Ketamine: Recent Evidence and Current Uses

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KEY POINTS

- Ketamine is a dissociative anaesthetic agent that at differing doses can be utilised as an analgesic, sedative, anaesthetic induction and anaesthetic maintenance agent.
- Ketamine has specific advantages over some of the other sedative and anaesthetic agents. Airway reflexes and tone are often preserved during ketamine sedation and it has an excellent haemodynamic profile.
- Ketamine has a unique role in prehospital, emergency and critical care medicine and is commonly used by anaesthetists all over the world.
- Research has suggested that use of optical isomers of ketamine may help reduce unwanted side effects.
- Ketamine appears to have beneficial anti-inflammatory, bronchodilatory and neuroprotective properties.

INTRODUCTION

Ketamine is a potent analgesic and dissociative anaesthetic agent that has been used since its discovery and synthesis in 1962. Ketamine's popularity is due to its unique ability to produce rapid sedative, analgesic and amnesic effects together with its beneficial secondary features. The latter include bronchodilation and maintenance of both airway reflexes and sympathetic nervous system tone.[1] Recent studies have also suggested previously unrecognised neuroprotective[2] and anti-inflammatory[3] properties.

Due to ketamine's unique properties and versatility it has gained increasing popularity in prehospital and emergency medicine as well as being used extensively by anaesthetists and anaesthetic assistants throughout the world. Newer uses include low-dose analgesic protocols, adjuvant therapy in local anaesthetic nerve blocks, applications in reactive airways disease, as well as procedural sedation for both routine and complex procedures in theatres, emergency departments and critical care units.

Despite the potential advantages of ketamine, it has not proved universally popular, due to its potentially troublesome ''emergence'' phenomena, its potential as a drug of abuse and the introduction of other sedative and analgesic drugs.

Research using isomers of ketamine, such as '*S*-(+)-ketamine,' a more potent N-methyl-D-aspartate receptor (NMDA) binder, has enabled the use of lower dosing for similar effects.[4] This reportedly results in a lower incidence of the traditional psychoactive side effects, whilst maintaining the beneficial effects of the drug.[5]

This article will review the pharmacology and varied uses of ketamine with reference to the current literature.

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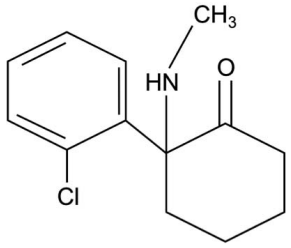

Figure 1. Chemical structure of ketamine. There is a chiral centre in the cyclohexanone ring giving the *S* and *R* isomers

PHARMACOLOGY

Ketamine is a derivative of the cyclo-hexamine (phencyclidine) anaesthetic agents used extensively in the 1950s. It is a noncompetitive NMDA receptor antagonist, which blocks the phencyclidine binding site on the NMDA receptor thereby stopping depolarisation of the neurone. These NMDA receptors are located at the spinal, thalamic, limbic and cortical levels. Ketamine therefore interferes with sensory input to higher centres of the central nervous system, affecting pain and emotional responses as well as memory, hence it is referred to as a "dissociative anaesthetic."[6] Ketamine also has some secondary effects on opioid receptors, which help to propagate its analgesic effect, as well as catecholamine, alpha and beta receptors.

Structural Formula

Ketamine (Figure 1) contains a chiral centre at the C-2 carbon of the cyclohexanone ring; this means there are two optical isomers; *S*-(+)-ketamine and *R*-(–)-ketamine. The S isomer is pharmacologically more active.

In the UK, ketamine is generally available as a racemic solution, a mixture of *R* (–) and *S* (+) isomers in equal amounts. It is available in a variety of concentrations: 10, 50 and 100 $mg{\cdot}ml^{-1}$. Optical-isomer *S*-(+)-ketamine (5 and 25 $mg{\cdot}ml^{-1}$ concentrations) is not currently available in the UK but is available in a number of European countries.

Pharmacokinetics

Distribution

Ketamine is highly lipid soluble but has low protein-binding ability. This allows rapid transfer across the blood brain barrier, leading to concentrations there that are generally 4 to 5 times greater than in the plasma. The distribution half-life is around 7 to 11 minutes.

Metabolism and Elimination

Ketamine is mostly metabolised in the liver (80%) into norketamine, which in itself has weak analgesic properties, around 20% to 30% the potency of ketamine. Peak levels of norketamine appear within the blood around 30 minutes after intravenous (IV) administration. Norketamine is then primarily hydroxylised via glucuronoconjugation and excreted in urine and bile.[5]

Pharmacodynamics

Central Nervous System

Ketamine produces a trance-like cataleptic state in which there is potent analgesia and sedation. Emergence symptoms affect 30% to 50% of people. The incidence is more common with higher doses. Symptoms can include a sense of unease, hallucinations, vivid dreams, floating sensations and delirium.

