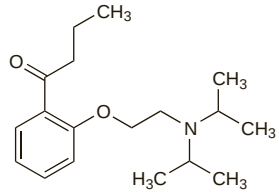
Ketocaine Hydrochloride *(rINNM)*

Chetocaina Cloridrata; Hidrocloruro de ketocaína; Kétocaïne, Chlorhydrate de; Ketocaini Hydrochloridum. 2′-(2-Di-isopropylaminoethoxy)butyrophenone hydrochloride.

Кетокаина Гидрохлорид

$C_{18}H_{29}NO_2,HCl$ = 327.9.

CAS — 1092-46-2 (ketocaine); 1092-47-3 (ketocaine hydrochloride).



(ketocaine)

Profile

Ketocaine hydrochloride is a local anaesthetic (p.1850) 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 *(BAN, rINN)*

S(−)-Bupivacaine; Levobupivacaína; Lévobupivacaïne; Levobupivacainum; Levobupivakaiini; Levobupivakain. (*S*)-1-Butyl-2-piperidylformo-2′,6′-xylidide.

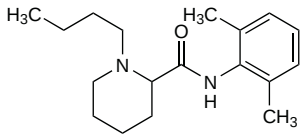
Левобупивакаин

$C_{18}H_{28}N_2O$ = 288.4.

CAS — 27262-47-1.

ATC — N01BB10.

ATC Vet — QN01BB10.



Levobupivacaine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levobupivacaína; Lévobupivacaïne, Chlorhydrate de; Levobupivacaini Hydrochloridum; Levobupivakain Hidroklorür.

Левобупивакаина Гидрохлорид

$C_{18}H_{28}N_2O,HCl$ = 324.9.

CAS — 27262-48-2.

ATC — N01BB10.

ATC Vet — QN01BB10.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850.

Levobupivacaine is contra-indicated for use in intravenous regional anaesthesia (Bier's block) and for paracervical block in obstetrics. The 0.75% solution is also 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.1855).

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.1851. 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.1855). Levobupivacaine is at least 97% bound to plasma proteins. After intravenous doses 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; the isoenzyme 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.1852. It is the S-enantiomer of bupivacaine (p.1854). 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 also contra-indicated for epidural blocks in obstetrics. (Local anaesthetic techniques are discussed on p.1853.)

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, should be given before commencing epidural block with levobupivacaine to detect inadvertent intravascular injection. Subsequent doses of levobupivacaine should be given in small increments. Levobupivacaine should be given in reduced doses to elderly, debilitated, or acutely ill patients.

- 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 have been expressed on the basis of body-weight: 1 to 2 mg/kg (0.4 mL/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, doses of levobupivacaine are 0.625 to 2.5 mg/kg (0.25 to 0.5 mL/kg) as a 0.25 or 0.5% solution.
- In the management of **acute pain** levobupivacaine 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, or a 0.0625% solution may be given in a dose of 5 to 12.5 mg (8 to 20 mL) per hour. For *postoperative pain* 10 to 25 mg (4 to 10 mL) per hour as a 0.25% solution, 12.5 to 18.75 mg (10 to 15 mL) per hour as a 0.125% solution, or 12.5 to 18.75 mg (20 to 30 mL) per hour as a 0.0625% solution may be given as an epidural infusion.

In some countries such as the UK, licensed product information recommends that a lower concentration such as the 0.125% solution should be used if other analgesics are also given for pain relief; in other countries product information has specifically stated that the 0.125% solution should only be used for adjunctive therapy with fentanyl or clonidine. 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 than 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)

Austral.: Chirocaine; ***Austria:*** Chirocaine; ***Belg.:*** Chirocaine; ***Braz.:*** Novabupi; ***Chile:*** Chirocaina; ***Cz.:*** Chirocaine; ***Fin.:*** Chirocaine; ***Fr.:*** Chirocaine; ***Gr.:*** Chirocaine; ***Hong Kong:*** Chirocaine; ***Hung.:*** Chirocaine; ***Irl.:*** Chirocaine; ***Ital.:*** Chirocaine; ***Mex.:*** Quirocaine; ***Neth.:*** Chirocaine; ***Norw.:*** Chirocaine; ***NZ:*** Chirocaine†; ***Philipp.:*** SensiBloq; ***Port.:*** Chirocaine; ***S.Afr.:*** Chirocaine; ***Singapore:*** Chirocaine; ***Spain:*** Chirocaine; ***Swed.:*** Chirocaine; ***Switz.:*** Chirocaine; ***Turk.:*** Chirocaine; ***UK:*** Chirocaine; ***USA:*** Chirocaine†; ***Venez.:*** Chirocaina.

