KETAMINE: A REVIEW

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Ketamine was first synthesized in 1962 at the Parke Davis Lab by Calvin Stevens. The original name for Ketamine was 'CI581'. 1965 saw the first accounts of the recreational use of ketamine - Professor Edward Domino described it as a potent psychedelic drug and coined the term 'dissociative anaesthetic'. In 1966 ketamine was patented by Parke-Davis for use as an anaesthetic in humans and animals. Ketamine was then used as a field anaesthetic by the U.S.A. during the Vietnam War.

Ketamine provides dissociative anaesthesia - a combination of profound analgesia with superficial sleep. This state is characterised by spontaneous ventilation, relative preservation of airway reflexes and haemodynamic stability, and explains why ketmaine has remained the anaesthetic drug of choice in the developing world and for mass casualties in the field.

Ketamine, a phencyclidine derivative, is soluble in water and is prepared with the sodium salt benzethonium chloride as a preservative. It is a basic compound and is dissolved in a solution of pH 3.5-5. The ketamine molecule contains an asymmetrical carbon atom with two optical isomers (enantiomers). The S(+) isomer is about three times more potent and longer acting as an anaesthetic than the R(-) isomer; the latter is thought to be the cause of some of the undesirable side effects.

Central Nervous System

Ketamine's site of action appears to be primarily in the thalamus and limbic systems, acting as an N-methyl-D-aspartate (NMDA) receptor non-competitive antagonist. It does not suppress respiratory drive unless high doses are used, or smaller doses given rapidly. The eyes often remain open with a slow nystagmic gaze along with preservation of the corneal and light reflexes. Glucose uptake in the auditory and somatosensory systems is reduced, suggesting selective deprivation of these senses (the thalamic and limbic regions show increased uptake. Ketamine produces high-amplitude slowing of the EEG, and case reports of successful treatment of status eplilepticus exist.

Historically, anaesthetists have regarded ketamine as contraindicated in patients with brain injury as the drug may increase intracranial pressure and alter haemodynamics. The previously accepted explanation was that the rise in mean arterial pressure caused a rise in cerebral perfusion pressure and therefore intracranial pressure. Recent evidence suggests that a rise in intracranial pressure may not always occur. Experimental data have shown ketamine to decrease cerebral infarct volume and improve outcome in experimentally head injured rats. Antagonism of the effects of extracellular neurotoxic glutamate may be a mechanism of action. An alternative explanation is that the NMDA antagonists simply induce cerebral vasodilatation, so improving perfusion of the watershed areas adjacent to the injury. One study[1] has compared sedation with midazolam/sufentanil and midazolam/ketamine in brain-injured patients and found both combinations effective. Importantly, no significant differences were observed between the two groups in the mean daily values of

Pharmacokinetics of ketamine	
Absorption	Well absorbed orally, nasally, rectally and intramuscularly Oral bioavailability 20%
Distribution	20-50% protein bound in plasma Volume of distribution 3L/Kg Distribution half life is 11 mins Recovery primarily due to redistribution from brain to periphery
Metabolism	N-demethylation & hydroxylation of the cyclohexylamine ring in the liver Some metabolites are pharmacologically active
Excretion	Urinary excretion of conjugated metabolites Clearance 17ml/kg/min Elimination half life 2.5 hours

intracranial pressure and cerebral perfusion pressure, and the numbers of intracranial pressure elevations were similar in both groups. When ketamine was administered to adults with traumatic brain or spinal cord injury, systemic haemodynamics were unaltered but the effects on intracranial pressure were not reported.[2]

Cardiovascular System

Blood pressure and heart rate are frequently raised after administration of ketamine. The drug causes direct depression of the myocardium and vasodilatation on direct exposure to smooth muscle. Despite this, due to central nervous system stimulation, haemodynamic stability is maintained. A rise in noradrenaline levels is detectable in the blood after ketamine administration, and this pressor response can be blocked by α- and β-adrenoceptor antagonists and sympathetic ganglion blockade. Ketamine also inhibits catecholamine uptake at sympathetic nerve terminals. Pulmonary vascular resistance can rise and an increase in pulmonary shunting can occur in patients with cardiac septal defects.