Cardiovascular

Ketamine appears to stimulate the sympathetic nervous system leading to increased cardiac output, tachycardia and increased blood pressure. Therefore, it should be used with caution in those with ischaemic heart disease. The exact mechanism of this is not known; however, it is proposed that ketamine may inhibit reuptake of circulating catecholamines. It has been noted in patients with chronic catecholamine depletion, such as the critically ill, that ketamine alone actually produces a negative inotropic effect. In patients with normal autonomic control the direct negative inotropic effect is often overridden by the central sympathetic response,[1] producing an overall increase or maintenance of blood pressure.[6]

Respiratory

In contrast to other available sedative and anaesthetic agents, airway tone and both pharyngeal and laryngeal reflexes are often preserved during ketamine use. However, in children younger than 12 months, airway reflexes are more variable and

unpredictable.[7] Ketamine may have a slight respiratory depressive effect via a decrease in the usual respiratory stimulant effect of raised $PaCO_2$ levels. This is especially noticeable after administration of large IV boluses, where transient periods of apnoea have been reported.[8] Ketamine has also been shown to cause bronchodilation, making it the induction agent of choice for patients with life-threatening asthma requiring mechanical ventilation.

Other Effects

Ketamine increases muscle tone, blood glucose and plasma cortisol and prolactin levels.[6] A potentially troublesome side effect is increased salivation and some authors advocate coadministration of antisialagogues, commonly atropine.[9]

USES AND CURRENT EVIDENCE

Sedation

Ketamine is increasingly being used in prehospital and emergency medicine for analgesia and sedation. It is ideally suited for the management of traumatic events such as reduction of fractures and the treatment of burns. The characteristic dissociative state seen with ketamine can be achieved with a dose range between 0.25 and 1.5 $mg{\cdot}kg^{-1}$ IV.

For procedural sedation in the emergency department, a loading dose administered over 30-60 seconds is recommended. This produces sedation within 1 minute, lasting 5-10 minutes. Large variation exists for recommended loading doses, from 0.25 to 1.0 $mg{\cdot}kg^{-1}$ IV for adults and 0.25 to 2.0 $mg{\cdot}kg^{-1}$ IV for children.[4] It should be noted that doses at the higher range are commonly used for induction of general anaesthesia. A single dose is adequate for shorter procedures, but for longer procedures, the dissociative state can be maintained with intermittent boluses of 0.5 $mg{\cdot}kg^{-1}$. Detailed clinical practice guidelines have been produced for using ketamine in the emergency department[10] but as with the use of any sedative drugs, relevant expertise and adequate monitoring are required. Minimum monitoring, where available, consists of continuous electrocardiogram, non-invasive blood pressure, oxygen saturation and end tidal CO_2 monitoring.

Ketamine can be used safely in combination with other drugs such as propofol for induction or sedation. Coadministration of these drugs reduces the required dose of each by around 50%,[4] reducing the incidence and severity of the side effects of both agents. It is proposed that through its sympathomimetic actions, ketamine reduces propofol-induced hypotension, whilst coadministration of propofol reduces the incidence of postprocedure agitation seen with ketamine alone. Randomised control trials have recently shown improved sedation when both drugs are used together compared with propofol alone.[11]

For cases where IV access is difficult, the use of intramuscular, oral or intranasal ketamine has been described with good effect. Time of onset of effect is usually longer for these routes when compared with IV administration and doses required show greater variability due to variations in vascularity and gastrointestinal absorption (see Table 1). Oral use of ketamine, either alone or in combination with paracetamol and diazepam, can be used for dressing changes, especially in burn patients, thus minimising visits to theatre. There is some degree of tachyphylaxis with repeat use.

Route of Administration	Bioavailability	Starting Dose[a]
Intravenous	100%	0.25-1 $mg{\cdot}kg^{-1}$ (adult)[b] 0.25-2 $mg{\cdot}kg^{-1}$ (children)[b] 1-2 $mg{\cdot}kg^{-1}$[c]
Intraosseous	100%	0.5-1 $mg{\cdot}kg^{-1}$[b] 1-2 $mg{\cdot}kg^{-1}$[c]
Intramuscular	93%	4-5 $mg{\cdot}kg^{-1}$[b] 8-10 $mg{\cdot}kg^{-1}$[c]
Oral	16%-20%	500 mg max (adult)[b] 3-15 $mg{\cdot}kg^{-1}$ (children)[b]
Nasal	45%-50%	0.25-4 $mg{\cdot}kg^{-1}$[b] 3-9 $mg{\cdot}kg^{-1}$[c]
Rectal	24%-30%	50 mg[b] 8-15 $mg{\cdot}kg^{-1}$[c]