Lidocaine *(BAN, rINN)*

Lidocaína; Lidocaïne; Lidocainum; Lidokaiini; Lidokain; Lidokaina; Lidokainas; Lignocaine. 2-Diethylaminoaceto-2′,6′-xylidide.

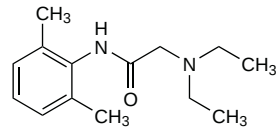
Лидокаин

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

CAS — 137-58-6.

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

ATC Vet — QC01BB01; QC05AD01; QD04AB01; QN01BB02; QR02AD02; QS01HA07; QS02DA01.



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

Ph. Eur. 6.2 (Lidocaine). A white or almost white, crystalline powder. M.p. 66° to 70°. Practically insoluble in water; very soluble in alcohol and in dichloromethane.

USP 31 (Lidocaine). 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.

Eutectic mixture. 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.

Lidocaine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de lidocaína; Lidocaïne, chlorhydrate de; Lidocaini hydrochloridum; Lidocaini Hydrochloridum Monohydricum; Lidokaiinihydrokloridi; Lidokain Hidroklorür; Lidokain-hidroklorid; Lidokain-hydrochlorid monohydrát; Lidokainhydroklorid; Lidokaino hidrochloridas; Lidokainy chlorowodorek; Lignoc. Hydrochlor.; Lignocaine Hydrochloride; Lignokain Hidroklorür.

Лидокаина Гидрохлорид

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

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

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

ATC Vet — QC01BB01; QC05AD01; QD04AB01; QN01BB02; QR02AD02; QS01HA07; QS02DA01.

NOTE. LIDFLN is a code approved by the BP 2008 for use on single unit doses of eye drops containing 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.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Lidocaine Hydrochloride). A white, or almost white, crystalline powder. M.p. 74° to 79°. Very soluble in water; freely soluble in alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 31 (Lidocaine Hydrochloride). A white, odourless, crystalline powder. M.p. 74° to 79°. Very soluble in water and in alcohol; soluble in chloroform; insoluble in ether.

Incompatibility. 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 hydrochloride, noradrenaline acid tartrate, or isoprenaline may begin to deteriorate within several hours of admixture with lidocaine hydrochloride as 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 lidocaine solutions by infusion, see under Administration in Uses and Administration, p.1852. For its effect on the stability of local anaesthetic solutions and the pain associated with their injection, see p.1852.

Stability. Although there was no decrease in the lidocaine content of lidocaine hydrochloride and adrenaline injection during transport and storage under tropical conditions, the content of adrenaline 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 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 lidocaine onto the plastic and did not occur when 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.1850.

Effects on the CNS. Suspected psychotic reactions have been reported in 6 patients given intravenous lidocaine for the treatment of cardiac disorders.[1] In another case,[2] 2 patients developed signs of cerebral ataxia after topical use of lidocaine for endoscopy.

When compared with other local anaesthetics, lidocaine may be associated with an increased risk of neurotoxic complications when used for spinal anaesthesia, (see under Adverse Effects of Central Block, p.1850).

1. Turner WM. Lidocaine and psychotic reactions. *Ann Intern Med* 1982; **97:** 149–50.
2. Perney P, *et al.* Transitory ataxia related to topically administered lidocaine. *Ann Pharmacother* 2004; **38:** 828–30.

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

True hypersensitivity reactions, including dermatitis, are rare (see also p.1850) 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 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 lidocaine is relatively common and can occur as a result of acute overdosage after poor control of intravenous maintenance infusions or accidental injection of concentrated solutions. However, it more commonly results from inadvertent intravascular dosage 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 given subcutaneously.[2] Although the bioavailability of lidocaine is low it may be sufficient to result in significant toxicity when swallowed[1] and there have been reports of CNS effects, seizures, and death in children[3-7] and adults[8-10] after the ingestion of topical solutions and after the use of viscous preparations in the mouth. Death has also ensued after gargling with a 4% lidocaine solution.[11] Lidocaine is absorbed from mucous membranes and serious toxicity has been reported after urethral[12] or rectal[13] instillation of 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. Serious adverse effects of epidural anaesthesia are rare but 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.1851.

