

Ketamine

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Summary

Ketamine is a very versatile inexpensive drug and plays an invaluable role in the developing world. In regions where access and funding for a wider range of drugs is problematic, its broad range of clinical applications is ideal. Its good safety profile and ease of storage makes it ideal for use in areas where refrigerators, complex monitoring, electricity and oxygen may all be in short supply or unreliable. Ketamine is also finding increasing use in both the acute and chronic pain settings and research is still ongoing into a potential neuroprotective effect for ketamine in brain injury.

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You are in a small rural hospital with limited drugs, some basic intubation equipment and a self-inflating bag. Your only oxygen is from a concentrator and the electricity supply is unreliable. Your monitoring is a manual sphygmomanometer and pulse oximeter. Consider the following real life cases. How might you manage them?

- 1 A 22-year-old man has been admitted with a gunshot wound to the abdomen. He is shocked from major internal bleeding and requires a laparotomy. You have a very small supply of inotropes and want to try not to use them. What will you do for induction and maintenance of anaesthesia?
- 2 A 2-year-old boy needs repair of his hernia. He is extremely frightened of the hospital and its staff. You know that obtaining intravenous access will be difficult and you lack the facilities for an inhalational induction. How will you anaesthetise this child?
- 3 A 37-year-old woman is recovering from 45% burns; she needs dressing changes which are very painful every 2 days. She has very few sites left for intravenous access and you don't want to use them as she has further surgery to come. She is also needle phobic. How will you manage the sedation she requires for dressing changes?
- 4 The laparotomy patient (case 1) is back on the ward. He has severe postoperative pain but you have been unable to get any morphine or pethidine this month. How can you manage his postoperative pain?
- 5 A 25-year-old man has had his leg amputated after a motorcycle accident. He has troublesome phantom limb pain. You have tried giving him amitriptyline and carbamazepine but without effect. What could be your third-line option?

6 An 18-year-old girl has been admitted with severe asthma. You have been asked to see her, as she has not improved with bronchodilators, intravenous aminophylline and steroids. She is getting tired and her saturations are falling. Can you do anything to help? Ketamine is the only anaesthetic available which has analgesic, hypnotic and amnesic effects. It produces a state of dissociative anaesthesia resulting from electrophysiological dissociation between the limbic and cortical systems. When used correctly, it is a very useful and versatile drug.

Pharmacology

Ketamine is a phencyclidine derivative described in 1965, and first used in clinical practice in the 1970s. Its receptor binding has not been fully elucidated but includes an antagonist action at N-methyl-D-aspartate (NMDA) receptors throughout the central nervous system. The most common commercial preparation is a racemic mixture of two enantiomers, S(+) ketamine and R(–) ketamine. A single enantiomer preparation of S(+) ketamine is now available in some countries. S(+) ketamine has four times the affinity of R(–) ketamine for the NMDA receptor and also binds to mu and kappa opioid receptors. Its anaesthetic potency is three times that of the racemic mixture [1]. The incidence of side-effects is the same at equal plasma concentrations for both enantiomers, but as lower doses of S(+) ketamine are required due to its higher potency, fewer side-effects and shorter recovery times are seen with the single enantiomer preparation. The R(–) enantiomer has a greater effect on

airway smooth muscle relaxation and for this reason the racemic mixture may be more suited for patients with bronchospasm [2].

Ketamine is metabolised in the liver to an active metabolite – norketamine. This has a potency of around one-third that of ketamine. The ketamine metabolites are then excreted renally with an elimination half-life of 2–3 h in adults [3].

The racemic mixture of ketamine is available in three different concentrations: 10 mg.ml⁻¹, 50 mg.ml⁻¹ and 100 mg.ml⁻¹. The 50 mg.ml⁻¹ concentration is the most commonly stocked because it can be used for intramuscular administration or diluted for intravenous use. Whilst the intravenous preparation can be taken orally, it has a very bitter taste and an oral elixir is now available. The single enantiomer S(+) preparation is available in two different formulations: 5 mg.ml⁻¹ and 25 mg.ml⁻¹.

