metabolic pathways include hydroxylation of the cyclohexone ring and conjugation with glucuronic acid. The beta phase half-life is about 2.5 hours. Ketamine is excreted mainly in the urine as metabolites. It crosses the placenta.

◊ References.

1. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth* 1981; **53:** 27–30.
2. Grant IS, *et al.* Pharmacokinetics and analgesic effects of IM and oral ketamine. *Br J Anaesth* 1981; **53:** 805–9.
3. Grant IS, *et al.* Ketamine disposition in children and adults. *Br J Anaesth* 1983; **55:** 1107–11. **14:** 144P.
4. Geisslinger G, *et al.* Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. *Br J Anaesth* 1993; **70:** 666–71.
5. Malinovsky J-M, *et al.* Ketamine and norketamine plasma concentrations after iv, nasal and rectal administration in children. *Br J Anaesth* 1996; **77:** 203–7.

Uses and Administration

Ketamine is an anaesthetic given by intravenous injection, intravenous infusion, or intramuscular injection. It produces dissociative anaesthesia characterised by a trance-like state, amnesia, and marked analgesia which may persist into the recovery period. There is often an increase in muscle tone and the patient's eyes may remain open for all or part of the period of anaesthesia. Ketamine is used in general anaesthesia for diagnostic or short surgical operations that do not require skeletal muscle relaxation, for the induction of anaesthesia to be maintained with other drugs, and as a supplementary anaesthetic (see p.1780). It also has good analgesic properties in subanaesthetic doses. It is considered to be of particular value in children requiring frequent repeated anaesthesia. Recovery is relatively slow.

Ketamine is given as the hydrochloride but doses are expressed in terms of the equivalent amount of base; ketamine hydrochloride 1.15 mg is equivalent to about 1 mg of ketamine.

- For induction in adults and children the dose given by *intravenous injection* may range from the equivalent of 1 to 4.5 mg/kg of ketamine; a dose of 2 mg/kg given intravenously over 60 seconds usually produces surgical anaesthesia within 30 seconds of the end of the injection and lasting for 5 to 10 minutes.
- The initial *intramuscular* dose may range from 6.5 to 13 mg/kg; an intramuscular dose of 10 mg/kg usually produces surgical anaesthesia within 3 to 4 minutes lasting for 12 to 25 minutes. For diagnostic or other procedures not involving intense pain an initial intramuscular dose of 4 mg/kg has been used. Additional doses may be given for maintenance.
- For induction by *intravenous infusion* a total dose of 0.5 to 2 mg/kg is usually given at an appropriate infusion rate. Maintenance is achieved with 10 to 45 micrograms/kg per minute, the infusion rate being adjusted according to response.

Use should be preceded by atropine or another suitable antimuscarinic. Diazepam or another benzodiazepine may be given before surgery or as an adjunct to ketamine to reduce the incidence of emergence reactions.

The *S*-isomer, esketamine, is also given for similar uses in anaesthesia.

◊ Reviews.

1. Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. *Br J Anaesth* 1996; **77:** 441–4.

Administration. Although ketamine hydrochloride is usually given intravenously or intramuscularly, oral[1,2] and rectal[3] dosage has been used successfully in children. Intranasal use of ketamine with midazolam in a neonate requiring anaesthesia has also been reported.[4] Unfortunately the onset of sedation with these three routes is too slow for emergency procedures and therefore a jet-injector of ketamine was developed[5] to provide non-traumatic, painless, and rapid anaesthesia in children. Intranasal and transdermal use may be useful in the management of pain (below); oral, rectal, and subcutaneous routes have also been tried.[6]

1. Tobias JD, *et al.* Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. *Pediatrics* 1992; **90:** 537–41.
2. Gutstein HB, *et al.* Oral ketamine preanesthetic medication in children. *Anesthesiology* 1992; **76:** 28–33.
3. Lökken P, *et al.* Conscious sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. *Scand J Dent Res* 1994; **102:** 274–80.
4. Louon A, *et al.* Sedation with nasal ketamine and midazolam for cryotherapy in retinopathy of prematurity. *Br J Ophthalmol* 1993; **77:** 529–30.
5. Zsigmond EK, *et al.* A new route, jet-injection for anesthetic induction in children–ketamine dose-range finding studies. *Int J Clin Pharmacol Ther* 1996; **34:** 84–8.
6. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother* 2002; **16:** 27–35.