In general 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. Lidocaine is metabolised in the liver and must be given with caution to patients with hepatic impairment. The plasma half-life of lidocaine may be prolonged in conditions that reduce hepatic blood flow such as cardiac and circulatory failure. Metabolites of lidocaine may accumulate in patients with renal impairment.

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

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving lidocaine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Cerebrovascular disorders. Lidocaine 5 mg/kg by intravenous infusion over 30 minutes was associated with a 12% reduction in cerebral blood flow in healthy subjects although this returned to normal within 60 minutes.[1] Cerebral blood flow in patients with diabetes was lower than in healthy subjects, but was unaffected by 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. 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 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 lidocaine and glycinexylidide removed during haemodialysis have been provided.[2,3] 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 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.1851.

The clearance of lidocaine may be reduced by propranolol and cimetidine (see below). The cardiac depressant effects of lidocaine are additive with those of beta blockers and of other antiarrhythmics. Additive cardiac effects may also occur when lidocaine is given with intravenous phenytoin; however, the long-term use of phenytoin and other enzyme-inducers may increase dosage requirements of lidocaine (see Antiepileptics, below). Hypokalaemia produced by acetazolamide, loop diuretics, and thiazides antagonises the effect of lidocaine.

Antiarrhythmics. Lidocaine toxicity, arising from the use of an oral preparation containing 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 lidocaine with *ajmaline*,[2] *amiodarone*,[3,4] or *tocainide*.[5] Delirium has been reported in a patient who received lidocaine 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 lidocaine due to induction of drug-metabolising microsomal enzymes. Phenytoin can also increase plasma concentrations of α_1-acid glycoprotein and thereby reduce the free fraction of lidocaine in plasma.[3]

The cardiac depressant effects of 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-lidocaine concentrations have occurred with *propranolol*,[1-4] owing to a reduction in the clearance of lidocaine from plasma. A similar interaction has occurred with *nadolol*[3] and *metoprolol*,[2] although in another study[5] metoprolol did not alter the pharmacokinetics of lidocaine. The hepatic metabolism of 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 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. The reduction in clearance produced by propranolol seems to be mainly by direct inhibition of metabolism rather than by lowering of hepatic blood flow.[4]

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** (suppl 1): 21S–28S.

H_2-antagonists. There have been numerous studies[1-4] of the interaction between *cimetidine* and lidocaine but differences between the studies make interpretation of the overall clinical significance of the results difficult. Cimetidine appears to reduce the hepatic metabolism of lidocaine; it may also reduce its clearance by decreasing hepatic blood flow. Significant increases in plasma-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 lidocaine.[5] Since it is not possible to identify those patients at risk all patients receiving both drugs 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 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 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 lidocaine to treat *cocaine*-induced arrhythmias as lidocaine may enhance toxicity.[2]

1. Goolkasian DL, *et al.* Displacement of lidocaine from serum α -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 lidocaine is discussed under Atracurium, p.1903.

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

Pharmacokinetics

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 lidocaine is rapidly and widely distributed into highly perfused tissues followed by redistribution into skeletal muscle and adipose tissue. Lidocaine is bound to plasma proteins, including α_1-acid glycoprotein (AAG). The extent of binding is variable but is about 66%. Plasma protein binding of lidocaine depends in part on the concentrations of both lidocaine and AAG. Any alteration in the concentration of AAG can greatly affect plasma concentrations of 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.

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 doses. Metabolism in the liver is rapid and about 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 lidocaine and since their half-lives are longer than that of 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 lidocaine. Reduced clearance of lidocaine has been found in patients with heart failure, alcoholic liver disease, or chronic or viral hepatitis. Drugs that alter hepatic blood flow or induce drug-metabolising microsomal enzymes can also affect the clearance of lidocaine (see Interactions, above). Renal impairment does not affect the clearance of lidocaine but accumulation of its active metabolites can occur.

Lidocaine crosses the placenta and blood-brain barrier; it is distributed into breast milk.

See also under Local Anaesthetics, p.1852.

