible interaction between neuromuscular blockers and antiarrhythmics including lignocaine [lidocaine] is discussed under Atracurium, p.1334.

Oral contraceptives. For mention of the effect of oral contraceptives on the protein binding of lignocaine [lidocaine], see under Protein Binding in Pharmacokinetics, below.

Pharmacokinetics

Lignocaine [lidocaine] is readily absorbed from the gastrointestinal tract, from mucous membranes, and through damaged skin. Absorption through intact skin is poor. It is rapidly absorbed from injection sites including muscle.

After an intravenous dose lignocaine [lidocaine] is rapidly and widely distributed into highly perfused tissues followed by redistribution into skeletal muscle and adipose tissue. Lignocaine [lidocaine] is bound to plasma proteins, including α_1-acid glycoprotein (AAG). The extent of binding is variable but is approximately 66%. Plasma protein binding of lignocaine [lidocaine] depends in part on the concentrations of both lignocaine [lidocaine] and AAG. Any alteration in the concentration of AAG can greatly affect plasma concentrations of lignocaine [lidocaine] (see under Protein Binding, below).

Plasma concentrations decline rapidly after an intravenous dose with an initial half-life of less than 30 minutes; the elimination half-life is 1 to 2 hours but may be prolonged if infusions are given for longer than 24 hours or if hepatic blood flow is reduced.

Lignocaine [lidocaine] is largely metabolised in the liver and any alteration in liver function or hepatic blood flow can have a significant effect on its pharmacokinetics and dosage requirements. First-pass metabolism is extensive and bioavailability is about 35% after oral administration. Metabolism in the liver is rapid and approximately 90% of a given dose is dealkylated to form monoethylglycinexylidide and glycinexylidide. Both of these metabolites may contribute to the therapeutic and toxic effects of lignocaine [lidocaine] and since their half-lives are longer than that of lignocaine [lidocaine], accumulation, particularly of glycinexylidide, may occur during prolonged infusions. Further metabolism occurs and metabolites are excreted in the urine with less than 10% of unchanged lignocaine [lidocaine]. Reduced clearance of lignocaine [lidocaine] has been found in patients with heart failure, alcoholic liver disease, or chronic or viral hepatitis. Concomitant therapy with drugs that alter hepatic blood flow or induce drug-metabolising microsomal enzymes can also affect the clearance of lignocaine [lidocaine] (see under Interactions, above). Renal impairment does not affect the clearance of lignocaine [lidocaine] but accumulation of its active metabolites can occur.

Lignocaine [lidocaine] crosses the placenta and blood-brain barrier; it is distributed into breast milk.

See also under Local Anaesthetics, p.1303.

◊ References.

1. Nattel S, *et al.* The pharmacokinetics of lignocaine and β-adrenoceptor antagonists in patients with acute myocardial infarction. *Clin Pharmacokinet* 1987; **13:** 293–316.

Absorption. SURFACE APPLICATION. Serum-lignocaine [lidocaine] concentrations were usually so low as to be unmeasurable in patients who gargled and expectorated 15 mL (300 mg) of a 2% viscous solution before endoscopy[1] and mean peak serum concentrations of lignocaine [lidocaine] were below those associated with toxicity following endotracheal application of 100 mg of lignocaine [lidocaine] by spray.[2] The relative bioavailability of lignocaine [lidocaine] has been found to be higher when applied to the upper respiratory tract than after administration to the lower respiratory tract.[3] Acceptably low plasma-lignocaine [lidocaine] concentrations were noted with the following regimen used before bronchoscopy: a 4% lignocaine [lidocaine] solution gargled for 30 seconds, a 2% solution sprayed onto the oropharynx, a 2% jelly applied to the oropharynx and nasal passages, and a 1% solution injected through a bronchoscope.[4] However, a fatality has been reported following the use of lignocaine [lidocaine] as a gargle (see Overdosage, above); the absorption of intranasal lignocaine [lidocaine] can also be highly variable.[5] For bronchoscopy, administration of lignocaine [lidocaine] by inhalation from a nebuliser rather than by direct spray may result in lower peak serum concentrations.[6]

Absorption of lignocaine [lidocaine] is generally poor through intact skin. However, there is some evidence that absorption may be greater following application to the skin of preterm infants.[7]

1. Fazio A, *et al.* Lidocaine serum concentrations following endoscopy. *Drug Intell Clin Pharm* 1987; **21:** 752–3.
2. Scott DB, *et al.* Plasma lignocaine concentrations following endotracheal spraying with an aerosol. *Br J Anaesth* 1976; **48:** 899–902.

3. McBurney A, *et al.* Absorption of lignocaine and bupivacaine from the respiratory tract during fibreoptic bronchoscopy. *Br J Clin Pharmacol* 1984; 17: 61–6.
4. Ameer B, *et al.* Systemic absorption of topical lidocaine in elderly and young adults undergoing bronchoscopy. *Pharmacotherapy* 1989; 9: 74–81.
5. Scavone JM, *et al.* The bioavailability of intranasal lignocaine. *Br J Clin Pharmacol* 1989; 28: 722–4.
6. Labedzki L, *et al.* Reduced systemic absorption of intrabronchial lidocaine by high-frequency nebulization. *J Clin Pharmacol* 1990; 30: 795–7.
7. Barrett DA, Rutter N. Percutaneous lignocaine absorption in newborn infants. *Arch Dis Child* 1994; 71: F122–F124.

Protein binding. Lignocaine [lidocaine] is markedly bound to α_1-acid glycoprotein (AAG), a plasma protein which is increased after trauma, surgery, burns, myocardial infarction, in chronic inflammatory disorders such as Crohn's disease, and in cancer. Protein binding may therefore be greatly increased in these conditions and reduced in neonates, the nephrotic syndrome, and in liver disease when AAG concentrations are lower than normal. This can result in an eightfold variation in the free fraction of lignocaine [lidocaine] between these conditions.[1] Measurement of free drug concentrations may be a better guide to dosage requirements than measurement of total plasma concentrations.[2] AAG concentrations may also be reduced by oestrogens[3] leading to a higher free fraction of lignocaine [lidocaine] in women than in men and the free fraction is further increased during pregnancy and in women taking oral contraceptives.[3,4] Protein binding may also be affected by other concomitant drug therapy or smoking (for further details, see under Interactions, above and Precautions, Smoking, above).

1. Routledge PA. Pharmacological terms: protein binding. *Prescribers' J* 1988; 28: 34–5.
2. Shand DG. α_1-Acid glycoprotein and plasma lidocaine binding. *Clin Pharmacokinet* 1984; 9 (suppl 1): 27–31.
3. Routledge PA, *et al.* Sex-related differences in the plasma protein binding of lignocaine and diazepam. *Br J Clin Pharmacol* 1; 11: 245–50.
M, Wood AJJ. Changes in plasma drug binding and α_1-acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther* 1981; 29: 522–6.

Uses and Administration

Lignocaine [lidocaine] is a local anaesthetic of the amide type with actions and uses similar to those described on p.1304. It is used for infiltration anaesthesia and regional nerve blocks. It has a rapid onset of action and anaesthesia is obtained within a few minutes depending on the site of administration; it has an intermediate duration of action. The speed of onset and duration of action of lignocaine [lidocaine] are increased by the addition of a vasoconstrictor and absorption into the circulation from the site of injection is reduced. It is generally given as the hydrochloride. The carbonated solution of lignocaine [lidocaine] is also available in some countries for injection (see p.1304). Lignocaine [lidocaine] is also a useful surface anaesthetic but it should be remembered that it may be rapidly and extensively absorbed following topical application to mucous membranes and systemic effects may occur. Hyaluronidase (p.1620) has been added to preparations of lignocaine [lidocaine] used for surface and infiltration anaesthesia but it may also enhance systemic absorption. (Local anaesthetic techniques are discussed on p.1304.)

Lignocaine [lidocaine] is included in some injections, such as depot corticosteroids, to prevent pain, itching, and other local irritation. Lignocaine [lidocaine] sodium has also been included in intramuscular injections of some antibacterials to reduce the pain on administration.

Lignocaine [lidocaine] is also a class Ib antiarrhythmic used in the treatment of ventricular arrhythmias, especially after myocardial infarction. It has been given by intravenous infusion in the treatment of refractory status epilepticus.

USE IN LOCAL ANAESTHESIA.

The dose of lignocaine [lidocaine] hydrochloride used for local anaesthesia depends on the site of injection and the procedure used. Specific licensed doses for individual procedures are not generally available in the UK, although US product information often includes them (see below). When given with adrenaline [epinephrine], the suggested general **maximum single dose** of lignocaine [lidocaine] hydrochloride is 500 mg; without adrenaline [epinephrine], the recommended maximum single dose in the UK is 200 mg and in the USA, 300 mg, except for spinal anaesthesia (see below). Lignocaine [lidocaine] hydrochloride solutions containing adrenaline [epinephrine] 1 in 200 000 are used for infiltration anaesthesia and nerve blocks; higher concentrations of adrenaline [epinephrine] are seldom necessary, except in dentistry, in which case, solutions of lignocaine [lidocaine] hydrochloride with adrenaline [epinephrine] 1 in 80 000 may be used. Doses should be reduced in children, the elderly, and in debilitated patients. A test dose, preferably with adrenaline [epinephrine], should be given before commencing epidural block to detect inadvertent intravascular or subarachnoid administration.

The following doses have been recommended for individual **local anaesthetic procedures** in the USA:

- For percutaneous *infiltration anaesthesia*, 5 to 300 mg (1 to 60 mL of a 0.5% solution, or 0.5 to 30 mL of a 1% solution).
- The dosage in *peripheral nerve block* depends on the route of administration. For brachial plexus block 225 to 300 mg (15 to 20 mL) as a 1.5% solution is used; for intercostal nerve block 30 mg (3 mL) is given as a 1% solution; for paracervical block a 1% solution is used in a dose of 100 mg (10 mL) on each side, repeated not more frequently than every 90 minutes; for paravertebral block a 1% solution may be used in doses of 30 to 50 mg (3 to 5 mL); a 1% solution is recommended for pudendal block in doses of 100 mg (10 mL) on each side; for retrobulbar block a 4% solution may be used in doses of 120 to 200 mg (3 to 5 mL).
- For *sympathetic nerve block* a 1% solution is recommended; doses are 50 mg (5 mL) for cervical block and 50 to 100 mg (5 to 10 mL) for lumbar block.
- For *epidural anaesthesia* 2 to 3 mL of solution is needed for each dermatome to be anaesthetised but usual total doses and recommended concentrations are: lumbar epidural 250 to 300 mg (25 to 30 mL) as a 1% solution for analgesia and 225 to 300 mg (15 to 20 mL) as a 1.5% solution or 200 to 300 mg (10 to 15 mL) as a 2% solution for anaesthesia, and for thoracic epidural a 1% solution may be used at doses of 200 to 300 mg (20 to 30 mL). In obstetric caudal analgesia 200 to 300 mg (20 to 30 mL) is used as a 1% solution and in surgical caudal anaesthesia a 1.5% solution may be used in doses of 225 to 300 mg (15 to 20 mL). For continuous epidural anaesthesia, the maximum doses should not be repeated more frequently than every 90 minutes.
- A hyperbaric solution of 1.5% or 5% lignocaine [lidocaine] hydrochloride in glucose 7.5% solution is available for *spinal anaesthesia*; adrenaline [epinephrine] should not be used. Doses of up to 50 mg (1 mL) as a 5% solution and 9 to 15 mg (0.6 to 1 mL) as a 1.5% solution have been used during labour for a normal vaginal delivery. Up to 75 mg (1.5 mL) as the 5% solution has been used for caesarean section and 75 to 100 mg (1.5 to 2 mL) for other surgical procedures.
- For *intravenous regional anaesthesia* a 0.5% solution without adrenaline [epinephrine] has been used in doses of 50 to 300 mg (10 to 60 mL); a maximum dose of 4 mg per kg body-weight has been recommended for adults.