Routes of administration

Ketamine may be administered by a variety of routes as it is both water and lipid soluble. Intravenous, intramuscular, oral, rectal, subcutaneous, epidural and transnasal routes have all been used. Following intravenous administration bioavailability is 90%, but by the oral or rectal routes bioavailability is only 16%. After oral administration there is a delay in achieving peak effect compared to intravenous administration (15–30 min compared with 1–5 min) and peak serum concentrations are only one-fifth of those found after parenteral administration. These differences are due to incomplete gastro-intestinal absorption and first pass metabolism. Following oral administration of ketamine, norketamine levels are three times higher than with intravenous administration and this is thought to have a significant role in the analgesic effects of oral ketamine [4]. Ketamine may be used epidurally either as an adjunct to local anaesthetics or alone. It binds to NMDA receptors in the dorsal horn of the spinal cord and greatly prolongs the analgesia provided by single-shot epidural techniques. Early attempts to use ketamine epidurally produced neurotoxicity. This was demonstrated to be due to the preservative used in epidural preparations [5]. The preservative-free ketamine preparation must be used for epidural administration.

Clinical effects of ketamine

Respiratory system

During ketamine anaesthesia the airway is usually well maintained with some preservation of pharyngeal and laryngeal reflexes. This is not guaranteed, however, and standard techniques for prevention of aspiration and

maintenance of a patent airway must be used when required. Ketamine has had a reputation for increased rates of laryngeal spasm. Many of these reports may be due to partial airway obstruction, which is very common with ketamine and usually responds to simple airway manoeuvres. Pooled data have shown that laryngospasm with ketamine sufficient to require intubation occurred in only 0.02% of cases compared with 1.75% of cases performed with agents other than ketamine [6].

When ketamine is given slowly, respiration is usually well maintained. After rapid intravenous injection transient apnoea is occasionally seen, but this is easily managed with a brief period of bag-mask ventilation. These apnoeas are thought to be due to a reduced responsiveness to carbon dioxide with the high peak concentrations of ketamine seen after rapid injection. There is evidence that this apnoea may be seen more frequently in neonates [7].

Ketamine acts as a bronchodilator probably by two different mechanisms – firstly, via a central effect inducing catecholamine release, thereby stimulating β_2 adrenergic receptors, resulting in bronchodilation, and secondly, via inhibition of vagal pathways to produce an anticholinergic effect acting directly on bronchial smooth muscle [8]. Whilst there is positive randomised controlled trial evidence for the use of ketamine for moderate to severe asthma in children [9], this has not been demonstrated in adults, although there are many case reports and small series attesting to its effectiveness.

Cardiovascular system

Ketamine produces an increase in blood pressure, stroke volume and heart rate whilst maintaining systemic vascular resistance. These effects usually reach a maximum about 2 min after injection and settle over 15–20 min. There is a wide variation in individual response, and occasionally there can be a large rise in blood pressure, unrelated to a pre-operative history of hypertension. It is thought that these adrenergic responses are mediated centrally and the use of centrally depressant premedication such as benzodiazepines can blunt this effect [10].

These properties mean that ketamine is an ideal agent for the shocked patient but less appropriate for patients with severe ischaemic heart disease. Whilst ketamine has been shown to increase coronary blood flow, the benefit of this is probably negated by its effect on increased myocardial oxygen demand [11].

Central nervous system

Ketamine produces dissociative anaesthesia (detached from surroundings). This is characterised by the patient often having their eyes open and making reflex

movements during anaesthesia and surgery. It has a slower onset than other intravenous anaesthetic agents after an intravenous bolus (1–5 min). The duration of action depends on the route of administration (20–30 min for intramuscular and 10–15 min for intravenous).

Sometimes these reflex movements can be troublesome, especially in fit, strong, young men. They may be decreased by a slight increase in dosage of ketamine, but further increases in dose are unlikely to improve the situation and may actually increase the reflex movements. Alternative strategies are to give further doses of benzodiazepines or analgesics (bearing in mind the increased risk of respiratory depression). Occasionally it may be necessary to swap to an alternative form of anaesthesia.

Frequent repeated sedation or anaesthesia with ketamine such as that often experienced by burns patients can lead to tolerance with increasingly large doses being required. This tolerance generally lasts for 3 days.