Table 1. Routes of administration of ketamine and dose range in children and adults (Reproduced from Marland and Ellerton [4]) The doses quoted above produce a continuum of effects from mild sedation through to full anaesthetic induction. As with administration of any sedative medication, relevant expertise and adequate monitoring is required. In children, variable dosing has been proposed for intranasal, intraosseous and intramuscular routes and there is a lack of consensus in the literature on specific dosing. Examples of paediatric dosing regimes are provided in some of the referenced articles.[29]
[a]Note: Ketamine should be titrated to the required clinical effect. [b]Analgesic and sedation dose. [c]Anaesthetic dose. Note there is some overlap in dosing between sedation and anaesthetic doses.

The main side effects limiting ketamine's use during shorter procedures are agitation and emergence symptoms. Both are more common with higher doses. Benzodiazepines have been shown to be effective at reducing the incidence of emergence phenomena. Use of midazolam (0.07-0.1 $mg \cdot kg^{-1}$), diazepam (0.15-0.3 $mg \cdot kg^{-1}$and lorazepam (2-4 mg) have all been described.[8] Recovering patients in a quiet and controlled environment with ample reassurance has also been shown to reduce the incidence and severity of emergence symptoms following ketamine sedation.

CASE STUDY 1: PREHOSPITAL CARE

A normally fit and well 6-year-old girl was witnessed to have fallen 6 feet from a wall onto concrete and is complaining of severe pain in her right ankle. She is 45 minutes from the closest hospital and a specialist paramedic ambulance crew is in attendance. She did not lose consciousness and there is no report of any head injury. Primary survey findings are as follows:

<C>: no catastrophic haemorrhage
A + B: Patent airway, self-ventilating, oxygen saturation 99% on air.
C: Haemodynamically stable, all peripheral pulses present but prolonged capillary refill time in her right foot (5 second versus 2 seconds for other peripheries).
D: Glasgow Coma Scale 15, equal and reactive pupils, blood sugar level normal.
E: Fracture dislocation of right ankle, no other obvious injuries.

Due to the diminished perfusion of her foot and the distance from hospital the decision is made to reduce the fracture on scene.

Consider the available options for sedation and analgesia to allow manipulation.

In this case a combination of fentanyl and ketamine was used to induce a dissociative state. After commencement of full monitoring (Electrocardiogram, pulse oximetry non-invasive blood pressure and end tidal CO_2) initial doses of 0.5 $mcg \cdot kg^{-1}$ of fentanyl and 0.2 $mg \cdot kg^{-1}$ of ketamine were given. Gentle traction was applied but this was not tolerated due to pain. Therefore, a further 0.25 $mcg \cdot kg^{-1}$ of fentanyl and 0.2 $mg \cdot kg^{-1}$ of ketamine was given with good effect, allowing for successful reduction, dressing and splinting with a vacuum splint. Onward transfer was uneventful.

Induction and Maintenance of Anaesthesia

Ketamine is also being increasingly commonly used in hospital and prehospital environments as an anaesthetic induction and maintenance agent for emergency situations. In rapid sequence induction an IV dose of 1 to 2 $mg \cdot kg^{-1}$ produces dissociative anaesthesia within 1 to 2 minutes of administration. This is generally longer than the short 'arm-to-brain' time for rapid unconsciousness seen with more traditional IV induction agents such as propofol or thiopentone. However, in circumstances where haemodynamic control is important, such as trauma or sepsis, ketamine has significant advantages. It has also been shown to have other important benefits including allowing for improved preoxygenation in agitated patients when reduced doses (0.25-0.5 $mg \cdot kg^{-1}$ IV) may be given prior to full induction of anaesthesia.[12] A reduced dose of ketamine for induction should be considered in shocked patients due to concerns about inadequate sympathomimetic action within this patient group.

The use of ketamine for total intravenous anaesthesia (TIVA) in combination with muscle relaxants has been described less frequently in the literature. Ketamine use has been reported both as a sole agent and in conjunction with other hypnotics such as propofol and benzodiazepines. Potential indications for ketamine TIVA include cardiogenic shock, hypovolaemia and pericardial tamponade, particularly in low-resource areas where access to vasoactive drugs may be limited. Ketamine TIVA has also been described in paediatric anaesthesia with good effect.[8]

Anaesthesia can be maintained using intermittent boluses of IV ketamine (0.5 $mg \cdot kg^{-1}$), or by continuous infusion at 10 to 30 $mcg \cdot kg^{-1} \cdot min^{-1}$ titrated according to effect. Discontinuing the infusion 20 to 30 minutes prior to the end of surgery allows adequate clearance. It is worth noting that electroencephalography and bispectral index monitoring have no role in monitoring the depth of anaesthesia induced by ketamine.