Lignocaine [lidocaine] may be used in a variety of formulations for **surface anaesthesia**.

- Lignocaine [lidocaine] ointment is used for *anaesthesia of skin and mucous membranes* with a maximum recommended total dose of 20 g of 5% ointment (equivalent to 1 g of lignocaine [lidocaine] base) in 24 hours.
- Gels are used for *anaesthesia of the urinary tract* and the dose used varies in different countries. The manufacturers in the UK have suggested the following doses given as a 2% gel: in females 100 to 200 mg of lignocaine [lidocaine] hydrochloride inserted into the urethra several minutes before examination; in males 400 mg instilled in 2 portions, or 600 to 800 mg in 3 or 4 portions. The doses used in the USA are lower: in females 60 to 100 mg of lignocaine [lidocaine] hydrochloride inserted into the urethra several minutes before examination; in males 100 to 200 mg used before catheterisation and 600 mg before sounding or cystoscopy.
- A dose of 200 to 400 mg of a 2% gel is also recommended in the UK for *analgesia during endoscopy*. A quantity of the gel containing about 100 mg of lignocaine [lidocaine] hydrochloride is also used to lubricate tubing for *endotracheal insertion*.
- Topical solutions are used for *surface anaesthesia of mucous membranes of the mouth, throat, and upper gastrointestinal tract*. For painful conditions of the mouth and throat a 2% solution may be used: 300 mg (15 mL) may be rinsed and ejected or, for pharyngeal pain, the solution is gargled and swallowed if necessary; it should not be used more frequently than every 3 hours. The recommended maximum daily dose in the USA for topical oral solutions is 2.4 g. Doses of 40 to 300 mg as a 4% solution (1 to 7.5 mL) are used before bronchoscopy, bronchography, laryngoscopy, oesophagoscopy, endotracheal intubation, and biopsy in the mouth and throat. Lignocaine [lidocaine] in a strength of 10% has also been used as a spray for application to mucous membranes for the prevention of pain during various procedures including use in otorhinolaryngology, dentistry, introduction of instruments into the respiratory and gastrointestinal tracts, and in obstetrics. The dose depends on the extent of the site to be anaesthetised; 10 to 50 mg is generally sufficient for dentistry and otorhinolaryngology; for other procedures, the maximum dose in a 24-hour period is 200 mg. For laryngotracheal anaesthesia 160 mg of lignocaine [lidocaine] hydrochloride as a 4% spray is instilled as a single dose into the lumen of the larynx and trachea.
- Lignocaine [lidocaine] is used *rectally* as suppositories, ointments, and creams in the treatment of haemorrhoids and other painful perianal conditions.
- *Eye drops* containing lignocaine [lidocaine] hydrochloride 4% with fluorescein are used in tonometry.
- A *eutectic mixture* containing lignocaine [lidocaine] base 2.5% and prilocaine base 2.5% is applied as a cream under an occlusive dressing to produce *surface anaesthesia of the skin* before procedures requiring needle puncture, surgical treatment of localised lesions, and split skin grafting; it has been used similarly, but without an occlusive dressing, before removal of genital warts (see also under Surface Anaesthesia, below).
- Other methods of dermal delivery include a *transdermal patch* of lignocaine [lidocaine] 5% for the treatment of pain associated with postherpetic neuralgia, and an *iontophoretic drug delivery system* incorporating lignocaine [lidocaine] and adrenaline [epinephrine].

USE IN ARRHYTHMIAS.

For the treatment of **ventricular arrhythmias** lignocaine [lidocaine] is given *intravenously* as the hydrochloride. It may be used in advanced cardiac life support for cardiac arrest due to ventricular fibrillation and pulseless ventricular tachycardia when direct current shocks (together with adrenaline [epinephrine]) have failed to restore a normal rhythm. For adults, a dose of 1 to 1.5 mg per kg body-weight can be given and repeated after 3 to 5 minutes to a total dose of 3 mg per kg if necessary. The *endotracheal* route has been employed when intravenous access cannot be obtained, although doses should probably be larger than those employed intravenously; the precise endotracheal dose has not yet been established, however.

Lignocaine [lidocaine] is also used in other ventricular arrhythmias in which the patient is in a more stable condition. In these circumstances lignocaine [lidocaine] hydrochloride is usually given as a loading dose followed by an infusion. Usual doses are 50 to

100 mg or 1 to 1.5 mg per kg as a direct *intravenous injection* at a rate of 25 to 50 mg per minute. If no effect is seen within 5 to 10 minutes of this loading dose, it may be repeated once or twice to a maximum dose of 200 to 300 mg in 1 hour. A *continuous intravenous infusion* is usually commenced after loading, at a dose of 1 to 4 mg per minute. It is rarely necessary to continue this infusion for longer than 24 hours, but in the event that a longer infusion is required, the dose may need to be reduced to avoid potential toxicity resulting from an increase in the half-life. Dosage may need to be reduced in patients with heart failure or liver disorders.

In emergency situations, lignocaine [lidocaine] hydrochloride has also been given for arrhythmias by *intramuscular* injection into the deltoid muscle in a dose of 300 mg, repeated if necessary after 60 to 90 minutes.

Action. For a comparison of the vasoactivity of lignocaine [lidocaine] and some other local anaesthetics, see p.1304.

Burns. Lignocaine [lidocaine] given intravenously has been reported to have produced pain relief in a few patients with second-degree burns.[1]

1. Jönsson A, *et al.* Inhibition of burn pain by intravenous lignocaine infusion. *Lancet* 1991; 338: 151–2.

Cardiac arrhythmias. Lignocaine [lidocaine] is classified as a class Ib antiarrhythmic drug (p.787) and may be used in the treatment of ventricular arrhythmias, including those associated with cardiac arrest and myocardial infarction. It is usually administered intravenously (see above). Some forms of ventricular tachycardia may be terminated by the use of lignocaine [lidocaine]; the overall treatment options are described under Cardiac Arrhythmias, p.794. Lignocaine [lidocaine] may also be used during advanced cardiac life support (p.790).

Lignocaine [lidocaine] has been considered for the *prophylaxis* of ventricular fibrillation in patients with proven or suspected myocardial infarction. However, while some studies have identified a protective effect,[1,2] in others this has not been shown to be accompanied by a reduction in mortality and might even have increased it.[3,4] Nevertheless, one review of the available evidence[5] concluded that lignocaine [lidocaine] prophylaxis was a reasonable policy for patients at highest risk of ventricular fibrillation such as those with acute transmural infarction, under 65 years of age, and within 6 hours of the onset of infarction symptoms.

It has been suggested that the increased mortality sometimes seen with lignocaine [lidocaine] might be associated with the duration of administration; one study[6] found that patients who received a bolus dose of lignocaine [lidocaine] followed by a 40-hour continuous infusion for prophylaxis of ventricular arrhythmias experienced more episodes of heart failure than patients who received the bolus dose followed by an 8-hour infusion.

1. Horwitz RI, Feinstein AR. Improved observational method for studying therapeutic efficacy: suggestive evidence that lidocaine prophylaxis prevents death in acute myocardial infarction. *JAMA* 1981; 246: 2455–9.
2. Koster RW, Dunning AJ. Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction. *N Engl J Med* 1985; 313: 1105–10.
3. MacMahon S, *et al.* Effects of prophylactic lidocaine in suspected acute myocardial infarction: an overview of results from the randomized, controlled trials. *JAMA* 1988; 260: 1910–16.
4. Hine LK, *et al.* Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. *Ann Intern Med* 1989; 149: 2694–8.
5. Nattel S, Arenal A. Antiarrhythmic prophylaxis after acute myocardial infarction: is lidocaine still useful? *Drugs* 1993; 45: 9–14.
6. Pharand C, *et al.* Lidocaine prophylaxis for fatal ventricular arrhythmias after acute myocardial infarction. *Clin Pharmacol Ther* 1995; 57: 471–8.

Hiccup. A protocol for the management of intractable hiccups may be found under Chlorpromazine, p.667. Lignocaine [lidocaine] is one of a large number of drugs that has been tried in the treatment of hiccups without strong evidence of their efficacy. It has been given in the form of a 2% viscous solution taken by mouth. Nebulised lignocaine [lidocaine] has also been tried.[1]

1. Neeno TA, Rosenow EC. Intractable hiccups: consider nebulized lidocaine. *Chest* 1996; 110: 1129–30.

Intubation. Lignocaine [lidocaine] has produced conflicting results when used to attenuate the pressor response and rise in intra-ocular pressure induced by procedures such as tracheal intubation.[1-5] For an overall discussion of this problem, see under Anaesthesia, p.1331.

1. Tam S, *et al.* Attenuation of circulatory responses to endotracheal intubation using intravenous lidocaine: a determination of the optimal time of injection. *Can Anaesth Soc J* 1985; 32: S65.
2. Murphy DF, *et al.* Intravenous lignocaine pretreatment to prevent intraocular pressure rise following suxamethonium and tracheal intubation. *Br J Ophthalmol* 1986; 70: 596–8.
3. Drenger B, Pe'er J. Attenuation of ocular and systemic responses to tracheal intubation by intravenous lignocaine. *Br J Ophthalmol* 1987; 71: 546–8.
4. Miller CD, Warren SJ. IV lignocaine fails to attenuate the cardiovascular response to laryngoscopy and tracheal intubation. *Br J Anaesth* 1990; 65: 216–19.
5. Mostafa SM, *et al.* Effects of nebulized lignocaine on the intraocular pressure responses to tracheal intubation. *Br J Anaesth* 1990; 64: 515–17.