In recovery the patient may become agitated – this is due to hallucinations following ketamine anaesthesia. The reported frequency of these hallucinations varies widely from 5 to 30%. The incidence of hallucinations is lowest in children. Increased incidence is associated with female sex, large doses of ketamine and rapid intravenous boluses. Hallucinations can be reduced by premedication with benzodiazepines (usually diazepam 0.15 mg.kg^{-1} orally 1 h pre-operatively or 0.1 mg.kg^{-1} intravenously on induction) or, alternatively, promethazine, which has the added advantage of an anti-emetic effect. Promethazine may be given as an oral premedication (age 2–5 years 15–20 mg per os (p.o.), 5–10 years 20–25 mg p.o.) or intravenously at induction (25–50 mg intravenously in the adult). It is not recommended for use in children less than 2 years old due to the risk of severe respiratory depression. Other benzodiazepines that have been used successfully include midazolam ($0.05\text{--}0.1 \text{ mg.kg}^{-1}$ intravenously) and lorazepam (2–4 mg intravenously in the adult). Small doses of propofol and thiopental have also both been used successfully to attenuate hallucinations. Rescue doses of benzodiazepines can be given in recovery for patients experiencing distressing hallucinations but care must always be taken that they are being appropriately monitored. One of the most effective methods to prevent emergence hallucinations is to allow the patient to recover undisturbed in a quiet area; however, in some tragic cases this has resulted in unsupervised recovery with fatal airway obstruction.

Ketamine is a potent analgesic and may be used as the sole analgesic agent intra-operatively. Balanced anaesthesia, with co-administration of opiates or tramadol intra-operatively, reduces the amount of ketamine required for maintenance of anaesthesia. This shortens the recovery

time and reduces the incidence of some of the side-effects of ketamine but increases the risk of intra-operative respiratory depression.

In addition to its intra-operative analgesic effects, ketamine is increasingly used in both acute and chronic pain settings in the developed and developing world. Studies have shown that the use of intra-operative ketamine leads to reduced morphine consumption post-operatively in adults, even when the ketamine is not continued into the postoperative period [12]. It is thought that the mechanism for this may be related to the antagonistic effects of ketamine at the NMDA receptor, which is implicated in 'wind-up'. 'Wind-up' is a phenomenon whereby the nerves that conduct pain signals from the dorsal horn of the spinal cord become sensitised. Painful stimuli are then experienced as causing greater pain than previously.

Ketamine at low doses has also been shown to be an effective postoperative analgesic with a tolerable side-effect profile in most patients [13, 14]; it is especially useful in patients who have a tolerance to opiates [15]. There are increasing reports in the literature of the use of ketamine in chronic pain states such as complex regional pain syndromes [16], phantom limb pain [17] and central and peripheral neuropathic pain [18]. Whilst both intravenous infusions and oral ketamine have been effective, patients appear to experience fewer side-effects with oral ketamine (perhaps because a greater portion of the analgesic effect in oral dosing is due to norketamine, which does not have hallucinogenic properties).

Ketamine has traditionally been regarded as absolutely contra-indicated in patients with head injuries. There is increasing evidence, however, to suggest this may not be the case. In spontaneously breathing volunteers, ketamine increases cerebral blood flow, but during controlled ventilation and sedation in brain-injured patients, the intracranial pressure does not rise. In spontaneously breathing patients a rise in arterial $p\text{CO}_2$ has been identified as the major factor responsible for the rise in intracranial pressure with ketamine [19]. In one study, cerebral perfusion pressure was improved due to the better maintenance of blood pressure with a combination of ketamine and midazolam compared with fentanyl and midazolam [20].

There is now also some laboratory evidence of a possible role for ketamine in neuroprotection. Animal studies demonstrate that ketamine can attenuate injury from ischaemia. The putative model is that blockade of the NMDA receptor prevents transduction of signals to destructive intracellular mechanisms [21].

Ketamine has been shown to have both pro- [22] and anti-convulsant [23] effects. Due to the uncertainty of its

effect in any one patient it is probably best avoided in epilepsy.

In patients with schizophrenia, ketamine may reactivate psychoses. In patients without psychiatric disease there are no long-term psychotic reactions from the use of ketamine. Ketamine should be avoided in patients with a history of psychosis.

Gastro-intestinal tract

Ketamine increases salivation, which can lead to airway problems such as laryngeal spasm or obstruction. It may also make the taping of tracheal tubes more difficult. To reduce salivation, atropine is usually given either as premedication ($20 \mu\text{g.kg}^{-1}$ intramuscularly to maximum 0.5 mg) 30 min pre-operatively or at the time of induction intravenously ($10\text{--}20 \mu\text{g.kg}^{-1}$ to maximum 0.5 mg). Alternatively, glycopyrrolate may be used (0.01 mg.kg^{-1} to maximum 0.2 mg intravenously) When used for sedation in the Intensive Care Unit (ICU), the effects of ketamine on the gastro-intestinal system may be an advantage, as enteral feed is better tolerated with ketamine sedation than with opioids [24]. Ketamine has a greater propensity to cause nausea and vomiting compared to thiopental or propofol; however, due to its opioid-sparing effects in the peri-operative period, the overall incidence of postoperative nausea and vomiting is reduced [25].