Respiratory System

Apnoea is unusual unless ketamine is administered rapidly or another respiratory depressant drug (e.g. an opioid) is given. Airway reflexes and skeletal muscle tone are relatively preserved, but salivary and tracheobronchial secretions are increased. Aspiration is still a potential hazard despite the retention of protective reflexes. Ketamine has a bronchodilator action that may be mediated either via an increase in blood catecholamines or by its direct smooth muscle relaxant effect. A valuable property for patients with asthma.

System Effects	
CVS	↑ heart rate, ↑ blood pressure ↑ CVP, ↑ CO, baroreceptor function is maintained and dysrhythmias are uncommon
RS	Bronchodilation, ↑ RR, relative preservation of airway reflexes
CNS	↑ Cerebral blood flow/metabolic rate and intraocular pressure
AS	Nausea and vomiting, ↑ salivation
GU	↑ uterine tone
Other	Emergence delirium/dreams/ hallucinations

Stereoisomers of ketamine

The S(+) isomer is 3-4 times more potent as an analgesic with a faster clearance and less side effects than the R(-). Thus, S+ ketamine has been studied more recently.

Preservative free S(+) ketamine with a low dose of bupivicaine intrathecally has been shown to provide a more rapid motor and sensory block, shorter duration of action and less motor blockade in elderly males.

The addition of preservative free caudal S(+) ketamine to bupivicaine prolongs the duration of postoperative analgesia. IV S(+) ketamine combined with a plain bupivicaine caudal provides no better analgesia than caudal bupivicaine alone, suggesting that the main analgesic effect of caudal S(+) ketamine is due to a neuroaxial rather than a systemic effect.

In another study[5] the duration of analgesia was significantly longer in a ketamine/ropivicaine caudal anaesthesia group than in a plain ropivicaine group. The subjects in the ropivicaine alone group needed significantly more doses of postoperative analgesia. There were no significant differences between the groups in the incidence of postoperative nausea, vomiting, sedation, emergence delirium, nightmares, motor block or urinary retention.

In addition S(+) ketamine 1.0mg/kg for caudal block in children can produce surgical and postoperative analgesia equivalent to that of bupivacaine.6

Ketamine and Obstetric Anaesthesia

Ketamine supports maternal blood pressure which may be important in the face of significant maternal hypotension. There is a dose dependent rise in maternal blood pressure that makes ketamine less suitable for use in pre-eclampsia. In elective caesarean section, ketamine 1mg/kg does not increase maternal blood pressure at induction or intubation any higher than with thiopentone 4mg/kg.

Ketamine very rapidly passes through the placenta, and ketamine levels in cord blood exceed the levels in the maternal venous blood as early as 1 min 37s after the injection. The ketamine levels in cord blood reach a maximum in the period 1 min 37s to 2 min 5s after the injection.

Apgar scores are similar in neonates delivered abdominally after induction of anaesthesia with ketamine 1mg/kg or thiopentone 3mg/kg. Induction with ketamine 2mg/kg is associated with neonatal depression and increased uterine tone.

Ketamine 10 - 20mg iv has been used to provide analgesia for labour and can be repeated every 2-5 minutes but should not exceed 1mg/kg in 30 minutes and the total dose should not exceed 100mg.

With regards to the teratogenic effects of ketamine in early pregnancy, no specific reproductive studies have been performed in humans, but in rats 120mg/kg im failed to produce teratogenic effects. In contrast, large doses produced neural tube defects in chick embryos.

In the U.S.A. ketamine has been given the FDA fetal risk category C - i.e. should only be given if the benefit outweighs the risk.

Ketamine as an additional analgesic

Ketamine has been studied in combination with other analgesics with varying results. When ketamine, 0.25mg/kg was given to patients whose pain was poorly controlled with i.v. morphine, pain scores were improved.[4] The ketamine treated patients also experienced reduced nausea and vomiting than those receiving placebo. In contrast, when patients undergoing anterior cruciate ligament repair received S(+) ketamine as well as opioids, no benefit was seen.[3] Ketamine may also reduce acute tolerance to morphine.