Migraine and cluster headache. Despite periodic renewed interest, lignocaine [lidocaine] has so far failed to find an accepted role in the management of migraine (p.449) or cluster headache (p.449). Lignocaine [lidocaine] has been tried for the emergency parenteral treatment of migraine, but in a comparative study with dihydroergotamine or chlorpromazine it was found to be less effective than either.[1] Intranasal instillation of lignocaine [lidocaine] has produced rapid relief of headache in some patients with acute migraine (though early relapse was common),[2] and has also been reported to be effective in aborting individual attacks of headache during cluster periods in patients with cluster headache.[3,4]

1. Bell R, *et al.* A comparative trial of three agents in the treatment of acute migraine headache. *Ann Emerg Med* 1990; 19: 1070–82.
2. Maizels M, *et al.* Intranasal lidocaine for treatment of migraine: a randomized, double-blind, controlled trial. *JAMA* 1996; 276: 319–21.
3. Kittrelle JP, *et al.* Cluster headache: local anesthetic abortive agents. *Arch Neurol* 1985; 42: 496–8.
4. Robbins L. Intranasal lidocaine for cluster headache. *Headache* 1995; 35: 83–4.

Neuropathic pain syndromes. Lignocaine [lidocaine] may be useful in the management of some types of neuropathic pain syndromes (p.7). The pain of *postherpetic neuralgia* has been significantly reduced by the application of lignocaine [lidocaine] 5% transdermal patches;[1,2] a eutectic mixture of lignocaine [lidocaine] and prilocaine has also been of benefit (see Surface Anaesthesia below). Syndromes where intravenous lignocaine [lidocaine] therapy has been tried include *diabetic neuropathy*[3] and *central neuropathic pain* associated with stroke or spinal cord injury.[4]

1. Rowbotham MC, *et al.* Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996; 65: 39–44.
2. Comer AM, Lamb HM. Lidocaine patch 5%. *Drugs* 2000, 59: 245–9.
3. Kastrup J, *et al.* Treatment of chronic painful diabetic neuropathy with intravenous lidocaine infusion. *BMJ* 1986; 292: 173.
4. Attal N, *et al.* Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology* 2000; 54: 564–74.

Pleurodesis. Lignocaine [lidocaine] has been instilled intrapleurally as a 1% solution in doses of up to 300 mg to relieve the severe chest pain associated with the use of tetracycline for pleurodesis.[1-3] While the larger doses were significantly more effective[2] toxic plasma concentrations were less likely to occur if a dose of 3 mg per kg body-weight or less was used.[3]

1. Harbecke RG. Intrapleurally given tetracycline with lidocaine. *JAMA* 1980; 244: 1899–1900.
2. Sherman S, *et al.* Optimum anesthesia with intrapleural lidocaine during chemical pleurodesis with tetracycline. *Chest* 1988; 93: 533–6.
3. Wooten SA, *et al.* Systemic absorption of tetracycline and lidocaine following intrapleural instillation. *Chest* 1988; 94: 960–3.

Status epilepticus. Lignocaine [lidocaine] hydrochloride may be used to control status epilepticus (p.341) resistant to more conventional treatment. It has a rapid onset of action but its effect is short-lived and continuous infusion may be necessary.[1] It should also be noted that doses producing high plasma concentrations of lignocaine [lidocaine] can result in CNS toxicity including seizures.[1] Recurrence of seizures associated with the withdrawal of prolonged lignocaine [lidocaine] therapy may be due to its accumulated metabolites exerting an excitatory effect on the nervous system when the inhibitory effect of lignocaine [lidocaine] is being reduced.[2]

Lignocaine [lidocaine] was used instead of diazepam for 42 episodes of status epilepticus in 36 patients who either had limited pulmonary reserve or who had not responded to intravenous diazepam.[3] Lignocaine [lidocaine] 1.5 to 2 mg per kg body-weight (usually a dose of 100 mg) was administered as a single intravenous dose over 2 minutes. This dose was repeated once if there was no positive response to the first dose (11 episodes) or the seizures recurred (19 episodes). Subsequently a continuous infusion of lignocaine [lidocaine] at a rate of 3 to 4 mg per kg per hour was given in the 7 episodes that recurred after the second dose; 5 of these showed a positive response. The 11 episodes not responding to the first dose did not respond to the second dose or to a continuous infusion.

1. Bauer J, Elger CE. Management of status epilepticus in adults. *CNS Drugs* 1994; 1: 26–44.
2. Wallin A, *et al.* Lidocaine treatment of neonatal convulsions, a therapeutic dilemma. *Eur J Clin Pharmacol* 1989; 36: 583–6.
3. Pascual J, *et al.* Role of lidocaine (lignocaine) in managing status epilepticus. *J Neurol Neurosurg Psychiatry* 1992; 55: 49–51.

Surface anaesthesia. EUTECTIC MIXTURES. A cream, containing lignocaine [lidocaine] 2.5% and prilocaine 2.5% in a eutectic mixture, can produce local anaesthesia when applied topically to intact skin and appears to be of value in a number of minor medical or surgical procedures both in adults and in children.[1-3] Applications that have been tried include venepuncture for blood sampling, intravenous or arterial cannulation, retrobulbar injections, lumbar puncture, curettage of molluscum contagiosum lesions, genital wart removal, split skin grafting, laser treatment, extracorporeal shock wave therapy, separation of preputial adhesions, and circumcision. It has also been tried as an anaesthetic for the ear drum in preparation for otological procedures such as myringotomy and grommet insertion but is potentially ototoxic and should not be used in the presence of a perforation. Postherpetic neuralgia (p.7) has also been treated with some success.[4,5]

The eutectic cream is usually applied to skin under an occlusive dressing for at least 60 minutes although it has been suggested that for children aged 1 to 5 years 30 minutes may be sufficient.[6] The manufacturers suggest a maximum application time of 5 hours. The onset and duration of the effect may be affected by the site of application.[2] When used for the removal of genital warts an occlusive dressing is not necessary and the application time recommended by the manufacturer is 5 to 10 minutes. The level of anaesthesia begins to decline after 10 to 15 minutes when applied to the genital mucosa and any procedure should be started immediately.

Systemic absorption of lignocaine [lidocaine] and prilocaine appears to be minimal when applied to intact skin[6] even after treating large areas or leaving the cream in place for many hours.[7] Nevertheless, the UK manufacturers recommend that it should not be used for children under 1 year of age as excessive absorption can lead to methaemoglobinaemia, owing to the presence of prilocaine (see under Methaemoglobinaemia, p.1302). However, eutectic mixtures of lignocaine [lidocaine] and prilocaine have been used to reduce the pain of puncture procedures[8] and for circumcision[9] in neonates, and appear to be safe and efficacious. Indeed, in some other countries including the USA, the cream is licensed for use in neonates provided that their gestational age is at least 37 weeks and that those aged 3 months or less are monitored for methaemoglobin levels; it should not be used in infants under the age of 1 year who are receiving treatment with methaemoglobin-inducing drugs.

The eutectic cream should not be used on wounds or mucous membranes (except for genital warts in adults) and should not be used for atopic dermatitis. It should not be applied to or near the eyes because it causes corneal irritation, and it should not be instilled in the middle ear. It should be used with caution in patients with anaemia or congenital or acquired methaemoglobinaemia. Transient paleness, redness, and oedema may occur following application.

Some studies suggest that a topical gel formulation of amethocaine [tetracaine] 4% can produce longer and more rapid anaesthesia than the above lignocaine [lidocaine] with prilocaine cream (see Surface Anaesthesia, under Uses and Administration of Amethocaine, p.1305). It has also been suggested[10] that topical amethocaine [tetracaine] may have practical advantages over the eutectic mixture of lignocaine [lidocaine] and prilocaine, which has to be applied for at least one hour, and causes vasoconstriction at the site of application which can make venepuncture difficult.

1. Lee JJ, Rubin AP. Emla cream and its current uses. *Br J Hosp Med* 1993; 50: 463–6.
2. Buckley MM, Benfield P. Eutectic lidocaine/prilocaine cream: a review of the topical anaesthetic/analgesic efficacy of a eutectic mixture of local anaesthetics (EMLA). *Drugs* 1993; 46: 126–51.
3. Koren G. Use of the eutectic mixture of local anesthetics in young children for procedure-related pain. *J Pediatr* 1993; 122 (suppl): S30–S35.
4. Litman SJ, *et al.* Use of EMLA cream in the treatment of postherpetic neuralgia. *J Clin Anesth* 1996; 8: 54–7.
5. Kost RG, Straus SE. Postherpetic neuralgia—pathogenesis, treatment, and prevention. *N Engl J Med* 1996; 335: 32–42.
6. Hanks GW, White I. Local anaesthetic creams. *BMJ* 1988; 297: 1215–16.
7. Scott DB. Topical anaesthesia of intact skin. *Br J Parenter Ther* 1986; 7: 134–5.
8. Gourrier E, *et al.* Use of EMLA® cream in a department of neonatology. *Pain* 1996; 68: 431–4.
9. Taddio A, *et al.* Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. *N Engl J Med* 1997; 336: 1197–1201.
10. Russell SCS, Doyle E. Paediatric anaesthesia. *BMJ* 1997; 314: 201–3.

Tinnitus. Tinnitus is the perception of a noise that arises or appears to arise within the head.

Objective tinnitus may be audible to others and arises from lesions outside the auditory system. Subjective tinnitus (tinnitus aurium) originates from sites within the auditory system and is perceived only by the patient. A simple and remediable cause of tinnitus can be impacted ear wax. Tinnitus is often associated with head injury, vertigo, and hearing loss, including age-related and noise-induced hearing loss. It may also be a symptom of an underlying disorder such as Ménière's disease, may be associated with anxiety or depressive disorders, or may be a manifestation of drug toxicity (for example with aspirin or quinine). In such cases, treatment of the underlying disorder or removal of the offending drug can resolve the tinnitus.

Treatment of tinnitus is difficult although reassurance and counselling are often effective in helping patients to tolerate their condition. Maskers or, if the tinnitus is associated with hearing loss, hearing aids are also used; surgery is rarely indicated. Treatment with a wide variety of drugs has been tried. Intravenous lignocaine [lidocaine] has proven to be effective in reducing or eliminating tinnitus but the effect only lasts for a few hours and is, therefore, impractical for most patients. Efforts to find an effective oral analogue of lignocaine [lidocaine] have not, so far, been successful. Other drugs that have been tried include the antiepileptics carbamazepine and phenytoin,

and the loop diuretic frusemide [furosemide], but unacceptable adverse effects limit their use.

References.
1. Luxon LM. Tinnitus: its causes, diagnosis, and treatment. *BMJ* 1993; 306: 1490–1.
2. Robson AK, Birchall JP. Management of tinnitus. *Prescribers' J* 1994; 34: 1–7.
3. Coles RRA. Drug treatment of tinnitus in Britain. In: Reich GE, Vernon JA, eds. *Proceedings of the fifth international tinnitus seminar.* Portland: American Tinnitus Association, 1995.
4. Vesterager V. Tinnitus—investigation and management. *BMJ* 1997; 314: 728–31.
5. Simpson JJ, Davies WE. Recent advances in the pharmacological treatment of tinnitus. *Trends Pharmacol Sci* 1999; 20: 12–18.

