

Ketamine: Its use in the emergency department

Andries Cromhout
Emergency Department, Wellington Hospital, Wellington, New Zealand

Abstract

Ketamine has been known to the medical world for over 30 years, yet is not widely used to its full potential. It is often considered to be a 'third world' drug only. In light of a recent increase in interest in its use in the developed world, this review is for emergency physicians to use as a quick reference.

Key words: *conscious sedation, ketamine.*

Introduction

Ketamine has been used clinically for over 35 years. Several large studies document that it has a wide margin of safety.^{1–7} It is unique in its ability to safely provide simultaneous anxiolysis, analgesia and amnesia, while maintaining airway and breathing reflexes and being cardiovascular-stable. Despite widespread use in the developing world (where it is administered safely thousands of times daily, mostly by non-anaesthetists with poor monitoring equipment), there is a reluctance to use the drug in the ED in many parts of the world, not just in Australia and New Zealand.

Ketamine produces dissociative sedation, which in the words of Green and Krauss is a trance-like cataleptic state characterised by profound analgesia, sedation, amnesia and immobilisation, with retention of protective airway reflexes, spontaneous respirations and cardiopulmonary stability.⁸ This unique state of cortical dissociation permits painful procedures to be performed effectively.

It is particularly well suited to paediatric procedures and provides better sedation with fewer respiratory complications than midazolam/fentanyl.^{9,10}

Pharmacology

Pharmacokinetics

- Rapidly absorbed after parenteral administration
- Plasma half-life is 2–4 h
- Highly lipid soluble (crosses blood–brain barrier easily)
- Quickly distributed into highly vascular organs, including brain, with subsequent redistribution to less perfused tissues; distribution half-life is approximately 7–11 min.
- Hepatic metabolism within the cytochrome P₄₅₀ system with formation of water soluble conjugates. (Some of the metabolites, notably norketamine, have some potency, but do not penetrate the central nervous system [CNS] sufficiently enough to cause hypnosis.)
- About 90% of ketamine is excreted in the urine, mostly as metabolites, with only 2–4% as unchanged drug.
- Approximately 5% is recovered in faeces
- Ketamine has a wide therapeutic index, thus there is a low chance of lethal overdose.⁴

Correspondence: Dr Andries Cromhout, Emergency Department, Wellington Hospital, Riddiford Street, Wellington, New Zealand.
Email: andre.cromhout@ccdhb.org.nz

Andries Cromhout, MBChB, Registrar.

Pharmacodynamics

Mechanism of action

- The primary site of action is in the CNS in the thalamocortical pathways and the limbic system, where it binds to a site on post-synaptic NMDA channels. Ketamine enters and blocks the open channel and inhibits glutamate activation of the channel non-competitively, thereby inhibiting the excitatory effect of glutamate on neurones in the CNS.
- It also reduces presynaptic release of glutamate.
- Ketamine antagonizes muscarinic and nicotinic acetylcholine receptors. It is thought that action at the nicotinic receptor is responsible for behavioural side-effects.

Systemic effects

1. Cardiovascular system:
 - Direct myocardial depressant
 - This is overshadowed *in vivo* by stimulation of sympathetic CNS outflow, resulting in positive inotropy and chronotropy: (i) Increase in heart rate ($\pm 20\%$), arterial blood pressure (± 25 mmHg rise in systolic pressure) and cardiac output, usually peaks 2–4 min after intravenous administration and 10–20 min after intramuscular injection. (ii) The predominant effect of ketamine on the cardiovascular system is thought to be due to decreased catecholamine reuptake.
2. Central nervous system:
 - May cause increase in cerebral blood flow, oxygen consumption and intracranial pressure: (i) In a small series of patients with intracranial CSF obstruction, it was associated with an increase in intracranial pressure. (ii) These increases were not seen in patients who had intracranial pathology without obstruction.¹¹
 - Animal studies has shown ketamine to produce a marked neuroprotective effect, mediated by antagonism of NMDA channels on central neurones, thereby preventing calcium influx during states of neurocellular ischaemia — may have promise in the future treatment of stroke.¹²
3. Respiratory system:
 - A slight decrease in the respiratory rate for 2–3 min
 - Brief apnoea is occasionally seen; this is generally associated with rapid intravenous administration or large doses.
 - Bronchodilation — mediated by effects on the central sympathetic system, causing an increase

in circulating catecholamines as well as direct relaxant effect on airway smooth muscle.¹³