Skeletal muscle

Ketamine increases skeletal muscle tone. This is most noticeable after the initial intravenous bolus and gradually decreases. It may be improved by administration of benzodiazepines. It is rarely a problem intra-operatively although, in muscular young men, especially those requiring manipulation of fractures, relaxation with benzodiazepines or even muscle relaxants may be required.

Eyes

Induction with ketamine produces a small rise in intra-ocular pressure which is still sustained 15 min into anaesthesia. In human studies this rise has not been found to be clinically significant and is smaller than that produced by laryngoscopy [26]. The putative mechanism for this rise is increased tone of the extra-ocular muscles coupled with increased blood flow due to the increased cardiac output and a rise in arterial $p\text{CO}_2$ seen with ketamine. Balanced anaesthesia with controlled ventilation helps to reduce these effects and in addition reduces the nystagmus otherwise commonly seen with ketamine anaesthesia. Ketamine can therefore be safely used for intra-ocular procedures. In the case of the open eye or glaucoma, ketamine is still best avoided in favour of

agents that produce no rise in intra-ocular pressure and that can attenuate the response to intubation.

Placenta

Ketamine crosses the placenta. Newborn infants after Caesarean section under ketamine anaesthesia will therefore be partially anaesthetised and should be cared for accordingly.

Thyroid

Ketamine has been reported to produce hypertension and supraventricular tachycardia in patients who are hyperthyroid or receiving thyroxine. For this reason it is recommended to avoid ketamine in these patients.

Metabolic

Ketamine produces a serum rise in porphyric markers but no clinical evidence of porphyria. If an alternative, non-porphyrin-inducing agent to ketamine is available, it should be used.

Practical examples

1 Intravenous ketamine for induction and maintenance

A 22-year-old man has been admitted with a gunshot wound to the abdomen. He is shocked from major internal bleeding and requires a laparotomy.

Ketamine is an ideal anaesthetic agent in this case due to its cardiovascular effects of raising the blood pressure and heart rate; all other anaesthetic agents tend to have a cardiac depressant effect. Induction can be performed with intravenous ketamine ($1\text{--}2 \text{ mg.kg}^{-1}$ slowly), atropine ($10\text{--}20 \mu\text{g.kg}^{-1}$) and diazepam (0.1 mg.kg^{-1}). It is still possible to perform a modified rapid sequence intubation with ketamine, despite its slower onset time.

There are several options for maintenance including:

- Intermittent boluses of intravenous ketamine (0.5 mg.kg^{-1}) given according to patient's response – pupil size, heart rate, blood pressure, movement, etc.
- Ketamine infusion. Put 500 mg of ketamine in a 500-ml bag of saline or dextrose. The drip rate will need to be adjusted according to the patient's response. In patients breathing spontaneously, run this at $2 \text{ drops.kg}^{-1}.\text{min}^{-1}$ (non-micro drip intravenous chamber 15 drops.ml^{-1}). Paralysed ventilated patients will require a reduced dose.

Generally, the ketamine will need to be discontinued 10–20 min before the end of the operation to avoid delayed emergence.

This technique for laparotomy is best used with non-depolarising muscle relaxants (avoid pancuronium, as hypertension may result). It is possible, although difficult, to perform the laparotomy under ketamine alone.

2 Use of intramuscular ketamine

A 2-year-old boy needs repair of his hernia. He is extremely frightened of the hospital and its staff. You know that obtaining intravenous access will be difficult and you lack the facilities for an inhalational induction.

This child is clearly going to be unco-operative and either intravenous access or gas induction will be difficult. In these circumstances intramuscular ketamine is very useful.

There are several options:

- Induce anaesthesia with intramuscular ketamine ($5\text{--}10\text{ mg.kg}^{-1}$) + atropine ($20\text{ }\mu\text{g.kg}^{-1}$), mixing drugs in the same syringe. Onset of anaesthesia will start about 5 min after injection. The disadvantage of this technique is that it requires a relatively large intramuscular injection. Although most textbooks quote $8\text{--}10\text{ mg.kg}^{-1}$ for induction, in many cases a much smaller dose (5 mg.kg^{-1}) is sufficient. Hallucinations are usually less common in children than adults and the routine addition of diazepam reduces the safety margin of ketamine in small infants. If troublesome hallucinations occur in recovery they may be treated with a small dose of intravenous diazepam.
- Sedate with intramuscular ketamine (2 mg.kg^{-1}) + atropine ($20\text{ }\mu\text{g.kg}^{-1}$). After 5 min you will have a docile child who can co-operate with either cannulation or inhalational induction.