Analgesia

Ketamine is a potent analgesic. It acts as an NMDA antagonist, which as discussed previously, produces dissociative analgesia. However, at lower doses it has been shown to desensitise central pain pathways and modulate opioid receptors.[13] Studies have demonstrated that administration of small doses of ketamine perioperatively can reduce opioid requirements by up to 50%.[14]

Examples of perioperative analgesia regimes include intraoperative ketamine infusions, postoperative infusions, low-dose bolus regimes and patient-controlled analgesia. All have been described in detail in a Cochrane review from 2006.[14] This review provides evidence of the efficacy of perioperative ketamine in providing effective analgesia; however, it does not conclude on optimal dosing or method of delivery. In one randomised controlled trial of postoperative patients following major abdominal surgery who were monitored in the intensive care unit, ketamine was administered with an initial IV bolus of 0.5 $mg \cdot kg^{-1}$ followed by an infusion of 2 $mcg \cdot kg^{-1} \cdot min^{-1}$ for the first 24 hours, followed by 1 $mcg \cdot kg^{-1} \cdot min^{-1}$ for the next 24 hours.[15] This resulted in a significant reduction of morphine use postoperatively.

In the emergency department and prehospital environment, low-dose ketamine regimes have also been described for pain management. Typically suggested doses are between 0.1 and 0.2 $mg \cdot kg^{-1}$ IV. In one study, a bolus dose of 0.1 $mg \cdot kg^{-1}$ IV ketamine was given in conjunction with opioids to patients with a variety of presentations, including abdominal pain, lacerations, fractures and dislocations.[16] This produced effective analgesia over 120 minutes and reduced opioid requirements and, although some side effects were noted in the group treated with ketamine, most were considered minor and tolerable.

Through desensitisation of central pain pathways, there is some evidence to suggest that ketamine may be helpful in patients undergoing surgery who are chronic opioid users. Several studies in these populations have shown a reduction in opioid use over 48 hours and improved pain scores at 6 weeks following intraoperative IV ketamine.[17] Recently there has also been interest in using intraoperative ketamine to prevent chronic postsurgical pain. A recent meta-analysis looked at studies using low-dose ketamine versus placebo intraoperatively and followed patients up at 3, 6 and 12 months.[18] The results showed postsurgical pain was reduced at 3 and 6 months, although there was no significant difference between the groups at 12 months. Although initial studies are promising, larger, more rigorous studies are required to explore the potential role that ketamine plays in persistent postsurgical pain.

Reactive Airways Disease

Ketamine has bronchodilatory effects and has been shown to be effective in patients with acute bronchospasm. Ketamine's effect on the airways is thought to be through modulation of the inflammatory cascade. A recent review has shown that there may be a role for ketamine in asthma that is unresponsive to conventional treatment.[19] The authors noted that patients who received ketamine improved clinically, had lower oxygen requirements and in some cases avoided invasive ventilation. Mechanically ventilated patients who received ketamine for severe bronchospasm showed improved gas exchange, reduced inspiratory pressures, improved minute ventilation and often went on to be successfully weaned off ventilation. No major adverse effects with ketamine were reported in this review of 244 patients. The review included a mix of case reports, case series, observational studies and randomised controlled trials. Highly variable loading doses from 0.1 to 2.0 $mg \cdot kg^{-1}$ were used in the studies and depending upon the initial response, the dose used for continuous infusion ranged from 0.15 to 2.5 $mg \cdot kg^{-1} \cdot hr^{-1}$. Due to the small sample size and wide variety of loading and infusion doses, further research is needed in this area.