◊ 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-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 lidocaine were below those associated with toxicity following endotracheal application of 100 mg of lidocaine by spray.[2] The relative bioavailability of 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-lidocaine concentrations were noted with the following regimen used before bronchoscopy: a 4% 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 lidocaine as a gargle (see Overdosage, above); the absorption of intranasal lidocaine can also be highly variable.[5] For bronchoscopy, inhalation of lidocaine from a nebuliser rather than a direct spray may result in lower peak serum concentrations.[6]

Absorption of lidocaine is generally poor through intact skin. However, there is some evidence that absorption may be greater after 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. 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 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 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 Antiepileptics under Interactions, above and Precautions, Smoking, above).

1. Routledge PA. Pharmacological terms: protein binding. *Prescribers' J* 1988; **28:** 34–5.
2. Shand DG. α -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* 1981; **11:** 245–50.
4. Wood M, Wood AJJ. Changes in plasma drug binding and α -acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther* 1981; **29:** 522–6.

Uses and Administration

Lidocaine is a local anaesthetic of the amide type with actions and uses similar to those described on p.1852. 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; it has an intermediate duration of action. The speed of onset and duration of action of 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. Lidocaine hydrochloride monohydrate 1.23 g or anhydrous lidocaine hydrochloride 1.16 g are both equivalent to about 1 g of lidocaine. A carbonated solution of lidocaine is also available in some countries for injection (see p.1852). Lidocaine is also a useful surface anaesthetic but it may be rapidly and extensively absorbed following topical application to mucous membranes, and systemic effects may occur. Hyaluronidase (p.2321) has been added to preparations of lidocaine used for surface and infiltration anaesthesia but may enhance systemic absorption. (Local anaesthetic techniques are discussed on p.1853.)

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

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

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. 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 up to 300 mg (30 mL) is used as a 0.5% or 1% solution and in surgical caudal analgesia 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% lidocaine hydrochloride in glucose 7.5% solution is available for *spinal anaesthesia*; adrenaline 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 has been used in doses of 50 to 300 mg (10 to 60 mL); a maximum dose of 4 mg/kg has been recommended for adults.

Lidocaine may be used in a variety of formulations for **surface anaesthesia**.

- 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 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 60 to 100 mg of lidocaine hydrochloride inserted into the urethra several minutes before examination; in males 200 mg instilled initially followed by 60 to 100 mg. A 1% gel may also be used. The doses used in the USA are similar: in females 60 to 100 mg of lidocaine hydrochloride as a 2% gel is inserted into the urethra several minutes before examination; in males 100 to 200 mg is used before catheterisation and 600 mg before sounding or cystoscopy.

  A gel may also be applied for the treatment of *major aphthae* in immunocompromised patients; a dose of 20 to 30 mg (2 to 3 mL) as a 1% gel or 40 to 60 mg (2 to 3 mL) as a 2% gel is used. A maximum volume of up to 15 mL is recommended within 24 hours.
- 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. 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 lidocaine hydrochloride as a 4% solution is sprayed or instilled as a single dose into the lumen of the larynx and trachea.
- Lidocaine is used *rectally* as suppositories, sprays, ointments, and creams in the treatment of haemorrhoids and other painful perianal conditions.
- *Eye drops* containing lidocaine hydrochloride 4% with fluorescein are used in tonometry.
- A *eutectic mixture* containing 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 lidocaine 5% for the treatment of pain associated with postherpetic neuralgia, and an *iontophoretic drug delivery system* incorporating lidocaine and adrenaline. A transdermal patch containing lidocaine 70 mg with tetracaine 70 mg is also available for surface anaesthesia, as is an *intradermal injection system* delivering lidocaine hydrochloride 500 micrograms.

USE IN ARRHYTHMIAS.

For the treatment of **ventricular arrhythmias** 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) have failed to restore a normal rhythm. For adults, a usual dose of 1 to 1.5 mg/kg can be given and repeated as necessary to a maximum total dose of 3 mg/kg. 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.

Lidocaine is also used in other ventricular arrhythmias in which the patient is in a more stable condition. In these circumstances 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/kg as a direct *intravenous injection* at a rate of 25 to 50 mg/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/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 the elderly and in patients with heart failure or liver disorders.

In emergency situations, 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 lidocaine and some other local anaesthetics, see p.1852.

Burns. 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. Lidocaine is classified as a class Ib antiarrhythmic drug (p.1153) and may be used in the treatment of ventricular arrhythmias, including those associated with cardiac arrest and myocardial infarction, although other drugs are usually preferred (see Cardiac Arrhythmias, p.1160). It is usually given intravenously (see above). Lidocaine may also be used during advanced cardiac life support (p.1156).