Ketamine as a premedicant

Ketamine has been used in the premedication of children using different routes and doses. Oral ketamine 8mg/kg has been shown to be an effective premedicant for in-patient children although recovery from anaesthesia is longer. Lower doses of ketamine have been studied when combined with benzodiazepines. For example oral ketamine 3mg/kg combined with oral midazolam 0.5mg/kg as premedication did not significantly alter recovery times after sevoflurane anaesthesia compared to midazolam alone.

The use of intranasal ketamine is gaining popularity as a premedicant and as an analgesic in the emergency room. In children, 3mg/kg, diluted to 2ml with saline (1ml per nostril) can allow pleasant and rapid separation from parents, cooperative with monitoring and of mask inhalation induction and also has not been shown to cause prolonged recovery or delayed discharge home. Plasma concentrations of norketamine peak about 2 hours after the administration of nasal ketamine (slower than rectal ketamine). Nasal doses of 3mg/kg produce a large enough plasma concentration to produce analgesia and sedation but not anaesthesia.

Premedication for ketamine anaesthesia

Atropine or glycopyrrolate are often given intravenously before the induction of ketamine anaesthesia to reduce secretions. Glycopyrrolate is the better choice due to its lower psychotropic and chronotropic effects (it is a quaternary ammonium compound which does not cross the blood brain barrier). The increase in heart rate at intubation has been shown to be significantly higher following atropine than following glycopyrrolate.

Oral clonidine premedication (5mcg/kg) has been shown to reduce the hypertensive response to ketamine.

Other areas of interest

- Some studies suggest that ketamine provides better intubating conditions than thiopentone after administration of a neuromuscular blocker
- A ketamine/midazolam combination provided better surgical conditions (collapsed intestinal loops) and better recovery during prolonged abdominal surgery when compared to halothane/nitrous oxide/oxygen anaesthesia.
- Prophylactic low-dose ketamine (0.5mg/kg i.v. 20 mins prior to the end of surgery) was found to be effective in preventing postoperative shivering.
- Ketamine reduces the need for inotropic support in septic patients. In animal models of endotoxic shock, ketamine reduces pulmonary damage by enhancing haemodynamic stability and reducing pulmonary hypertension and extravasation.

In some difficult situations non-anaesthetists have been trained to use ketamine. In Nepal, 679 cases of ketamine anaesthesia for simple ophthalmic procedures were successfully carried out by paediatricians with experience in paediatric resuscitation. Also the use of ketamine anesthesia has been described at high altitude, by primary-care physicians without a specialist training in anesthesia. At a low dose of 2.0 mg/kg, ketamine produced a dissociative anaesthesia whilst not depressing the hypoxic drive, or interfering with the pharyngeal or laryngeal reflexes. Supplemental oxygen was useful in the recovery phase for the less acclimatized individuals. However it is important to remember that ketamine is an anaesthetic drug, and as such should not be seen as simply a sedative agent.

The laryngeal mask airway is not easy with ketamine anaesthesia since ketamine maintains some degree of laryngeal and pharyngeal tone.

Using IV ketamine

- Premedicate with an antisialogogue (e.g. atropine 10-20mcg/kg)
- Anaesthesia: give 1-2mg/kg in small increments initially to avoid episodes of apnoea. For example 30mg boluses every 60 secs to a total of 100mg in a 70kg man. Onset is rapid (1-2 mins) with a duration of 10 minutes. Anaesthesia can be maintained by repeated boluses 0.5mg/kg every 15-20 minutes or by continuous infusion 2-4 mg/kg/hr.
- (Add 500mg of ketamine to 500ml of a crystalloid solution. Spontaneous ventilation = 1 drop/kg/min (4mg/kg/hr); Controlled ventilation = 0.5 drop/kg min (2mg/kg/hr). The infusion is stopped roughly 30 minutes prior to the end of surgery.[7]

- Diazepam 0.1-0.2mg/kg helps to reduce intraoperative movement and also limits postoperative delirium.
- Analgesia - 0.5mg/kg produces rapid and profound analgesia

Using IM ketamine

- Ideal for children and for painful repeated procedures. Atropine can be mixed with ketamine for a single injection.
- Anaesthesia: 6-8mg/kg. Onset is gradual over 5-10 minutes and is preceded by intense analgesia. IM titration of maintenance doses is difficult but 5 mg/kg every 30min is usually adequate. An easier technique is to prolong anaesthesia using IV supplements.
- Analgesia - 2-4mg/kg. Onset is again 5-10 minutes