Preparations

BP 2001: Lidocaine and Adrenaline Injection; Lidocaine and Chlorhexidine Gel; Lidocaine Gel; Lidocaine Injection; Sterile Lidocaine Solution;
USP 25: Lidocaine Hydrochloride and Dextrose Injection; Lidocaine Hydrochloride and Epinephrine Injection; Lidocaine Hydrochloride Injection; Lidocaine Hydrochloride Jelly; Lidocaine Hydrochloride Oral Topical Solution; Lidocaine Hydrochloride Topical Solution; Lidocaine Ointment; Lidocaine Oral Topical Solution; Lidocaine Topical Aerosol; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment.

Proprietary Preparations (details are given in Part 3)
Aust.: Lidocorit; Neo-Xylestesin; Neo-Xylestesin forte and Neo-Xylestesin special; Neurolid†; Xylanaest; Xylocain; Xylocard; Xyloneural; *Austral.:* Fargo†; Lignospan; Nurocain; Nurocain with Sympathin; Seda-Gel; Stud 100; Xylocaine; Xylocaine Special Adhesive; Xylocard; *Belg.:* Linisol; Otoralgyl; Xylocaine; Xylocaine Visqueuse; Xylocard; *Braz.:* Hypocaina; Lidocord; Xylestesin; Xylocaina; *Canad.:* Afterburn; Family Medicated Sunburn Relief†; Lidodan; Solarcaine Lidocaine; Xylocaine; Xylocard; Zilactin-L; *Denm.:* Xylocain; *Fin.:* Lidocard; Xylocain; *Fr.:* Dynexan; Mesocaine; Otoralgyl†; Xylocaine; Xylocard; *Ger.:* Anaesthol†; Gelicain; Haemo-Exhirud Bufexamac Zapfchen; Heneural; Licain; Lidesthesin; Lidocaton†; Lidoject; LidoPosterine; Neo-Lidocaton†; Nor-Anaesthol†; Rowo-629; Sagittaproct; Xylestesin-A, Xylestesin centro; Xylestesin-S; Xylestesin, Xylestesin-F; Xylocain; Xylocain f.d. Kardiologie; Xylocitin; Xylocitin cor; Xyloneural; *Hong Kong:* Xylocaine; Xylocard; *Irl.:* Xylocaine; Xylocard; *Israel:* Esracain; LidoPen; Stud 100; Xylocaine; *Ital.:* Basicaina; Ecocain; Lident Adrenalina; Lident Andrenor; Lidosen; Lidrian; Luan; Odontalg; Ortodermina; Xilo-Mynol; Xylocaina; Xylonor; *Jpn:* Penles; *Mex.:* Pisacaina; Rucaina; Uvega; Xlyocaina; *Neth.:* Dentinox†; Otalgan; Xylocaine; Xylocard; *Norw.:* Xylocain; Xylocard†; *NZ:* Nurocain; Virasolve; Xylocaine; Xylocard; *Port.:* Lidonostrum; Lincaina; Xilonibsa; Xylocaina†; Xylocard†; *S.Afr.:* Lignospan Special; Peterkaien; Remicaine; Remicard; Xylocaine; Xylotox; *Singapore:* Xylocaine; Xylocard; *Spain:* Aeroderm; Curadent; Llorentecaina Noradrenal; Octocaine; Xilonibsa; Xylocaina; Xylonor 2% Sin Vasoconst; Xylonor Especial; *Swed.:* Xylocain; Xylocain tung; Xylocard; *Switz.:* Kenergon; Lidocaton†; Lignospan; Luboglissg†; Neurodol Tissugel; Rapidocaine; Sedagul; Solarcaine; Xylesine; Xylestesin-F; Xylestesin-S "special"; Xylocain; Xylocard; Xyloneural; Xylonor†; *Thai.:* Docaine; Lidocation; Lidocaton; Neo-Lidocaton; Xylocaine; Xylocard; *UAE:* Ecocain; *UK:* Laryng-O-Jet; Lignostab-A; Rinstead; Strepsils Pain Relief Spray; Vagisil; Xylocaine; Xylocaine 2% Plain; Xylocard†; Xylotox; *USA:* Anestacon; Dentipatch; Dermaflex†; Dilocaine; Dr Scholl's Cracked Heel Relief; Duo-Trach Kit; ELA-Max; Lidoderm; Lidoject; LidoPen; Nervocaine; Nulicaine†; Octocaine; Xylocaine; Zilactin-L.

Multi-ingredient: numerous preparations are listed in Part 3.

Mepivacaine Hydrochloride (7633-e)

epivacaine Hydrochloride *(BANM, rINNM).*

Mepivacaini Chloridum; Mepivacaini Hydrochloridum. (1-Methyl-2-piperidyl)formo-2',6'-xylidide hydrochloride.

$C_{15}H_{22}N_2O,HCl = 282.8$.

CAS — 96-88-8 (mepivacaine); 22801-44-1 ((±)-mepivacaine); 1722-62-9 (mepivacaine hydrochloride).

Pharmacopoeias. In *Eur.* (see p.vi), *Jpn,* and *US.*

Pharmacopoeial description

Ph. Eur.: A white crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.0.

USP 25: A white, odourless, crystalline solid. Freely soluble in water and in methyl alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of about 4.5.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1304.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1302.

Porphyria. Mepivacaine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

For interactions associated with local anaesthetics, see p.1303.

◊ Studies *in vitro* showed that bupivacaine dramatically reduced the binding of mepivacaine to α-1-acid glycoprotein.[1]

1. Hartrick CT, *et al.* Influence of bupivacaine on mepivacaine protein binding. *Clin Pharmacol Ther* 1984; 36: 546–50.

Pharmacokinetics

Mepivacaine is about 78% bound to plasma proteins. The plasma half-life has been reported to be about 2 to 3 hours in adults and about 9 hours in neonates. It is rapidly metabolised in the liver and less than 10% of a dose is reported to be excreted unchanged in the urine. Over 50% of a dose is excreted as metabolites into the bile but these probably undergo enterohepatic circulation as only small amounts appear in the faeces. Several metabolites are also excreted via the kidneys and include glucuronide conjugates of hydroxy compounds and an *N*-demethylated compound, 2',6'-pipecoloxylidide. Mepivacaine crosses the placenta.

See also under Local Anaesthetics, p.1303.

Pregnancy. There is considerable transfer of mepivacaine across the placenta following maternal administration and the ratio of fetal to maternal concentrations[1] is about 0.7. Although neonates have a very limited capacity to metabolise mepivacaine it appears they are able to eliminate the drug.[2]

1. Lurie AO, Weiss JB. Blood concentration of mepivacaine and lidocaine in mother and baby after epidural anesthesia. *Am J Obstet Gynecol* 1970; 106: 850–6.
2. Meffin P, *et al.* Clearance and metabolism of mepivacaine in the human neonate. *Clin Pharmacol Ther* 1973; 14: 218–25.

Uses and Administration

Mepivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p.1304. It is mainly used for infiltration anaesthesia, peripheral nerve block, and epidural block. (Local anaesthetic techniques are discussed on p.1304.) Mepivacaine has a rapid onset and an intermediate duration of action. The speed of onset and duration of action are increased by the addition of a vasoconstrictor and absorption into the circulation from the site of injection is reduced.

The dosage of mepivacaine hydrochloride varies with the site of injection and the type of **local anaesthetic procedure**. In adults, the **maximum single dose** of mepivacaine hydrochloride should not generally exceed 400 mg and the total dose in 24 hours should not exceed 1 g. Doses should be reduced in the elderly, in debilitated patients, and in those with cardiac or hepatic impairment. A suggested maximum dose for children, especially for those less than 3 years of age, is 5 to 6 mg per kg body-weight. Concentrations of less than 2% should also be used for children less than 3 years of age.

For *infiltration anaesthesia* up to 400 mg as a 1% (40 mL) or 0.5% (80 mL) solution is used. For *dental infiltration and nerve block* a 2% solution with a vasoconstrictor or a 3% plain solution is used. For anaesthesia at a single site in the jaw a dose of 36 mg (1.8 mL) as the 2% solution or 54 mg (1.8 mL) as the 3% solution is used. For anaesthesia of the entire oral cavity 180 mg (9 mL) as the 2% solution or 270 mg (9 mL) as the 3% solution is used. Some recommend that no more than 400 mg should be administered at a single dental sitting.

For *peripheral nerve blocks*, namely *cervical, brachial plexus, intercostal,* and *pudendal blocks*, 1 or 2% solutions may be used in doses of 50 to 400 mg (5 to 40 mL) as a 1% solution, or 100 to 400 mg (5 to 20 mL) as a 2% solution. For pudendal block half of the dose is injected on each side. For *paracervical block* a dose of up to 100 mg (10 mL) as a 1% solution on each side has been suggested allowing an interval of 5 minutes between sides. This may be repeated at an interval of not less than 90 minutes, and for a combined paracervical and pudendal block up to 150 mg (15 mL) as a 1% solution is injected on each side. For therapeutic nerve block in the management of pain 10 to 50 mg (1 to 5 mL) as a 1% solution or 20 to 100 mg (1 to 5 mL) as a 2% solution may be given.

For *epidural block* usual doses are: 150 to 300 mg (15 to 30 mL) as a 1% solution, 150 to 375 mg (10 to 25 mL) as a 1.5% solution, or 200 to 400 mg (10 to 20 mL) as a 2% solution. Hyperbaric solutions of mepivacaine hydrochloride without adrenaline [epinephrine] have also been used for *spinal block.*

Mepivacaine has been included in the intramuscular injections of other drugs to minimise the pain produced at the injection site.

Mepivacaine has also been used as a surface anaesthetic but other local anaesthetics such as lignocaine [lidocaine] are more effective.

Action. For a comparison of the vasoactivity of mepivacaine and some other local anaesthetics, see p.1304.

Preparations

USP 25: Mepivacaine Hydrochloride and Levonordefrin Injection; Mepivacaine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Aust.: Scandicain; Scandonest; *Austral.:* Carbocaine; Scandonest; *Belg.:* Scandicaine; *Canad.:* Carbocaine; Polocaine; *Denm.:* Carbocain; Scandonest; *Fr.:* Carbocaine; *Ger.:* Meaverin; Meaverin "A" mit Adrenalin†; Meaverin "N" mit Noradrenaline†; Meaverin hyperbar; Mecain; Mepicaton†; Mepihexal; Mepivastesin; Scandicain; *Israel:* Tevacaine; *Ital.:* Carbocaina; Mepi-Mynol; Mepicain; Mepident; Mepiforan; Mepyl; Optocain; Pericaina; Scandonest; *Neth.:* Scandicaine; *Norw.:* Carbocain; *Port.:* Scandinibsa; *S.Afr.:* Carbocaine; Scandonest; *Spain:* Isogaine; Scandinibsa; *Swed.:* Carbocain; *Switz.:* Mepicaton†; Scandicain; Scandonest; *Thai.:* Mepicaton; *USA:* Carbocaine; Carbocaine with Neo-Cobefrin; Isocaine; Polocaine.

Multi-ingredient: *Ger.:* Meaverin; Thesit.