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 of lidocaine,[1,2] in others it was not shown to reduce mortality and might even have increased it,[3,4] and thus is no longer generally recommended.

It has been suggested that the increased mortality sometimes seen with lidocaine might be associated with the duration of treatment; a study[5] found that patients who received a bolus dose of 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. Pharand C, *et al.* Lidocaine prophylaxis for fatal ventricular arrhythmias after acute myocardial infarction. *Clin Pharmacol Ther* 1995; **57:** 471–8.

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p.976. 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 intravenously, or in the form of a 2% viscous solution taken by mouth. Nebulised lidocaine has also been tried.[1]

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

Intubation. 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.1900.

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 interest, lidocaine has so far failed to find an accepted role in the management of migraine (p.616) or cluster headache (p.616). 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] While some workers have found that intranasal instillation of lidocaine has produced rapid relief of headache in some patients with acute migraine (though early relapse was common)[2] others have found it to be ineffective.[3] It has also been reported to be effective in aborting individual attacks of headache during cluster periods in patients with cluster headache.[4,5] However, most patients do not appear to obtain complete pain relief.

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. Blanda M, *et al.* Intranasal lidocaine for the treatment of migraine headache: a randomized, controlled trial. *Acad Emerg Med* 2001; **8:** 337–42.
4. Kittrelle JP, *et al.* Cluster headache: local anesthetic abortive agents. *Arch Neurol* 1985; **42:** 496–8.
5. Robbins L. Intranasal lidocaine for cluster headache. *Headache* 1995; **35:** 83–4.

Neuropathic pain syndromes. Lidocaine may be useful in the management of some types of neuropathic pain syndromes (p.8). The pain of *postherpetic neuralgia* has been significantly reduced by the application of lidocaine 5% transdermal patches[1-3] although a systematic review[4] found insufficient evidence to recommend its use as first-line therapy; intravenous lidocaine[5] and a eutectic mixture of lidocaine and prilocaine (see Surface Anaesthesia below) have also been of benefit. Other syndromes where intravenous lidocaine therapy has been tried include *diabetic neuropathy*[6] and *central neuropathic pain* associated with stroke or spinal cord injury.[7]

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. Davies PS, Galer BS. Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia. *Drugs* 2004; **64:** 937–47.
4. Khaliq W, *et al.* Topical lidocaine for the treatment of postherpetic neuralgia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 22/04/08).
5. Attal N, *et al.* Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. *Neurology* 2004; **62:** 218–25.
6. Kastrup J, *et al.* Treatment of chronic painful diabetic neuropathy with intravenous lidocaine infusion. *BMJ* 1986; **292:** 173.
7. Attal N, *et al.* Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology* 2000; **54:** 564–74.

Pleurodesis. 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/kg 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. Lidocaine hydrochloride may be used to control status epilepticus (p.469) resistant to more conventional treatment, particularly in those with respiratory disease. 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 lidocaine can result in CNS toxicity including seizures.[1] Recurrence of seizures associated with the withdrawal of prolonged lidocaine therapy may be due to its accumulated metabolites exerting an excitatory effect on the nervous system when the inhibitory effect of lidocaine is being reduced.[2]

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] Lidocaine 1.5 to 2 mg/kg (usually a dose of 100 mg) was given 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 if the seizures recurred (19 episodes). Subsequently a continuous infusion of lidocaine at a rate of 3 to 4 mg/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. In a retrospective analysis[4] of 37 children with status epilepticus, lidocaine was effective in only 19 of 53 episodes; however, in a few cases it was effective where other drugs had failed, and those patients who responded did so rapidly (within 5 minutes of being given the drug).

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.
4. Hamano S-I, *et al.* Intravenous lidocaine for status epilepticus during childhood. *Dev Med Child Neurol* 2006; **48:** 220–2.

Surface anaesthesia. ***EUTECTIC MIXTURES.*** A cream containing lidocaine 2.5% and prilocaine 2.5% as a eutectic mixture can produce local anaesthesia when applied topically to intact skin. It appears to be of value in minor medical or surgical procedures in *adults* and *children*,[1-3] such as venepuncture, 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.9) 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.