Monitoring the patient during anaesthesia

- Careful monitoring of the airway is vital. Secretions can cause obstruction and although airway reflexes are preserved laryngospasm and aspiration can still occur. It is the author's practice to use a chin lift procedure to improve the airway whilst detecting the pattern of breathing on the palm of the hand.
- In the presence of normal respiratory physiology a supply of oxygen is preferable but not essential.
- Pulse oximetry is a valuable tool if available.
- Due to the cardiovascular effects of ketamine, hypotension is less common than when using other general anaesthetics. In the absence of a sphygmomanometer, palpation of the rate and quality of the pulse is effective.

Judging depth of anaesthesia

- Assessing depth of anaesthesia is difficult when using ketamine as there are few obvious signs. Spontaneous movement and eye opening may occur during adequate anaesthesia but are more common during subanaesthetic doses. It is worth noting that i.v. induction is rapid (30-60 sec slower than thiopentone) but that intense analgesia will be present in subanaesthetic doses.

Patients suitable for ketamine

- Children - nausea, vomiting and hallucinations are less common in children
- Burns (repeated painful procedures), trauma, radiotherapy
- Shocked patients
- Status asthmaticus

Patients unsuitable for ketamine

Avoid ketamine with:

- Hypertension
- Ischaemic heart disease
- Pre-eclampsia
- Raised intracranial pressure
- Open eye procedures
- Acute porphyrias

Difficulties during ketamine anaesthesia

- Excess secretions
- Preserved muscle tone - airway manipulation and surgical access can be difficult
- Assessing depth of anaesthesia
- Spontaneous muscle movement and "grunting"
- Irregular respiratory pattern with episodes of apnoea particularly in children under 12 months and following rapid iv induction
- Prolonged recovery time +/- nausea/vomiting/ hallucinations

Case report - analgesia for a multiply injured patient

An 18 yr old male was brought in by relatives following an attack in the early hours of the morning. There is an obvious compound fracture of the humerus, in addition to multiple lacerations to the abdomen and scalp. The patient

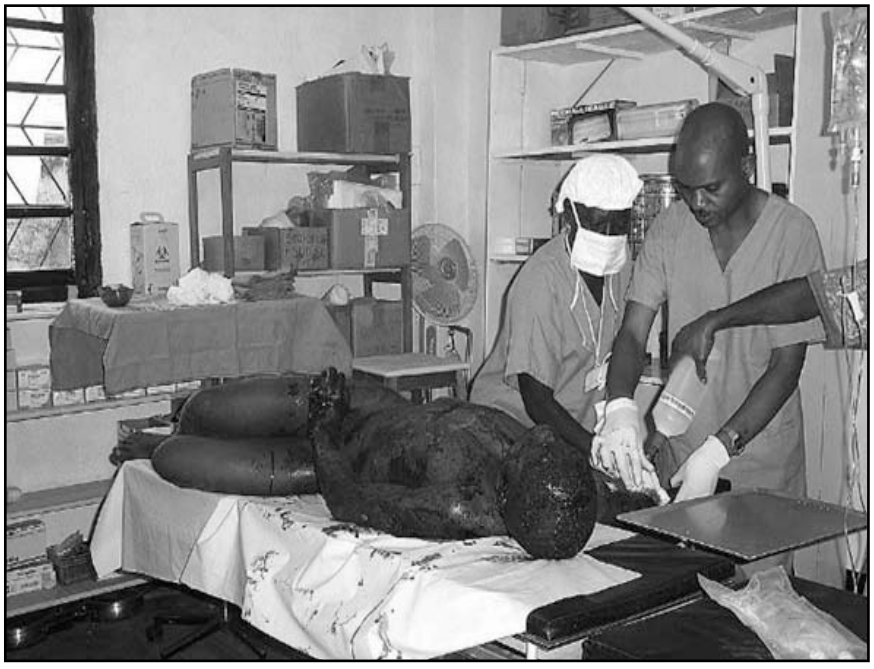

Figure 1.

is severely distressed and in obvious pain. The only anaesthetist available has been delayed at a security road block. The non-medically trained staff have been taught to use ketamine. They administer an analgesic dose of 210mg i.m. mixed with atropine and after 5 -10 minutes are able to splint the fracture, wash out wounds and apply pressure to the scalp lacerations before more experienced staff arrive.