Used as an adjunct in: Aust.: Estradurin; Triodurin†; *Belg.:* Estradurine; *Denm.:* Estradurin; *Fin.:* Estradurin; *Ger.:* Estradurin; *Hong Kong:* Nevramin; *Jpn:* Amasulin; Bestcall; Lilacillin; Pansporin; Takesulin; *Mex.:* Kedacillin; *Neth.:* Estradurin; *Norw.:* Estradurin; *Port.:* Linamin Plus; *Singapore:* Nevramin; *Swed.:* Estradurin; *Switz.:* Estradurin; *Thai.:* Nevramin; *UK:* Estradurin†.

Myrtecaine (12986-l)

Myrtecaine *(rINN).*

Nopoxamine. 2-[2-(10-Norpin-2-en-2-yl)ethoxy]triethylamine.

$C_{17}H_{31}NO = 265.4$.

CAS — 7712-50-7.

Profile

Myrtecaine is a local anaesthetic (p.1302) used topically as the base or laurilsulfate in rubefacient preparations for the treatment of muscle and joint pain. Myrtecaine laurilsulfate is also used in preparations with antacids for the symptomatic relief of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Aust.:* Acidrine; Algesal; Kalisyl†; Latesyl; Rheugesal; *Belg.:* Acidrine; *Fr.:* Acidrine; Algesal Suractive; *Ger.:* Acidrine; Algesal; Algesalona; *Ital.:* Acidrine; *Neth.:* Algesal Forte; *Port.:* Algesal; Latesil; *Spain:* Algesal; *Switz.:* Algesal; Algesalona.

Octacaine Hydrochloride (13036-x)

Octacaine Hydrochloride *(pINNM).*

3-Diethylaminobutyranilide hydrochloride.

$C_{14}H_{22}N_2O,HCl = 270.8$.

CAS — 13912-77-1 (octacaine); 59727-70-7 (octacaine hydrochloride).

Profile

Octacaine hydrochloride is a local anaesthetic (p.1302) that has been used for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Ger.:* Batrax; *Switz.:* Batramycine.

Oxetacaine (7638-c)

Oxetacaine *(BAN, rINN).*

Oxethazaine *(USAN);* Wy-806. 2,2'-(2-Hydroxyethylimino)bis[*N*-(αα-dimethylphenethyl)-*N*-methylacetamide].

$C_{28}H_{41}N_3O_3 = 467.6$.

CAS — 126-27-2 (oxetacaine); 13930-31-9 (oxetacaine hydrochloride).

ATC — C05AD06.

Pharmacopoeias. In *Br.* and *Jpn.*

Pharmacopoeial description

BP 2001: A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol; very soluble in chloroform; soluble in ethyl acetate.

Profile

Oxetacaine is an amide anaesthetic (p.1302) that is stated to have a prolonged action. It is administered by mouth in conjunction with antacids for the symptomatic relief of gastro-

oesophageal reflux disease (p.1204). It has also been used as the hydrochloride in ointments and suppositories for the relief of pain associated with haemorrhoids.

Preparations

Proprietary Preparations (details are given in Part 3)
Hong Kong: Strocain; *Ital.:* Emoren; *Jpn:* Strocain; *Singapore:* Strocain.

Multi-ingredient: *Aust.:* Tepilta; *Austral.:* Mucaine; *Belg.:* Muthesa†; *Braz.:* Droxaine; *Canad.:* Mucaine; *Fr.:* Mutesa; *Ger.:* Tepilta; *Hong Kong:* Mucaine; Oxema; *Irl.:* Mucaine; *Ital.:* Magnesia Bisurata Aromatic Plus; Mucoxin†; *NZ:* Mucaine; *Port.:* Betalgil; *S.Afr.:* Mucaine; *Singapore:* Mucaine; *Spain:* Natrocital; Roberfarin; Tepilta†; *Switz.:* Muthesa; *Thai.:* Mucaine; Strocain; *UK:* Mucaine.

Oxybuprocaine Hydrochloride

(7639-k)

Oxybuprocaine Hydrochloride *(BANM, rINNM).*
Benoxinate Hydrochloride; Oxybuprocaini Hydrochloridum.
2-Diethylaminoethyl 4-amino-3-butoxybenzoate hydrochloride.
$C_{17}H_{28}N_2O_3$,HCl = 344.9.
CAS — 99-43-4 (oxybuprocaine); 5987-82-6 (oxybuprocaine hydrochloride).

NOTE. BNX is a code approved by the BP 2001 for use on single unit doses of eye drops containing oxybuprocaine hydrochloride where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p.vi), *Jpn,* and *US.*

Pharmacopoeial description

Ph. Eur.: A white crystalline powder or colourless crystals. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 25: White or slightly off-white, crystals or crystalline powder, odourless or with a slight characteristic odour. Soluble 1 in 0.8 of water, 1 in 2.6 of alcohol, and 1 in 2.5 of chloroform; insoluble in ether. A 1% solution in water has a pH of 5.0 to 6.0.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1302.

Effects on the eyes. Fibrinous iritis and moderate corneal swelling occurred in 2 patients following the use of a 0.4% or 1% solution of oxybuprocaine hydrochloride for topical anaesthesia of the eye for minor surgery.[1] The effects may have been due to inadvertent entry of the drug into the anterior chamber of the eye.

1. Haddad R. Fibrinous iritis due to oxybuprocaine. *Br J Ophthalmol* 1989; 73: 76–7.

Interactions

For interactions associated with local anaesthetics, see p.1303.

Uses and Administration

Oxybuprocaine, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p.1304. It is used for surface anaesthesia (p.1304) and is reported to be less irritant than amethocaine [tetracaine] when applied to the conjunctiva in therapeutic concentrations.

Oxybuprocaine is used as the hydrochloride in a 0.4% solution in short ophthalmological procedures. One drop instilled into the conjunctival sac anaesthetises the surface of the eye sufficiently to allow tonometry after 60 seconds and a further drop after 90 seconds provides adequate anaesthesia for the fitting of contact lenses. Three drops at 90-second intervals produces sufficient anaesthesia after 5 minutes for removal of a foreign body from the corneal epithelium, or for incision of a Meibomian cyst through the conjunctiva. The sensitivity of the cornea is normal again after about 1 hour.

A 1% solution of oxybuprocaine hydrochloride is used for surface anaesthesia of the ear nose, and throat.

Preparations

BP 2001: Oxybuprocaine Eye Drops;
USP 25: Benoxinate Hydrochloride Ophthalmic Solution; Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Aust.: Fortasept†; Novain; *Belg.:* Novesine†; Unicaine†; *Fin.:* Oftan Obucain; *Fr.:* Cebesine; Novesine; *Ger.:* Benoxinat SE; Conjuncain-EDO; Novesine; Oxbarukain; *Hong Kong:* Novesin; *Israel:* Localin; *Ital.:* Novesina; *Port.:* Anestocil; *S.Afr.:* Novesin; *Singapore:* Novesin; *Spain:* Benoxinato†; Prescaina; *Switz.:* Novesin; *Thai.:* Novesin.

Multi-ingredient: *Aust.:* Flurekain; *Austral.:* Fluress; *Belg.:* Anesthesique Double†; *Canad.:* Fluress; *Fin.:* Oftan Flurekain; *Ger.:* Thilorbin; *Mex.:* Mentalgina; *NZ:* Fluress; *Port.:* Mebocaina; *Spain:* Anesti Doble; Fluotest†; *Swed.:* Fluress; *Switz.:* Collu-Blache; Mebucaine; *UAE:* B-Cool; *USA:* Flu-Oxinate; Fluorox; Flurate; Fluress; Flurox.

Parethoxycaine Hydrochloride (13082-m)

Parethoxycaine Hydrochloride *(rINNM).*
2-Diethylaminoethyl 4-ethoxybenzoate hydrochloride.
$C_{15}H_{23}NO_3$,HCl = 301.8.
CAS — 94-23-5 (parethoxycaine); 136-46-9 (parethoxycaine hydrochloride).

Profile

Parethoxycaine hydrochloride, a para-aminobenzoic acid ester, is a local anaesthetic (p.1302) that has been used in pastilles for painful conditions of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Maxicaine.

Pramocaine Hydrochloride (7642-l)

Pramocaine Hydrochloride *(BANM, rINNM).*
Pramoxine Hydrochloride; Pramoxinium Chloride. 4-[3-(4-Butoxyphenoxy)propyl]morpholine hydrochloride.
$C_{17}H_{27}NO_3$,HCl = 329.9.
CAS — 140-65-8 (pramocaine); 637-58-1 (pramocaine hydrochloride).
Pharmacopoeias. In *US.*

Pharmacopoeial description

USP 25: A white or almost white crystalline powder; it may have a faint aromatic odour. Freely soluble in water and in alcohol; soluble 1 in 35 of chloroform; very slightly soluble in ether. A 1% solution in water has a pH of about 4.5. Store in airtight containers.

Profile

Pramocaine hydrochloride is a local anaesthetic (p.1302) used for surface anaesthesia. It is used alone or with corticosteroids and other drugs, usually in a concentration of 1%, in a wide range of formulations for the relief of pain and itching associated with minor skin conditions and anorectal disorders. Initial burning or stinging may occur following topical application. It should not be used for the nose or eyes. The base has been used similarly .

Preparations

USP 25: Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Pramoxine Hydrochloride Cream; Pramoxine Hydrochloride Jelly.

Proprietary Preparations (details are given in Part 3)
Fr.: Tronothane; *Israel:* Anti Itch; *Ital.:* Tronotene; *S.Afr.:* Anugesic; *Spain:* Balsabit; Pramox; *USA:* Anti Itch†; Fleet Pain Relief; PramOtic; Prax; Proctofoam; Tronothane.

Multi-ingredient: *Belg.:* Nestosyl; *Canad.:* Anugesic-HC; Anusol Plus; Aveeno Anti-Itch; Hemorrhoid Ointment; Onguent Hemorrhoidal; PrameGel; Pramox HC; Proctodan-HC; Proctofoam-HC; Sarna-P; *Irl.:* Anugesic-HC; Proctofoam-HC; *Israel:* Epifoam; Proctofoam-HC; *Ital.:* Proctofoam-HC; *S.Afr.:* Anugesic; Proctofoam†; *UK:* Anugesic-HC; Proctocream HC†; Proctofoam-HC; *USA:* 1 + 1-F; Analpram-HC; Anusol; Aveeno Anti-Itch; Betadine Plus First Aid Antibiotics & Pain Reliever; Bite & Itch Lotion; Caladryl; Caladryl Clear; Cortane-B Otic; Cortic; Enzone; Epifoam; Hemorid For Women; Itch-X; Neosporin + Pain Relief; Oti-Med; Otomar-HC; Phicon; Phicon-F; PrameGel; Pramosone; Proctofoam-HC; Tri-Biozene; Tri-Otic; Tronolane; Zone-A; Zoto-HC.