- Bronchorrhoea may occur after ketamine administration
 - Upper airway reflexes are usually (but not always) maintained
4. Gastrointestinal tract:
 - Increased salivation
 5. Muscular system:
 - Muscle tone is often increased
 - Spontaneous movements may occur during anaesthesia but reflex response to surgery is uncommon
 6. Eyes:
 - Intra-ocular pressure rises for a short time after administration
 - Eye movements may continue throughout surgery and nystagmus is common
 - Corneal reflexes are usually preserved
 7. Psychotic effects:
 - May activate psychoses in schizophrenic patients
 8. Immunology:
 - Ketamine causes a significant reduction in leucocyte activation during sepsis, while it also suppresses pro-inflammatory cytokine production *in vitro*.
 9. Pregnancy:
 - Ketamine crosses the placenta easily and concentrations in the foetus are approximately equal to those in the mother.

Usage

1. Anaesthesia:
 - Has mainly been restricted to an induction agent in hypovolaemic or cardiovascular unstable patients
 - In the developing world as a single general anaesthetic agent
2. Sedation:
 - To produce sedation and analgesia for painful procedures in the ED
 - Ketamine has been successfully used as field sedation and analgesia for vehicle extraction and emergency amputations.¹⁴
3. Analgesia:
 - Acute post-operative pain
 - Analgesia for change of dressings (especially burns)
 - Said to have an opioid sparing effect
 - Used occasionally in chronic or neuropathic pain — controversial, as its effect is often limited by dose restrictions due to side-effects.

4. Immunology:

- Ketamine administration inhibited hypotension, metabolic acidosis and cytokine responses in rats injected with endotoxin. The results suggest that judicious use of ketamine as an anaesthetic agent may offer advantages in endotoxaemia.¹⁵

5. Asthma:

- Often used as an induction agent in severe asthmatics who need intubation and ventilation.¹⁶
- Limited literature evidence to support its use as treatment in patients with severe exacerbation of asthma. Several case studies suggest some benefit in mechanically ventilated patients with refractory severe asthma. The only clinical study of ketamine as conjunctive treatment in asthma failed to demonstrate any clear benefit in bronchodilation compared with standard therapy in treating exacerbations of asthma in the ED.¹⁷
- Used as a 'club drug' to help maintain the energy levels for dancing or to enhance the altered state of consciousness.¹⁸ Ingested orally or nasally as a powder; liquid ketamine may be smoked after application to cigarettes or taken intravenously or subcutaneously. Ketamine is abused primarily for its dissociative effects. It causes hallucinations, slowed time perception and delusions.

Doses

1. Intravenous:

- 1–2 mg/kg slowly IVI over 1–2 min. Faster administration may cause respiratory depression or apnoea and enhanced pressor response.
- Supplemental doses of 0.25–0.5 mg/kg can be given every 10 min as required, to a total of 5 mg/kg; onset of action within 1 min; mean duration of action about 6–15 min; mean recovery period about 60–90 min.

2. Intramuscular:

- 4–5 mg/kg¹⁹
- booster doses of 2–5 mg/kg every 10 min as required
- onset of action in 3–5 min
- duration of action up to 30 min, but depends on the total dose given
- mean recovery time about 90–150 min

3. Adjunctive medication:

- Controversial. Anticholinergic agents (glycopyrrolate or atropine) are often administered with

ketamine to prevent the hypersalivation that occurs in some patients. Dosage of atropine is 0.02 mg/kg with a minimal dose of 0.1 mg and a maximum of 0.5 mg; only needs to be given with the initial dose of ketamine. Benzodiazepines are still widely used with ketamine in order to reduce the incidence of the emergence phenomenon, but it increases respiratory depression and prolongs recovery, while it is debatable whether it actually decreases the incidence of the emergence phenomenon; dose of midazolam: 0.02 mg/kg.