Eutectic mixtures of lidocaine and prilocaine have also been used in *neonates* to reduce the pain of puncture procedures[7] and for circumcision,[8,9] and appear to be safe and efficacious. There has been concern that excessive absorption (particularly of prilocaine) might lead to methaemoglobinaemia (see p.1850), and UK licensing information recommends that the eutectic cream not be used in children less than 1 year old. However, there seems to be little evidence of this, and the *BNF* considers that it may be used under specialist supervision in infants over 1 month of age. Similarly, in 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 methaemoglobin values are monitored in those aged 3 months or less; it should not be used in infants under 1 year who are receiving methaemoglobin-inducing drugs.

Systemic absorption of both drugs from the eutectic cream appears to be minimal across intact skin[6] even after prolonged or extensive use.[10] However, it 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 tetracaine 4% can produce longer and more rapid anaesthesia than the above lidocaine with prilocaine cream (see Surface Anaesthesia, under Uses and Administration of Tetracaine, p.1872). It has also been suggested[11] that topical tetracaine may have practical advantages over the eutectic mixture of 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. Gourrier E, *et al.* Use of EMLA cream in a department of neonatology. *Pain* 1996; **68:** 431–4.
8. Taddio A, *et al.* Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. *N Engl J Med* 1997; **336:** 1197–1201.
9. Brady-Fryer B, *et al.* Pain relief for neonatal circumcision. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 16/06/05).
10. Scott DB. Topical anaesthesia of intact skin. *Br J Parenter Ther* 1986; **7:** 134–5.
11. 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. Intravenous 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 lidocaine have not, so far, been successful. Other drugs that have been tried include benzodiazepines such as alprazolam and clonazepam, the antiepileptics carbamazepine and phenytoin, tricyclic antidepressants, and the loop diuretic furosemide, but adverse effects limit their use. Ginkgo biloba has been tried but there are doubts about its value.

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.
6. Dobie RA. A review of randomized clinical trials in tinnitus. *Laryngoscope* 1999; **109:** 1202–11.
7. Lockwood AH, *et al.* Tinnitus. *N Engl J Med* 2002; **347:** 904–10.

Preparations

BP 2008: Lidocaine and Adrenaline Injection; Lidocaine and Chlorhexidine Gel; Lidocaine Gel; Lidocaine Injection; Lidocaine Ointment; Sterile Lidocaine Solution;

USP 31: Lidocaine and Prilocaine Cream; 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)