Prilocaine Hydrochloride (7643-y)

Prilocaine Hydrochloride *(BANM, USAN, rINNM).*
Astra-1512; L-67; Prilocaine Hydrochloridum; Propitocaine Hydrochloride. 2-Propylaminopropiono-*o*-toluidide hydrochloride.
$C_{13}H_{20}N_2O$,HCl = 256.8.
CAS — 721-50-6 (prilocaine); 1786-81-8 (prilocaine hydrochloride).

Pharmacopoeias. In *Eur.* (see p.vi) and *US. Eur.* also includes Prilocaine.

Prilocaine forms a mixture with lignocaine [lidocaine] that has a melting-point lower than that of either ingredient. This eutectic mixture is used in the preparation of topical dosage forms.

Pharmacopoeial description

Ph. Eur.: A white crystalline powder or colourless crystals. M.p. 168° to 171°. Freely soluble in water and in alcohol; very slightly soluble in acetone.

USP 25: A white odourless crystalline powder. M.p. 166° to 169°. Soluble 1 in 3.5 of water, 1 in 4.2 of alcohol, and 1 in 175 of chloroform; very slightly soluble in acetone; practically insoluble in ether.

pH of solutions. For a discussion of the effect that pH has on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1304.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1302.

Prilocaine has relatively modest toxicity compared with most amide-type local anaesthetics. However, dose-related methaemoglobinaemia and cyanosis, attributed to the metabolite *o*-toluidine, appear to occur more frequently with prilocaine than with other local anaesthetics (see Methaemoglobinaemia, p.1302). Symptoms usually occur when doses of prilocaine hydrochloride exceed about 8 mg per kg body-weight but the very young may be more susceptible. Methaemoglobinaemia has been observed in neonates whose mothers received prilocaine shortly before delivery and it has also been reported following prolonged topical application of a prilocaine/lignocaine [lidocaine] eutectic mixture in children. (See under Surface Anaesthesia in Lignocaine, p.1316 for precautions to be observed with such a eutectic mixture.) Methaemoglobinaemia may be treated by administering oxygen followed, if necessary, by an injection of methylene blue [methylthioninium chloride].

Prilocaine should be avoided in patients with anaemia, congenital or acquired methaemoglobinaemia, cardiac or ventilatory failure, or hypoxia.

Effects on the CNS. For reference to the prilocaine serum concentrations associated with CNS toxicity, see under Absorption in Pharmacokinetics, below.

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

Interactions

For interactions associated with local anaesthetics, see p.1303.

Methaemoglobinaemia may occur at lower doses of prilocaine in patients receiving concomitant therapy with other drugs known to cause such conditions (e.g. sulfonamides such as sulfamethoxazole in co-trimoxazole).

Neuromuscular blockers. For a possible interaction between *mivacurium* and prilocaine, see under Atracurium, p.1335.

Pharmacokinetics

Prilocaine is reported to be 55% bound to plasma proteins. It is rapidly metabolised mainly in the liver and also in the kidneys and is excreted in the urine mainly as metabolites. One of the principal metabolites excreted in the urine is *o*-toluidine, which is believed to cause the methaemoglobinaemia observed after large doses. Prilocaine crosses the placenta and during prolonged epidural anaesthesia may produce methaemoglobinaemia in the fetus. It is distributed into breast milk.

See also under Local Anaesthetics, p.1303.

Absorption. Peak serum concentrations of prilocaine hydrochloride attained after the use of 8.5 mL of a 1% solution for retrobulbar and facial nerve block were well below the concentration of 20 µg per mL associated with CNS toxicity due to prilocaine.[1]

1. Goggin M, *et al.* Serum concentrations of prilocaine following retrobulbar block. *Br J Anaesth* 1990; 64: 107–9.

Uses and Administration

Prilocaine is a local anaesthetic of the amide type with actions and uses similar to those described on p.1304. It has a similar anaesthetic potency to lignocaine [lidocaine]. However, it has a slower onset of action, less vasodilator activity, and a slightly longer duration of action; it is also less toxic. Prilocaine hydrochloride is used for infiltration anaesthesia and nerve blocks in solutions of 0.5%, 1%, and 2%; a 2% solution is used for epidural block and for analgesia, and for intravenous regional anaesthesia 0.5% solutions are used. A 3% solution with the vasoconstrictor felypressin (p.1283) or a 4% solution without are used for dental procedures. Carbonated solutions of prilocaine have also been tried in some countries in

epidural and brachial plexus nerve blocks (see under Administration, p.1304). Prilocaine is used for surface anaesthesia in a eutectic mixture with lignocaine [lidocaine]. (Local anaesthetic techniques are discussed on p.1304.)

The dosage used in various **local anaesthetic procedures** varies with the site of injection and the procedure used. The recommended **maximum single dose** in adults for prilocaine hydrochloride is 400 mg if used alone, or 300 mg if used with felypressin. Doses should be reduced for elderly or debilitated patients. The dose for children over 6 months of age is up to 5 mg per kg body-weight. For *dental infiltration* or *dental nerve blocks*, the usual adult dose of prilocaine hydrochloride without felypressin is 40 to 80 mg (1 to 2 mL) as a 4% solution; children under 10 years of age generally require about 40 mg (1 mL). The usual adult dose of prilocaine hydrochloride with felypressin 0.03 units per mL is 30 to 150 mg (1 to 5 mL) as a 3% solution; children under 10 years of age generally require 30 to 60 mg (1 to 2 mL).

A eutectic mixture (see p.1316) of prilocaine base 2.5% and lignocaine [lidocaine] base 2.5% is applied as a cream under an occlusive dressing to produce *surface anaesthesia* of the skin before procedures requiring needle puncture, surgical treatment of localised lesions, and split skin grafting; it has been used similarly, but without an occlusive dressing, before removal of genital warts.

tion. For a comparison of the vasoactivity of prilocaine and some other local anaesthetics, see p.1304.

Infiltration anaesthesia. Addition of felypressin at a concentration of 0.03 units per mL to prilocaine 3% injection did not reduce plasma concentrations of prilocaine after infiltration of a 60-mg dose into the upper premolar region.[1]

1. Cannell H, Whelpton R. Systemic uptake of prilocaine after injection of various formulations of the drug. *Br Dent J* 1986; 160: 47–9.

Preparations

BP 2001: Prilocaine Injection;
USP 25: Prilocaine and Epinephrine Injection; Prilocaine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Citanest; Citanest Dental; ***Belg.:*** Citanest; ***Braz.:*** Citanest; Citocaina; ***Canad.:*** Citanest; ***Denm.:*** Citanest Octapressin; ***Fin.:*** Citanest; Citanest Octapressin; ***Ger.:*** Xylonest; ***IrL:*** Citanest; Citanest with Octapressin; ***Ital.:*** Citanest con Octapressin; ***Mex.:*** Citanest Octapresin; ***Neth.:*** Citanest; Citanest Octapressine; ***Norw.:*** Citanest Octapressin; ***NZ:*** Citanest; Citanest Octapressin; ***Port.:*** Citanest Octapressin†; ***S.Afr.:*** Citanest Octopressin†; ***Spain:*** Citanest; Citanest Octapressin; ***Swed.:*** Citanest; Citanest Octapressin; ***Switz.:*** Xylonest; Xylonest-Octapressin; ***UK:*** Citanest; Citanest with Octapressin; ***USA:*** Citanest.

Multi-ingredient: ***Aust.:*** Emla; ***Austral.:*** Emla; ***Belg.:*** Emla; ***Braz.:*** Emla; Medicaina; ***Canad.:*** Emla; ***Denm.:*** Emla; ***Fin.:*** Citanest; Emla; ***Fr.:*** Emla; Emlapatch; ***Ger.:*** Emla; ***Hong Kong:*** Emla; ***Irl.:*** Emla; ***Israel:*** Emla; ***Ital.:*** Emla; ***Neth.:*** Emla; ***Norw.:*** Citanest; Emla; ***NZ:*** Emla; ***Port.:*** Emla; ***S.Afr.:*** Emla; ***Singapore:*** Emla; ***Spain:*** Emla; ***Swed.:*** Emla; ***Switz.:*** Emla; ***Thai.:*** Emla; ***UK:*** Emla; ***USA:*** Emla.

Procaine Hydrochloride (7644-j)

Procaine Hydrochloride *(BANM, rINNM).*

Allocaine; Ethocaine Hydrochloride; Novocainum; Procaini Hydrochloridum; Procainii Chloridum; Procainium Chloride; Syncaine. 2-Diethylaminoethyl 4-aminobenzoate hydrochloride.

$C_{13}H_{20}N_2O_2.HCl = 272.8$.
CAS — 59-46-1 (procaine); 51-05-8 (procaine hydrochloride).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vi), *Int.*, *Jpn*, *Pol.*, and *US.*

Incompatibility has been reported with aminophylline, barbiturates, magnesium sulfate, phenytoin sodium, sodium bicarbonate, and amphotericin B.

Pharmacopoeial description

Ph. Eur.: A white crystalline powder or colourless crystals. Very soluble in water; soluble in alcohol; practically insoluble in ether. A 2% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 25: Odourless, small, white crystals or white, crystalline powder. Soluble 1 in 1 of water and 1 in 15 of alcohol; slightly soluble in chloroform; practically insoluble in ether.

Stability of solutions. Degradation of procaine in a cardioplegic solution containing magnesium, sodium, potassium, and calcium salts was found to be temperature dependent.[1] At a storage temperature of 6° the shelf-life of the solution was 5 weeks and this was increased to 9 weeks when the storage temperature was −10°. Using carbon dioxide instead of nitrogen in the head space did not affect stability of procaine.

1. Synave R, *et al.* Stability of procaine hydrochloride in a cardioplegic solution containing bicarbonate. *J Clin Hosp Pharm* 1985; 10: 385–8.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1302.

Effects on the cardiovascular system. Severe hypotension leading to cardiac arrest and death developed in a patient following the infusion of 600 mg of procaine for malignant hyperthermia.[1]

1. MacLachlan D, Forrest AL. Procaine and malignant hyperthermia. *Lancet* 1974; i: 355.

Hypersensitivity. Of 600 persons with dermatitis or eczema submitted to patch testing with 2% aqueous solution of procaine hydrochloride, 4.8% gave a positive reaction.[1]

For reports of hypersensitivity including anaphylactic reactions associated with procaine and other local anaesthetics, see under Adverse Effects of Local Anaesthetics, p.1302.

1. Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; 83: 543–5.

Systemic lupus erythematosus. The limited theoretical risk from using procaine for local anaesthesia in patients who have had procainamide-induced systemic lupus erythematosus was aired some years ago.[1-3]

1. Dubois EL. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; 238: 2201.
2. Alarcón-Segovia D. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; 238: 2201.
3. Lee SL. Procaine anesthesia after procainamide-induced systemic erythematosus. *JAMA* 1977; 238: 2201.

Interactions

For interactions associated with local anaesthetics, see p.1303.

Diuretics. Concomitant administration of *acetazolamide* extends the plasma half-life of procaine.[1]

1. Calvo R, *et al.* Effects of disease and acetazolamide on procaine hydrolysis by red blood cell enzymes. *Clin Pharmacol Ther* 1980; 27: 179–83.