The author's preference is for the second option because the intramuscular injection is smaller and it can be performed safely in the waiting area on the mother's lap rather than in theatre, and is therefore less traumatic for the child. In either case, intravenous access should then be obtained. If intravenous access is impossible, then anaesthesia can be maintained with intramuscular ketamine ($3\text{--}5\text{ mg.kg}^{-1}$) repeated as required.

3 Oral ketamine sedation

A 37-year-old woman is recovering from 45% burns; she needs dressing changes every 2 days, which are very painful. She has very few sites left for intravenous access and you do not want to use them as she has further surgery to come. She is also needle phobic. How will you manage the sedation she requires for her dressing changes?

This woman requires recurrent sedation for painful burns dressings. Intravenous ketamine is possible, but in burns patients there are often limited sites for venous cannulation and these are best saved for trips to theatre. Intramuscular ketamine is also an option but requires relatively large painful intramuscular injections. Instead, the intravenous preparation of ketamine can be given orally.

Adult dose: 500 mg of ketamine + diazepam 5 mg.

Paediatric dose: 15 mg.kg^{-1} ketamine (you can use the intravenous preparation but it tastes very bitter and may have to be mixed with fruit juice).

The dressing change can usually start after 20–30 min; sedation starts earlier than anaesthesia. Responses may be unpredictable and onset time may take longer. There should always be equipment for suction and facemask ventilation available, and if possible, oxygen and a pulse oximeter.

4 Ketamine for postoperative analgesia

The laparotomy patient (Case 1) is back on the ward. He has severe postoperative pain but you have been unable to get any morphine or pethidine this month. How can you manage his postoperative pain?

Ketamine is a very good analgesic and can be used to treat severe pain when morphine is not available. Postoperatively it is limited by hallucinations; however, these are less of a problem when relatively low doses are used. For adult patients in severe pain a loading dose of $0.5\text{--}1\text{ mg.kg}^{-1}$ intramuscularly may be given. This can then be followed by an infusion of $60\text{--}180\text{ }\mu\text{g.kg}^{-1}.\text{h}^{-1}$ ($4\text{--}12\text{ mg.h}^{-1}$ for a 70-kg adult).

A practical regimen is to add 50 mg of ketamine to a 500-ml bag of saline or dextrose (0.1 mg.ml^{-1} of ketamine) and run this at $40\text{--}120\text{ ml.h}^{-1}$ (i.e. over 4–12 h for a 70-kg adult). This regimen is relatively safe as even if the whole infusion were to be given accidentally, the patient is unlikely to become deeply anaesthetised. The patient should still be closely monitored and anaesthetic help should be available if needed.

5 Use of ketamine for patients with chronic pain

A 25-year-old man has had his leg amputated after a motorcycle accident. He has troublesome phantom limb pain. You have tried giving him amitriptyline and carbamazepine but without effect. What could be your third-line option?

Many patients with amputations or nerve injuries have problems with chronic pain. The nature of neuropathic pain (this means originating from an injury to the nerves) usually has an unpleasant burning or shooting quality to it. When traditional first-line treatments for neuropathic pain such as amitriptyline or carbamazepine have failed, ketamine may also be added and has been shown to be successful in some patients.

A standard dosing regimen for an adult is 50 mg orally (use the intravenous preparation) three times a day (tds). This may be increased to 100 mg tds. Problems with hallucinations and salivation are rare. The ketamine may be discontinued after about 3 weeks of good pain control, reducing the dose gradually to see if the pain recurs. I have found this regimen especially useful in postoperative amputation patients for phantom limb pain and neuropathic pain after spinal cord injury.

6 Ketamine for the treatment of asthma

An 18-year-old girl has been admitted with severe asthma. You have been asked to see her, as she has not improved with bronchodilators, intravenous aminophylline and steroids. She is getting tired and her saturations are falling. Can you do anything to help?

Ketamine is an effective bronchodilator in some patients and can be tried if there is no response to conventional bronchodilators such as salbutamol and aminophylline. The doses of ketamine required are very low and problems with hallucinations rare. A loading dose of 0.2 mg.kg^{-1} intravenously is given initially followed by an infusion of $0.5 \text{ mg.kg}^{-1}.\text{h}^{-1}$ for 3 h. This may be continued if necessary. Close monitoring of the patient is required and an anaesthetist should be available.

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