Uses in Critical Care

Ketamine has a number of potential applications within critical care medicine, including sedation, analgesia and the treatment of persistent bronchospasm. Ketofol (ketamine and propofol in combination) has been shown to be effective for short-term sedation in a critical care population.[20] It is important to appreciate that in critically unwell patients ketamine's direct negatively inotropic effect agent may predominate over ketamine's usual positive or neutral cardiovascular response. There have been reported incidents of unexpected decreases in blood pressure and/or cardiac output following ketamine administration in some critically unwell patients; however, a large multicentre study of critically unwell septic patients revealed no adverse effects when using ketamine.[21] It has even been suggested that ketamine may have potential advantages compared to other agents in patients with severe sepsis (see case study 2). There is evidence to suggest that it may exert a protective anti-inflammatory effect, reducing the systemic effects of sepsis including hypotension and metabolic acidosis.[22]

Ketamine was initially thought to be contraindicated in patients with traumatic brain injuries or raised intracranial pressure. However, some studies have shown that ketamine can be helpful as a sedative within these patient groups. Its use has been associated with maintenance of cerebral perfusion pressure during stimulating interventions in a critical care population with brain injuries.[23] Its use in traumatic head injury remains contentious but current evidence (rated Oxford level 2b, GRADE C) suggests that ketamine does not increase intracranial pressure in severe traumatic brain injury patients that are sedated and ventilated and may in fact lower it.[24] Further research is required in this field before its use can be widely recommended.

CASE STUDY 2: SEPSIS

A 67-year-old man presents to the emergency department with a 2-day history of productive cough, confusion and fever. He is haemodynamically unstable with hypotension and tachycardia. He is diagnosed with a septicaemia secondary to presumed severe community-acquired pneumonia (CURB65 = 4). Initial treatment consists of IV fluids

and appropriate antibiotic therapy. Despite this, his clinical condition continues to deteriorate with worsening hypoxia, hypotension and metabolic acidosis. He is transferred to critical care for commencement of mechanical ventilation and cardiovascular support.

Consider the available induction agents along with the risks and benefits of using each.

In this case, the anaesthetic agent chosen was ketamine at a dose of 1.5 $mg \cdot kg^{-1}$. This was because of its cardiovascular stability when compared with alternative induction agents. There is also some evidence to suggest that ketamine has some anti-inflammatory properties.

Cautions and Limitations

Ketamine is considered to have a very good safety profile. Ketamine overdose has been manifested as prolonged sedation in case studies of children inadvertently receiving 5 to 100 times the recommended dosage.[6] A few isolated case studies of severe respiratory depression have been noted during routine administration of ketamine with other medications; however, mostly only transient apnoeic episodes have been reported following large IV boluses.

Absolute contraindications to IV ketamine as listed by the British National Formulary[25] are hypertension, preeclampsia or eclampsia, severe cardiac disease, stroke, raised intracranial pressure and acute porphyria. Ketamine is also not recommended in children aged $<$ 3 months and in patients with schizophrenia. Please refer to earlier sections within this article for further detail on the use of ketamine in patients with raised intracranial pressure and/or traumatic brain injury.

Developing World

Ketamine is currently used extensively throughout the world due to its versatility, availability and low side-effect profile. There has been discussion about its potential for misuse and whether greater controls worldwide are required. The World Health Organisation in 2015 concluded that due to the reliance on ketamine in some countries "controlling ketamine internationally could limit access to essential and emergency surgery, which would constitute a public health crisis in countries where no affordable alternatives exist."

Ketamine is one of the most available anaesthetic agents in low- to middle-income countries (LMICs).[26] A recent report found that in 12 LMICs, only 53% of facilities had reliable access to a functioning anaesthesia machine and only 52% had continuous access to pulse oximetry. On average 21% to 45% lacked basic airway management equipment. In this survey general inhalational anaesthesia was offered by only 58% of respondents but between 70% and 90% reported reliable access to ketamine.

A study attempting to quantify ketamine use in LMICs found a serious complication rate (i.e., death, cardiac arrest, apnoea, laryngospasm and aspiration) of only 0.15% in over 12 000 administrations of ketamine during routine and emergency surgeries.[27] This low rate of complications was often in the setting of variable practitioner skill and monitoring, suggesting that the safety margin of using ketamine in these situations is high.

Additional examples showing the varied uses of ketamine including use in LMICs can be found in the ATOW 27 by Craven and Alkhafaji.[28]

SUMMARY

Ketamine is a versatile drug with a unique profile that allows it to be successfully used for a multitude of situations worldwide. Its variable dosing means it can be used both as an induction agent with a good haemodynamic profile or in lower doses as a reliable sedative or analgesic drug. It has a vital role in prehospital and emergency medicine. As an adjunct during routine anaesthesia it can help reduce opioid requirements postoperatively. Its use in critical care includes sedation and management of refractory asthma; however, further research is required to elucidate its role in trauma and head injury patients. In the developing world, it is a vital and highly valued drug that allows performance of interventions and operations that may otherwise prove impossible, especially when resources are limited.

Ketamine still suffers from traditional stigma from doctors and the public alikeand it is often neglected due to concerns about psychological side effects. Increased availability of preparations of pure *S*-(+)-isomer ketamine may help increase its popularity.

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