Pharmacokinetics

Procaine is poorly absorbed from mucous membranes but is readily absorbed following parenteral administration. It is rapidly hydrolysed by plasma cholinesterase to para-aminobenzoic acid and diethylaminoethanol; some may also be metabolised in the liver. Only about 6% is bound to plasma proteins. About 80% of the para-aminobenzoic acid is excreted unchanged or conjugated in the urine. About 30% of the diethylaminoethanol is excreted in the urine, the remainder being metabolised in the liver.

See also under Local Anaesthetics, p.1303.

Uses and Administration

Procaine hydrochloride, a para-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p.1304. Because of its poor penetration of intact mucous membranes, procaine is ineffective for surface application and has been chiefly used by injection, although in general it has been replaced by lignocaine [lidocaine] and other local anaesthetics. It has a slow onset of action and a short duration of action. It has vasodilator activity and therefore a vasoconstrictor may be added to delay absorption and increase the duration of action. Procaine has mainly been used for infiltration anaesthesia, peripheral nerve blocks, and spinal block. (Local anaesthetic techniques are discussed on p.1304.) It has also been used in cardioplegic solutions to protect the myocardium during cardiac surgery.

For *infiltration anaesthesia* 0.25 to 0.5% solutions of procaine hydrochloride have been used in doses of 350 to 600 mg.

For *peripheral nerve block* a usual dose of 500 mg of procaine hydrochloride has been given as a 0.5% (100 mL), 1% (50 mL), or 2% (25 mL) solution. Doses up to 1 g have been used. For infiltration and peripheral nerve block adrenaline [epinephrine] has been added to solutions, in general to give a final concentration of 1 in 200 000 to 1 in 100 000.

Procaine hydrochloride has been used with propoxycaine in dentistry.

Procaine forms poorly soluble salts or conjugates with some drugs, for example penicillin, and is used to prolong their action after injection. It may also reduce the pain of injection.

Procaine-*N*-glucoside hydrochloride has been included in a preparation for gastrointestinal disorders, and procaine ascorbate has been included in a multivitamin preparation.

Action. For a comparison of the vasoactivity of procaine and some other local anaesthetics, see p.1304.

Preparations

USP 25: Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Procaine Hydrochloride and Epinephrine Injection; Procaine Hydrochloride Injection; Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Proprietary Preparations (details are given in Part 3)
Aust.: Geroaslan H3; Gerovital H3; Novanaest; ***Canad.:*** Novocain; ***Ger.:*** Hewedolor Procain; Lophakomp-Procain N; Novocain; Pasconeural-Injektopas 1%†; Procaneural; ***Hong Kong:*** Gerovital H3; ***Ital.:*** Lenident; ***Spain:*** Anestesia Loc Braun C/A; Venocaina†; ***Switz.:*** Syntocaine†; ***USA:*** Novocain.

Multi-ingredient: ***Aust.:*** Aslavital; Biolecit H3; Causat†; Gerontin; KH3; Regenerin; ***Austral.:*** Cardioplegia; ***Belg.:*** Otocalmine; Tympalgine; ***Braz.:*** Algidente; Auditol; Axol; Bismu-Jet; Claudemor; Colutoide; Dexa-Neuriberi; Dexador; Dexaneurin; Fonergin; Geri-Kan H3; KLGH 3; Malvosulfam; Otobel; Otoloide; Otonax; Oturga; Passaja; Pradente; Timpanol; Verlin; Visual; ***Denm.:*** Kardioplex; ***Fr.:*** Antiseptique-Calmante; Novitan†; Otylol; Rectophedrol†; X-Adene†; ***Ger.:*** Cardioplegin N; Causat B12 N; Causat N; Dodecatol N; Echtrovit-K†; Gero H3 Aslan; Hewedolor plus Coffein†; Impletol; KH3; NeyChondrin N (Revitorgan-Dilutionen N Nr 68); NeyPulpin N (Revitorgan-Dilutionen N Nr 10); Otalgan; Otodolor; Pasconeural-Injektopas; Revicain; Revicain comp; Revicain comp plus; Veno-Kattwiga N; ***Hong Kong:*** Cardioplegia; KH3; ***Israel:*** Bedodeka Antineuralgica; ***Ital.:*** Citroftalmina; Citroftalmina VC; Dentosedina; Ginvapast; Mios; Neo-Ustiol; Oftalzina; Otalgan; Otomidone; Otopax; Rinantipiol; Ustiosan; ***NZ:*** KH3; ***Port.:*** Claudemor; Gramixina; KH3†; Otalgan; Otocalma; ***S.Afr.:*** Universal Earache Drops; ***Singapore:*** Cardioplegia; ***Spain:*** Anestesia Loc Braun S/A; Anestina Braun†; Co Bucal; Coliriocilina Adren Astr; Dentol Topico; Eupnol; Hepadigest†; Higado Potenciado Medic†; Kanafosal; Kanafosal Predni; KH3 Powel; Neocolan; Nulacin Fermentos; Oftalmol Dexa†; Oftalmol Ocular; Otalgan; Otonasal; Otosedol; Tangenol; ***Switz.:*** Anaestalgin; Ginvapast; Nasello†; Otalgan; Otosan; ***Thai.:*** Cardioplegia; KH3; ***UK:*** KH3; ***USA:*** Ravocaine and Novocain†.

Used as an adjunct in: ***Braz.:*** Isacilin; ***Ger.:*** Eukalisan N; Redox-Injektopas†; ***Ital.:*** Neuroftal; ***Singapore:*** Alinamin B12; ***Spain:*** Sulmetin; Sulmetin Papaverina; ***USA:*** Hemocyte; Hytinic; Licoplex DS†.

Propanocaine Hydrochloride (7645-z)

Propanocaine Hydrochloride *(rINNM).*

467D_3. 3-Diethylamino-1-phenylpropyl benzoate hydrochloride.

$C_{20}H_{25}NO_2.HCl = 347.9$.
CAS — 493-76-5 (propanocaine); 1679-79-4 (propanocaine hydrochloride).

Profile

Propanocaine hydrochloride, a benzoic acid ester, is a local anaesthetic (p.1302) that has been used topically for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Lelong Irritations†; ***Spain:*** Detraine.

Propipocaine (19750-h)

Propipocaine *(rINN).*

Propoxypiperocaine. 3-Piperidino-4′-propoxypropiophenone.

$C_{17}H_{25}NO_2 = 275.4$.
CAS — 3670-68-6.

Profile

Propipocaine is a local anaesthetic (p.1302) that has been used for surface anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Nifucin†.

Propoxycaine Hydrochloride (7646-c)

Propoxycaine Hydrochloride *(rINNM).*

Propoxycainium Chloride. 2-Diethylaminoethyl 4-amino-2-propoxybenzoate hydrochloride.

$C_{16}H_{26}N_2O_3.HCl = 330.9$.
CAS — 86-43-1 (propoxycaine); 550-83-4 (propoxycaine hydrochloride).

Pharmacopoeias. In *US.*

Pharmacopoeial description

USP 25: A white odourless crystalline solid. It discolours on prolonged exposure to light and air. Soluble 1 in 2 of water, 1 in 10 of alcohol, and 1 in 80 of ether; practically insoluble in acetone and in chloroform. A 2% solution in water has a pH of about 5.4. Protect from light.

Profile

Propoxycaine hydrochloride, a para-aminobenzoic acid ester, is a local anaesthetic (p.1302). It has been used in a concentration of 0.4% in combination with procaine hydrochloride 2% solution with a vasoconstrictor for infiltration anaesthesia and nerve block in dental procedures. Propoxycaine has a more rapid onset and a longer duration of action than that of procaine.

Preparations

USP 25: Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***USA:*** Ravocaine and Novocain†.

Proxymetacaine Hydrochloride

(7647-k)

Proxymetacaine Hydrochloride *(BANM, rINNM).*

Proparacaine Hydrochloride. 2-Diethylaminoethyl 3-amino-4-propoxybenzoate hydrochloride.

$C_{16}H_{26}N_2O_3$,HCl = 330.9.

CAS — 499-67-2 (proxymetacaine); 5875-06-9 (proxymetacaine hydrochloride).

NOTE. PROX is a code approved by the BP 2001 for use on single unit doses of eye drops containing proxymetacaine hydrochloride where the individual container may be too small to bear all the appropriate labelling information. PROXFLN is a similar code approved for eye drops containing proxymetacaine hydrochloride and fluorescein sodium.

Pharmacopoeias. In *Br.* and *US.*

Pharmacopoeial description

BP 2001: A white or almost white, odourless or almost odourless, crystalline powder. Soluble in water and in chloroform; very soluble in dehydrated alcohol; practically insoluble in ether. A 1% solution in water has a pH of 5.7 to 6.4. Protect from light.

USP 25: A white to off-white, or faintly buff-coloured, odourless, crystalline powder. Soluble in water, in warm alcohol, and in methyl alcohol; insoluble in ether and in benzene.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1302.

A severe immediate-type corneal reaction to proxymetacaine may rarely occur. Allergic contact dermatitis has also been reported.

Effects on the skin. Exacerbation of Stevens-Johnson syndrome has been reported[1] in a woman after ophthalmic anaesthesia with proxymetacaine hydrochloride.

1. Ward B, *et al.* Dermatologic reaction in Stevens-Johnson syndrome after ophthalmic anesthesia with proparacaine hydrochloride. *Am J Ophthalmol* 1978; **86:** 133–5.

Interactions

For interactions associated with local anaesthetics, see p.1303.

Pharmacokinetics

See under Local Anaesthetics, p.1303.

Uses and Administration

Proxymetacaine hydrochloride, a meta-aminobenzoic acid ester, is a local anaesthetic with actions and uses similar to those described on p.1304. It is used for surface anaesthesia (p.1304) in ophthalmology in a concentration of 0.5%. Proxymetacaine is of similar potency to amethocaine [tetracaine] in equal concentrations and induces anaesthesia within about 20 seconds. The duration of action may be 15 minutes or longer. Instillation of 1 or 2 drops permits tonometry after 30 seconds. For removal of foreign bodies or sutures from the cornea 1 or 2 drops are instilled every 5 to 10 minutes for up to three doses, or 1 or 2 drops are instilled 2 to 3 minutes before the procedure. For deeper anaesthesia such as needed for cataract extraction 1 drop is instilled every 5 to 10 minutes to a total of 5 to 7 applications.

Trigeminal neuralgia. There have been anecdotal reports that proxymetacaine eye drops relieved trigeminal neuralgia (p.8) refractory to carbamazepine.[1,2] However, a controlled study failed to demonstrate any benefit.[3]

1. Zavon MR, Fichte CM. Trigeminal neuralgia relieved by ophthalmic anesthetic. *JAMA* 1991; **265:** 2807.
2. Zavon MR, Fichte CM. Trigeminal neuralgia relieved by optical anesthesia. *JAMA* 1991; **266:** 1649.
3. Kondziolka D, *et al.* The effect of single-application topical ophthalmic anesthesia in patients with trigeminal neuralgia: a randomized double-blind placebo-controlled trial. *J Neurosurg* 1994; **80:** 993–7.