Nonketotic hyperglycinaemia. Ketamine was tried with strychnine in a newborn infant with severe nonketotic hyperglycinaemia (p.2393) and resulted in neurological improvement, although motor development remained unsatisfactory.[1] It was thought that ketamine might act by blocking N-methyl-D-aspartate (NMDA) receptors, which are activated in the CNS by glycine.

1. Tegtmeyer-Metadorf H, *et al.* Ketamine and strychnine treatment of an infant with nonketotic hyperglycinaemia. *Eur J Pediatr* 1995; **154:** 649–53.

Pain. For a discussion of pain and its management, see p.2. Ketamine is used for its analgesic action in neuropathic or other pain unresponsive to conventional analgesics. (For mention of its use for outpatient procedures in children, see p.3.) Systematic reviews have found the evidence for such use to be limited,[1,2] and have also differed on its value for postoperative pain,[3-5] but it has been suggested[1] that ketamine is a reasonable third-line option for pain where standard analgesics have failed. Subcutaneous, intramuscular, intravenous, epidural, intrathecal, intranasal, transdermal, rectal, and oral routes have all been tried.[1,6]

1. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. *Anesth Analg* 2003; **97:** 1730–9.
2. Bell RF, *et al.* Ketamine as an adjuvant to opioids for cancer pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/06/05).
3. Elia N, Tramèr MR. Ketamine and postoperative pain—a quantitative systematic review of randomised trials. *Pain* 2005; **113:** 61–70.
4. Bell RF, *et al.* Perioperative ketamine for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 16/05/06).
5. Subramaniam K, *et al.* Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesth Analg* 2004; **99:** 482–95.
6. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother* 2002; **16:** 27–35.

Status epilepticus. For the suggestion that ketamine may be tried in refractory status epilepticus, see p.469.

Preparations

BP 2008: Ketamine Injection;
USP 31: Ketamine Hydrochloride Injection.

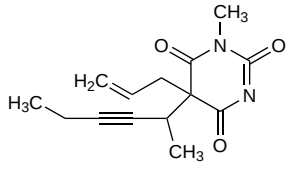
Proprietary Preparations (details are given in Part 3)
Arg.: Cost; Inducmina; Ketalar; Ketanest; ***Austral.:*** Ketalar; ***Austria:*** Ketanest; ***Belg.:*** Ketalar; ***Braz.:*** Ketalar; ***Canad.:*** Ketalar; ***Chile:*** Ketalar†; ***Cz.:*** Calypsol; Narkamon; ***Denm.:*** Ketalar†; ***Fin.:*** Ketalar; Ketanest; ***Ger.:*** Keta†; Ketanest; ***Gr.:*** Ketalar†; ***Hong Kong:*** Ketalar; ***Hung.:*** Calypsol; ***India:*** Ketalar; Ketmin; ***Indon.:*** Anesject; Ivanes; Ketalar; KTM; ***Irl.:*** Ketalar; ***Israel:*** Ketalar; ***Malaysia:*** Calypsol†; Ketava; ***Mex.:*** Ketalin; ***Neth.:*** Ketanest; ***Norw.:*** Ketalar; ***NZ:*** Ketalar; ***Philipp.:*** Ketaject; Ketamax; Ketazol; Quetanex; ***Pol.:*** Calypsol; Ketanest; ***Port.:*** Ketalar; ***Rus.:*** Calypsol (Калипсол); ***S.Afr.:*** Brevinaze; ***Spain:*** Ketolar; ***Swed.:*** Ketalar; ***Switz.:*** Ketalar; ***Thai.:*** Calypsol; Keta-Hameln†; Ketalar; ***Turk.:*** Ketalar; ***UK:*** Ketalar; ***USA:*** Ketalar; ***Venez.:*** Keiran.

Methohexital *(BAN, rINN)*

Méthohexital; Methohexitalum; Methohexitone; Metoheksitaali; Metohexital. (±)-5-Allyl-1-methyl-5-(1-methylpent-2-ynyl)barbituric acid; 1-Methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl)-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione.

Метогекситал

$C_{14}H_{18}N_2O_3$ = 262.3.
CAS — 151-83-7; 18652-93-2.
ATC — N01AF01; N05CA15.
ATC Vet — QN01AF01; QN05CA15.