Case report - an obstetric emergency

An emergency caesarean section for placental abruption is scheduled in a remote district hospital. The patient has had significant blood loss and has a weak thready pulse with a rate of 120/min. There is no working oxygen concentrator or laryngoscope available.

Large bore access is obtained and fluid resuscitation is initiated. The patient is placed in a 15^{o} left lateral tilt to avoid aorto-caval compression. An induction dose of ketamine 70mg i.v. is given in 10-20mg aliquots to avoid periods of maternal apnoea plus 600mcg of atropine is given i.v. to reduce oral secretions and therefore aid airway management.

Chin lift and jaw thrust are used to help maintain the airway whilst the exhaled breath on the palm of the hand helps the nurse to monitor the depth, rate and pattern of breathing. Further boluses of ketamine 10-20mg i.v. are given to maintain anaesthesia, although occasional limb movements and eye opening are noted. After clamping of the cord diazepam 5-10mg is administered i.v. to reduce emergence phenomena. Post operatively the patient is placed in the left lateral position in the recovery room.

Case report - anaesthesia for laparotomy

A young man is scheduled for a laparotomy following a bullet wound to the abdomen. Heart rate, blood pressure and oxygen saturation are stable.

Anaesthesia is induced using atropine 600mcg i.v. plus ketamine 100mg i.v. (in 20mg boluses every 60 seconds). An appropriate dose of a neuromuscular blocker is given followed by endotracheal intubation.

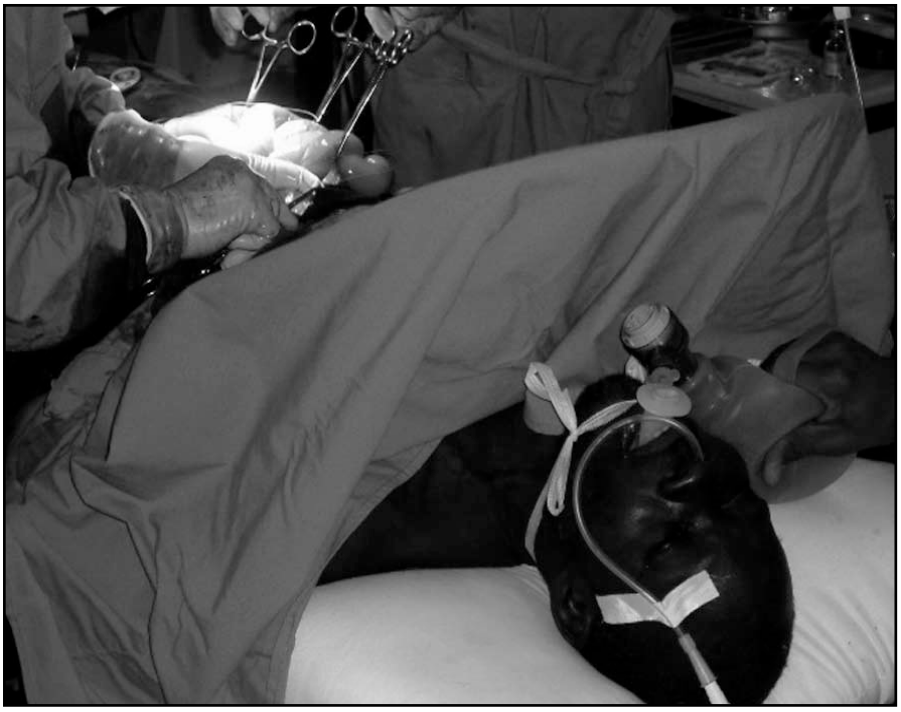

Figure 2.

Anaesthesia is maintained by a continuous infusion of ketamine:

500mg of ketamine is added to 500ml of a crystalloid solution; (controlled ventilation)
0.5 drop/kg/min = 2mg/kg/hr[7]

The infusion is stopped and diazepam 10 mg administered roughly 30 minutes prior to the end of surgery. Following reversal of neuromuscular blockade and an awake extubation the patient was nursed on his side in the recovery area.

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