Preparations

BP 2001: Proxymetacaine Eye Drops;
USP 25: Fluorescein Sodium and Proparacaine Hydrochloride Ophthalmic Solution; Proparacaine Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Austral.: Alcaine; Ophthetic; *Braz.:* Anestalcon; Visonest; *Canad.:* Ak-Taine; Alcaine; Diocaine; Ophthetic; *Ger.:* Chibro-Kerakain†; Proparakain-POS; *Hong Kong:* Alcaine; *Irl.:* Ophthaine†; *Mex.:* Alcaine; *Norw.:* Alcaine; *NZ:* Ophthetic; *S.Afr.:* Ophthetic†; *Singapore:* Alcaine; *Switz.:* Alcaine; *UK:* Ophthaine†; *USA:* Ak-Taine; Alcaine; Ocu-Caine; Ophthaine†; Ophthetic; Parcaine.

Multi-ingredient: *Canad.:* Fluoracaine; *USA:* Fluoracaine; Fluorocaine.

Quinisocaine Hydrochloride (7622-p)

Quinisocaine Hydrochloride *(BANM, rINNM).*

Chinisocainum Hydrochloride; Dimethisoquin Hydrochloride *(USAN);* Dimethisoquinium Chloride. 2-(3-Butyl-1-isoquinolyloxy)-*NN*-dimethylethylamine hydrochloride.

$C_{17}H_{24}N_2O$,HCl = 308.8.

CAS — 86-80-6 (quinisocaine); 2773-92-4 (quinisocaine hydrochloride).

Profile

Quinisocaine hydrochloride is a local anaesthetic (p.1302) available in some countries for use as a surface anaesthetic in the form of an ointment or cream in a concentration of 0.5% or as suppositories. It is used for the relief of pruritus, anogenital or anorectal irritation, and minor skin conditions.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Quotane; *Ger.:* Haenal†; Isochinol; *Switz.:* Isochinol.

Multi-ingredient: *Fr.:* Rectoquotane.

Ropivacaine Hydrochloride (7300-y)

Ropivacaine Hydrochloride *(BANM, rINNM).*

AL-281. (*S*)-2′,6′-Dimethyl-1-propylpiperidine-2-carboxanilide hydrochloride monohydrate.

$C_{17}H_{26}N_2O$,HCl,H_2O = 328.9.

CAS — 84057-95-4 (ropivacaine); 98717-15-8 (anhydrous ropivacaine hydrochloride); 132112-35-7 (ropivacaine hydrochloride monohydrate).

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1302.

Effects on the cardiovascular system. Ropivacaine is structurally related to bupivacaine, but data from extensive *animal* studies suggest that ropivacaine may be less cardiotoxic than bupivacaine.[1] Results from a study[2] in 12 healthy male volunteers support these data; at doses producing CNS symptoms cardiovascular changes, such as depression of conduction and diastolic function, were less pronounced with ropivacaine than with bupivacaine.

1. Cederholm I. Preliminary risk-benefit analysis of ropivacaine in labour and following surgery. *Drug Safety* 1997; **16:** 391–402.
2. Knudsen K, *et al.* Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; **78:** 507–14.

Interactions

For interactions associated with local anaesthetics, see p.1303.

Concomitant administration of ropivacaine with general anaesthetics, opioid analgesics, or drugs structurally related to amide-type local anaesthetics (e.g. certain antiarrhythmics) may result in potentiation of adverse effects.

The metabolism of ropivacaine is mediated by the cytochrome P450 isoenzyme CYP1A2 and the potential exists for interactions between ropivacaine and other drugs which inhibit or act as a substrate for this isoenzyme. Prolonged administration of ropivacaine should be avoided in patients treated with potent CYP1A2 inhibitors, such as fluvoxamine and verapamil. Plasma concentrations of ropivacaine may be reduced by enzyme-inducing drugs such as rifampicin.

Pharmacokinetics

Ropivacaine is about 94% bound to plasma proteins. The terminal elimination half-life has been reported to be 1.8 hours. It is extensively metabolised in the liver, predominantly by aromatic hydroxylation which is mediated by the cytochrome P450 isoenzyme CYP1A2; CYP3A4 plays a minor role in the metabolism of ropivacaine. The metabolites are excreted mainly in the urine; about 1% of a dose is excreted as unchanged drug. Some metabolites also have a local anaesthetic effect but less than that of ropivacaine. Ropivacaine crosses the placenta.

See also under Local Anaesthetics, p.1303.

Uses and Administration

Ropivacaine hydrochloride is a local anaesthetic of the amide type with actions and uses similar to those described on p.1304. It is a long-acting local anaesthetic, although onset and duration of action are dependent upon the administration site; the presence of a vasoconstrictor such as adrenaline [epinephrine] has no effect. Ropivacaine is used for epidural block, peripheral nerve block, and infiltration anaesthesia and field block. (Local anaesthetic techniques are discussed on p.1304.) At high doses ropivacaine produces surgical anaesthesia, whereas at lower doses it is used for the management of acute pain such as labour pain (p.6) and in postoperative analgesia (p.4).

Like bupivacaine (p.1306), ropivacaine has a differential blocking effect on nerve fibres and, at the lowest concentration used, there is good differentiation between sensory and motor block. The onset and duration of sensory block produced by ropivacaine is generally similar to that obtained with bupivacaine but the motor block is often slower in onset, shorter in duration, and less intense.

Ropivacaine hydrochloride is administered in concentrations of 0.2 to 1%. The dosage depends on the site of injection and the procedure used, as well as the status of the patient. The dose of ropivacaine should be reduced in the elderly, and in acutely ill or debilitated patients. A test dose of lignocaine [lidocaine] with adrenaline [epinephrine] should be given before commencing epidural block with ropivacaine to detect inadvertent intravascular administration.

For **surgical anaesthesia**, doses of ropivacaine hydrochloride for *lumbar epidural block* are 75 to 150 mg (15 to 30 mL) as a 0.5% solution, or 112.5 to 187.5 mg (15 to 25 mL) as a 0.75% solution, or 150 to 200 mg (15 to 20 mL) as a 1% solution; for caesarean section, doses are 100 to 150 mg (20 to 30 mL) as a 0.5% solution or 112.5 to 150 mg (15 to 20 mL) as a 0.75% solution. Doses for *thoracic epidural block* to establish a block for postoperative pain relief are 25 to 75 mg (5 to 15 mL) as a 0.5% solution or 37.5 to 112.5 mg (5 to 15 mL) as a 0.75% solution; the actual dose used depends on the level of the injection. For *peripheral nerve block* of major nerves such as the brachial plexus, typical doses are 175 to 250 mg (35 to 50 mL) as a 0.5% solution; 225 to 300 mg (30 to 40 mL) as a 0.75% solution has also been recommended for brachial plexus block. For *infiltration anaesthesia* and *field block* up to 200 mg (40 mL) as a 0.5% solution or up to 225 mg (30 mL) as a 0.75% solution may be used.

In the management of **acute pain** ropivacaine hydrochloride is used as a 0.2% solution for epidural block (0.5% solutions may be used for infiltration). Doses for *lumbar epidural block* are 20 to 40 mg (10 to 20 mL) as an initial bolus followed by 20 to 30 mg (10 to 15 mL) at intervals of not less than 30 minutes. Alternatively, 12 to 20 mg (6 to 10 mL) per hour may be given as a continuous epidural infusion; if additional pain relief is required, doses of up to 28 mg (14 mL) per hour may be given. Doses for *thoracic epidural block* are 12 to 28 mg (6 to 14 mL) per hour as a continuous infusion. For *infiltration anaesthesia* doses are 2 to 200 mg (1 to 100 mL) as a 0.2% solution or 5 to 200 mg (1 to 40 mL) as a 0.5% solution.

In children aged 1 year and over, ropivacaine hydrochloride may be used for the management of pre- and postoperative pain. A 0.2% solution is given in doses of 2 mg per kg body-weight (1 mL per kg) to achieve a *caudal epidural block.*

◊ References.

1. Markham A, Faulds D. Ropivacaine: a review of its pharmacology and therapeutic use in regional anaesthesia. *Drugs* 1996; **52:** 429–49.
2. McClure JH. Ropivacaine. *Br J Anaesth* 1996; **76:** 300–307
3. Morton C. Ropivacaine. *Br J Hosp Med* 1997; **58:** 97–100.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Naropin; *Austral.:* Naropin; *Belg.:* Naropin; *Canad.:* Naropin; *Denm.:* Naropin; *Fin.:* Naropin; *Fr.:* Naropeine; *Ger.:* Naropin; *Hong Kong:* Naropin; *Irl.:* Naropin; *Israel:* Narop; *Ital.:* Naropina; *Mex.:* Naropin; *Neth.:* Naropin; *Norw.:* Naropin; *NZ:* Naropin; *Port.:* Naropeine; *S.Afr.:* Naropin; *Singapore:* Naropin; *Spain:* Naropin; *Swed.:* Narop; *Switz.:* Naropin; *UK:* Naropin; *USA:* Naropin.

Multi-ingredient: *Austral.:* Naropin with Fentanyl.

Tolycaine Hydrochloride (7649-t)

Tolycaine Hydrochloride *(BANM, rINNM)*.

Methyl 2-(2-diethylaminoacetamido)-*m*-toluate hydrochloride.

$C_{15}H_{22}N_2O_3$,HCl = 314.8.

CAS — 3686-58-6 (tolycaine); 7210-92-6 (tolycaine hydrochloride).

Profile

Tolycaine hydrochloride is an amide local anaesthetic (p.1302) included in some preparations to reduce the pain of injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Used as an adjunct in: Ger.: Tardocillin.

Tricaine Mesilate (11077-y)

Metacaine Mesylate; Tricaine Mesylate. Ethyl 3-aminobenzoate methanesulphonate.

$C_{10}H_{15}NO_5S$ = 261.3.

CAS — 886-86-2.

Profile

Tricaine mesilate is a derivative of an isomer of benzocaine (see p.1306) and although it has been used as a local anaesthetic in human medicine it is now mainly used as an anaesthetic and tranquilliser for fish and other cold-blooded animals.

Trimecaine Hydrochloride (7650-l)

Trimecaine Hydrochloride *(rINNM)*.

Trimecainium Chloratum. 2-Diethylamino-2',4',6'-trimethylacetanilide hydrochloride.

$C_{15}H_{24}N_2O$,HCl = 284.8.

CAS — 616-68-2 (trimecaine); 1027-14-1 (trimecaine hydrochloride).

Profile

Trimecaine hydrochloride is an amide local anaesthetic (p.1302) included in some preparations to reduce the pain of injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Used as an adjunct in: Aust.: Ketazon; *Ger.:* Ketazon.

Martindale

The complete drug reference

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