Pharmacopoeias. In *US.*
USP 31 (Methohexital). A white to faintly yellowish-white crystalline odourless powder. M.p. 92° to 96° but the range between beginning and end of melting does not exceed 3°. Very slightly soluble in water; slightly soluble in alcohol, in chloroform, and in dilute alkalis.

Methohexital Sodium *(BANM, rINNM)*

Compound 25398; Enallynymalnatrium; Méthohexital Sodique; Methohexitone Sodium; Metohexital sódico; Natrii Methohexitalum.

Натрий Метогекситал

$C_{14}H_{17}N_2NaO_3$ = 284.3.
CAS — 309-36-4; 22151-68-4; 60634-69-7.
ATC — N01AF01; N05CA15.
ATC Vet — QN01AF01; QN05CA15.

Pharmacopoeias. *US* includes Methohexital Sodium for Injection.
USP 31 (Methohexital Sodium for Injection). A freeze-dried sterile mixture of methohexital sodium and anhydrous sodium carbonate as a buffer, prepared from an aqueous solution of methohexital, sodium hydroxide, and sodium carbonate. It is a white to off-white, essentially odourless, hygroscopic powder. pH of a 5% solution in water is between 10.6 to 11.6.

Incompatibility. Solutions of methohexital sodium are incompatible with acidic substances including a number of antibacterials, antipsychotics, neuromuscular blockers, antimuscarinics, and analgesics. Compounds commonly listed as incompatible include atropine sulfate, pethidine hydrochloride, metocurine iodide, fentanyl citrate, morphine sulfate, pentazocine lactate, silicones, suxamethonium chloride, tubocurarine chloride, and compound sodium lactate injection. Only preservative-free diluents should be used to reconstitute methohexital sodium; precipitation may occur if a diluent containing a bacteriostatic agent is used.

Stability. Solutions of methohexital sodium in Water for Injections are stable for at least 6 weeks at room temperature; however reconstituted solutions should be stored no longer than 24 hours as they contain no bacteriostatic agent. Solutions in glucose or sodium chloride injections are stable only for about 24 hours.

Adverse Effects and Precautions

As for Thiopental Sodium, p.1795.

Excitatory phenomena are more common and induction less smooth with methohexital than with thiopental. Methohexital should be used with caution, if at all, in patients with a history of epilepsy.

See also Adverse Effects and Precautions for General Anaesthetics, p.1779.

Incidence of adverse effects. In a study of 4379 uses of methohexital in 2722 dental patients the total dose ranged from 20 mg to 560 mg (with a mean of 151 mg), and the duration of treatment was 8 to 32 minutes.[1] Complications included: restlessness not controlled by diazepam (292 cases), respiratory complications (214), uncontrollable crying during recovery (73), pain along vein (45) with thrombophlebitis (5), jactitations (22), and allergic reactions (10).

1. McDonald D. Methohexitone in dentistry. *Aust Dent J* 1980; **25:** 335–42.

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

In a study[2] of 9 breast-feeding women undergoing general anaesthesia, it was estimated that the exposure of a breast-fed infant to methohexital would be less than 1% of the maternal dose after induction with methohexital. Breast feeding was not interrupted during the study and none of the infants appeared drowsy or sedated.

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 26/05/04)
2. Borgatta L, *et al.* Clinical significance of methohexital, meperidine, and diazepam in breast milk. *J Clin Pharmacol* 1997; **37:** 186–92.

Effects on the nervous system. Two case reports of seizures induced by methohexital in children with seizure disorders.[1] Seizures are considered a rare adverse effect of methohexital. In 48 000 patients given methohexital, only 3 developed clonic-type seizures.[2]

A case of a tonic-clonic seizure possibly due to an interaction between paroxetine and methohexital is discussed below.

1. Rockoff MA, Goudsouzian NG. Seizures induced by methohexital. *Anesthesiology* 1981; **54:** 333–5.
2. Metriyakool K. Seizures induced by methohexital. *Anesthesiology* 1981; **55:** 718.

Pain on injection. Methohexital is associated with severe pain particularly if veins on the back of the hands are used. The incidence of pain on injection may be reduced by using a forearm vein or by pre-injection with lidocaine.

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

Rebound anaesthesia. Rebound of anaesthesia with abolition of reflexes and depression of respiration occurred in a 6-year-old