Adverse reactions

1. Emergence phenomena:

- Disorientation, sensory and perceptual illusions and vivid dreams on recovery
- Incidence is lower in children less than 15 years and elderly patients
- Risk factors:⁷ age over 10 years; female sex; rapid IV administration; excessive noise or stimulation during recovery; prior personality disorders; patients who normally dream frequently
- No association with dosage

2. Cardiac stimulation, resulting in hypertension and tachycardia

3. Transient rash:

- Transient erythema (incidence of about 15%)
- Predominantly on face and neck

4. Nausea and vomiting

5. Hypersalivation

6. Laryngospasm: very rarely observed if no stimulation of vocal cords; incidence of less than 1%

7. May cause transient rise in intracranial pressure

8. Increased muscle tone

9. Apnoea may occur with high doses or rapid administration

10. Nystagmus

Reversal

Finck suggested in 1982 that ketamine may be partially reversed by naloxone,²⁰ but a more recent study by Mikkelsen showed that in sedative doses, neither the effects of ketamine, nor the ketamine-induced side-effects were influenced by naloxone.²¹

Contra-indications

- History of airway instability, tracheal surgery or tracheal stenosis
- High predisposition to laryngospasm or apnoea: active pulmonary or upper airway infection; age < 3 months; procedures involving stimulation of posterior pharynx
- Severe cardiovascular disease: angina; heart failure; hypertension
- Cerebral spinal fluid obstructive states: severe head injury; mass lesion in CNS; hydrocephalus
- Intra-ocular pressure pathology: glaucoma; acute globe injury
- Previous psychotic illness
- Porphyria
- Hypersensitivity
- Hyperthyroidism (possibility of severe tachycardia or hypertension)
- Full meal within 3–4 h (increased risk of aspiration).

Interactions

- Halothane: decreased hepatic clearance of ketamine, leading to prolonged recovery
- Benzodiazepines: cause prolonged recovery
- Inhalation anaesthetics: blocks the indirect cardiac stimulating of ketamine
- Thyroxine: can cause hypertension and supraventricular tachycardia
- Theophylline: may lower seizure threshold.

Recovery

Dissociation causes a sense of semiconscious bodily detachment as patients who underwent sedation wake up. Imagination can be confused with actual environmental stimuli during this period.

Recovery reactions are usually less in children and the elderly.

The degree of recovery agitation after ketamine sedation is significantly related to the degree of preprocedure agitation. Concurrent administration of midazolam has no measurable beneficial effect in diminishing recovery agitation, but may prolong recovery.^{22,23}

It is important to minimise physical contact, noise and stimulation during this period and not to try to wake patients prematurely.

Anticipated recovery is about 30 min to 2 h after administration.

Patients who undergo ketamine sedation may be discharged when:

- At least 30 minutes have passed since administration of last dose
- The patient's level of consciousness has returned to baseline
- Vital signs are within normal range
- The patient can verbalise appropriately for age
- The patient can stand unassisted without falling
- The patient is accompanied by a responsible adult at discharge.^{7,24}

Children should be carefully observed by a parent or guardian for 4 h after discharge, should not be allowed to walk independently for 2 h (ataxia may develop) and should ideally stay nil per mouth for an hour after discharge.

Adult patients should be told that driving, operating machinery or engaging in other hazardous activities is forbidden for 24 h or more after its use (depending on dose and other drugs employed).