Arg.: Fidecaina; Gobbicaina; Indican; Larjancaina; Regiocaina; Solvente Indoloro; Xylocaina; ***Austral.:*** Lignospan†; Nurocain; Stud 100; Xylocaine; Xylocaine Special Adhesive; Xylocard; ***Austria:*** Lidocorit; Neo-Xylestesin; Neo-Xylestesin forte; Xylanaest; Xylocain; Xylocard; Xyloneural; ***Belg.:*** Linisol†; Xylocaine; Xylocaine Visqueuse; Xylocard; ***Braz.:*** Dermomax; Gel-Lido; Lidial; Lidocabbott; Lidocalm†; Lidogel; Lidogeyer†; Lidojet†; Lidospray; Lidoston; Xylestesin; Xylocaina; ***Canad.:*** Afterburn; Betacaine; Lidodan; Solarcaine Lidocaine; Xylocaine; Xylocard; Zilactin-L; ***Chile:*** Calmante de Denticion†; Dentaliv; Dimecaina; Exido; Gelcain; Odongel; Prolong; Solin; Xylocaina; ***Cz.:*** Trachisan; Xylestesin-A†; Xylestesin†; Xylocaine; ***Denm.:*** Xylocain; Xyloplyin; ***Fin.:*** Lidocard; Xylocain; ***Fr.:*** Dynexan; Mesocaine; Versatis; Xylocaine; Xylocard; ***Ger.:*** Gelicain; Haemo-Exhirud Bufexamac; Heweneural; Licain; Lidesthesin; Lidocard; Lidoject; LidoPosterine; Rowo-629†; Trachisan Halsschmerztabletten; Xylestesin-A; Xylestesin centro†; Xylestesin-S†; Xylestesin, Xylestesin-F†; Xylocain; Xylocain f.d. Kardiologie; Xylocitin; Xylocitin cor; Xyloneural; ***Gr.:*** Ecocain†; Lidoderm; Osagel; Sensolid; Utiblack; Xylocaine; Xylol; Xylozan; ***Hong Kong:*** Xylestesin-A; Xylocaine; Xylocard†; ***India:*** Gesicain; Tivision; Xylocaine; Xylocard; ***Indon.:*** Extracaine; Garianes; Lidodex; Lidonest; Pehacain; Xylocaine; ***Irl.:*** Xylocaine; ***Israel:*** After Burn; Esracain; Lidocadren†; LidoPen; Stud 100; Xylocaine; ***Ital.:*** Basicaina; Ecocain; Lident Adrenalina†; Lident Andrenor†; Lidofast; Lidomol†; Lidosen; Lidrian; Luan; Odontalg; Ortodermina; Xilomyl; Xylocaina; Xylonor; Xyloplyina; ***Jpn:*** Penles; ***Malaysia:*** Denkan; Xylocaine; Xylocard†; ***Mex.:*** Betacaine; Hipoden; Pharmacaine; Pisacaina; Sensipharma; Sunicaine; Unicaine; Uvega; Xylocaina; ***Neth.:*** Dentinox; Lepan; Lignospan; Nolaid; Otalgan; Unguentum contra haemorrhoides PCH; Xylocaine; ***Norw.:*** Xylocain; ***NZ:*** Virasolve; Xylestesin-A; Xylocaine; Xylocard; ***Philipp.:*** Dentocaine; Lygnonex; Xylocaine; Xylocard; ***Pol.:*** Lidoposterin; Xylocaine; ***Port.:*** Lidonostrum; Lincaina; Octocaine; Xilonibsa; Xylocaina; Xylocard†; ***Rus.:*** Lidochlor (Лидохлор); Versatis (Версатис); ***S.Afr.:*** Lignospan Special†; Peterkaien; Remicaine; Remicard; Xylocaine; Xylotox; ***Singapore:*** Dube†; Xylocaine; ***Spain:*** Aeroderm†; Dermovagisil; Octocaine; Xilonibsa; Xylocaina; Xylonor 2% Sin Vasoconst; Xylonor Especial; ***Swed.:*** Xylocain; Xylocard; ***Switz.:*** Dynexan nouvelle formule; Kenergon; Lignospan†; Neo-Sinedol; Neurodol Tissugel; Rapidocaine; Sedagul; Solarcaine; Xylesine; Xylestesin-F†; Xylestesin-S "special"†; Xylocain; Xylocard; Xyloneural; Xyloplyin†; ***Thai.:*** Docaine; LD-Caine; Lido Spray†; Lidocation; Lidocaton†; Neo-Lidocaton†; Udocaine; Xylocaine; Xylocard†; ***Turk.:*** Anestol; Aritmal; Jetokain; Jetosel; Ksilidin; Lidobag; Lidosel; Lokalen; Xylocain; ***UAE:*** Ecocain; ***UK:*** Dequaspray; Laryng-O-Jet; Lignostab-A†; Premjact; Stud; Vagisil; Versatis; Xylocaine; Xylotox†; ***USA:*** Anestacon; Anestafoam; Dentipatch; Dilocaine; Dr Scholl's Cracked Heel Relief; Duo-Trach Kit; L-M-X4; LidaMantle; Lidoderm; LidoPen; Lidosense†; Lidosite; LTA; Nervocaine; Octocaine; Xylocaine; Zilactin-L; Zingo; ***Venez.:*** Cifarcaina; Farmacaina; Nenedent; Xylocaina†.

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

Mepivacaine Hydrochloride

(BANM, rINNM)

Hidrocloruro de mepivacaína; Mépivacaïne, chlorhydrate de; Mepivacaini Chloridum; Mepivacaini hydrochloridum; Mepivakainihydrokloridi; Mepivakain-hidroklori d; Mepivakain-hydrochlorid; Mepivakainhydroklorid; Mepivakaino hidrochloridas. (1-Methyl-2-piperidyl)formo-2′,6′-xylidide hydrochloride.

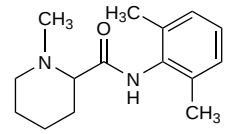
Мепивакаина Гидрохлорид

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

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

ATC — N01BB03.

ATC Vet — QN01BB03.



(mepivacaine)

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

Ph. Eur. 6.2 (Mepivacaine Hydrochloride). A white or almost 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 31 (Mepivacaine Hydrochloride). 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.1852.

Adverse Effects, Treatment, and Precautions

As for Local Anaesthetics in general, p.1850.

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.1851.

Local anaesthetics. 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