Accepted 18 December 2002

References

1. Krauss B, Green SM. Sedation and analgesia for procedures in children. *N. Engl. J. Med.* 2000; **342**: 938–45.
2. Green SM, Rothrock SG, Lynch EL *et al.* Intramuscular ketamine for pediatric sedation in the emergency department: Safety profile in 1022 cases. *Ann. Emerg. Med.* 1998; **31**: 688–97.
3. Dachs RJ, Innes GM. Intravenous ketamine sedation of pediatric patients in the emergency department. *Ann. Emerg. Med.* 1997; **29**: 146–50.
4. Green SM, Clark R, Hostetler MA *et al.* Inadvertent ketamine overdose in children; Clinical manifestations and outcome. *Ann. Emerg. Med.* 1999; **34**: 492–7.
5. McCarthy EC, Mencio GA, Walker LA *et al.* Ketamine sedation for the reduction of children's fractures in the emergency department. *J. Bone Joint Surg. Am.* 2000; **82-A**: 912–8.
6. Holloway VJ, Husain HM, Saetta JP, Gautam V. Accident and emergency department led implementation of ketamine sedation in paediatric practice and parental response. *J. Accid. Emerg. Med.* 2000; **17**: 25–8.
7. Priestley SJ, Taylor J, McAdam CM, Francis P. Ketamine sedation for children in the emergency department. *Emerg. Med.* 2001; **13**: 82–90.
8. Green SM, Krauss B. The semantics of ketamine. *Ann. Emerg. Med.* 2000; **36**: 480–2.
9. Kennedy RM, Porter FL, Miller JP *et al.* Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopedic emergencies. *Pediatrics* 1998; **102**: 956–63.

10. McGlone R, Fleet T, Durham S, Hollis S. A comparison of intramuscular ketamine with high dose intramuscular midazolam with and without intranasal flumazenil in children before suturing. *Emerg. Med. J.* 2001; **18**: 34–8.
11. Mayberg TS. Ketamine does not increase cerebral blood flow velocity or intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. *Anesth. Analg.* 1995; **81**: 84–9.
12. Pfenninger E. Neuroprotection by Ketamine at the cellular level. *Anaesthetist* 1997; **46**: S47–54.
13. Sato T. Ketamine relaxes airway smooth muscle contracted by endothelin. *Anesth. Analg.* 1997; **84**: 900–6.
14. Cottingham R, Thomson K. Use of ketamine in prolonged entrapment. *J. Accid. Emerg. Med.* 1994; **11**: 189–91.
15. Taniguchi T, Shibata K, Yamamoto K. Ketamine inhibits endotoxin-induced shock in rats. *Anesthesiology* 2001; **95**: 928–32.
16. L'Hommedieu CS. The use of ketamine for the emergency intubation of patients with status asthmaticus. *Ann. Emerg. Med.* 1987; **16**: 568–71.
17. Howton JC, Rose J, Duffy S *et al.* Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. *Ann. Emerg. Med.* 1996; **27**: 170–5.
18. Weiner AL, Vieira L, McKay CA, Bayer MJ. Ketamine abusers presenting to the emergency department: a case series. *J. Emerg. Med.* 2000; **18**: 447–51.
19. Green SM, Hummel CB, Wittlake WA *et al.* What is the optimal dose of intramuscular ketamine for pediatric sedation? *Acad. Emerg. Med.* 1999; **6**: 21–6.
20. Finck AD, Ngai SH. Opiate receptor mediation of ketamine analgesia. *Anesthesiology* 1982; **56**: 291–7.
21. Mikkelsen S, Ilkjaer S, Brennum J *et al.* The effect of naloxone on ketamine-induced effects on hyperalgesia and ketamine-induced side effects in humans. *Anesthesiology* 1999; **90**: 1539–45.
22. Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B. Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. *Ann. Emerg. Med.* 2000; **35**: 229–38.
23. Wathen JE, Roback MG, Mackenzie T, Bothner JP. Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized, controlled, emergency department trial. *Ann. Emerg. Med.* 2000; **36**: 579–88.
24. Li J. *Ketamine: Emergency Applications*. [Cited Jan 2003.] Available from URL: <http://www.emedicine.com/emerg/topic802.htm>

