Ketamine

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Phencyclidine which is chemically similar to ketamine was introduced into clinical practice in 1958. Although phencyclidine proved useful as an anaesthetic, it produced severe adverse psychological effects in the recovery period. Ketamine, then named C1581, is one of 200 phencyclidine derivatives which were investigate subsequently and proved to be the most promising. It was synthesized as Ketalar in 1962, first used on American soldiers during the Vietnam War and released for civilian use in 1970.

It was originally hoped that ketamine would be used as a sole agent for anaesthesia, inducing analgesia, amnesia, loss of consciousness, and immobility. However, because of its adverse psychological effects and the availability of other induction agents, its use diminished rapidly. Recently, the availability of *S*-(+)-ketamine has regenerated interest in its clinical use, because it has greater potency and fewer side effects.

Pharmacology

The ketamine molecule [2-(*O*-chlorophenyl)-2-methylamino cylohexanone] has a molecular weight of 238. The racemic mixture is prepared in a slightly acidic solution (pH 3.5–5.5), is freely water-soluble, and has a pK_a of 7.5. There is a chiral centre with two optical isomers (enantiomers) (Fig. 1). Ketamine has a high lipid solubility (5–10 times that of thiopental) and crosses the blood-brain barrier faster. It undergoes demethylation and hydroxylation of the cyclohexanone ring. The metabolites are conjugated and excreted in the urine. Norketamine has 20–30% of the activity of the parent compound.[1] Its other pharmacokinetic attributes are detailed in Table 1.

Mechanism of action

Ketamine acts on the central nervous system (CNS) and has local anaesthetic properties. Its effects are mediated primarily by non-competitive antagonism at the *N*-methyl-D-aspartate (NMDA) receptor Ca^{2+} channel pore. NMDA channel block appears to be the primary mechanism of the anaesthetic and analgesic action of ketamine (at the CNS and also at spinal cord receptors). In addition, it reduces the presynaptic release of glutamate. The *S* (+) enantiomer has a three- to four-fold greater affinity for the NMDA receptor than the *R*(−) form.[2]

Other mechanisms of action of ketamine include interaction with opioid receptors, with a preference for mu and kappa receptors; this interaction with opioid receptors is complex. The affinity of ketamine for these receptors is 10 times less than that for the NMDA channel, and it has been confirmed in humans that naloxone does not antagomize the analgesic effects of ketamine. There is also evidence that ketamine has an antagonistic interaction with monoaminergic, muscarinic, and nicotinic receptors. Indeed, ketamine produces anticholinergic symptoms (e.g. tachycardia and bronchodilatation). Ketamine at high doses has local anaesthetic properties; these may be through its ability to inhibit neuronal sodium channels.

Isomers

The chiral centre of the cyclohexanone ring permits the existence of two enantiomers. Ketamine enantiomers exhibit pharmacological and clinical differences (summarized in Table 2). *S*-(+)-ketamine has greater affinity than *R*-(−)-ketamine at phencyclidine binding sites on the NMDA receptor. There are no significant differences in pharmacokinetic properties between enantiomers and the racemic mixture.[2] *S*-(+)-ketamine has been shown to be twice as potent as the racemic mixture in producing anaesthesia and analgesia, and thrice as potent as *R*-(−)–ketamine.[2] Animal studies suggest that the *R*-(−) enantiomer of ketamine is a more potent relaxant of acetylcholine-induced airway smooth muscle contraction than the *S*(+) enantiomer. This difference appears to be caused by differential actions on receptor-linked calcium channels.[3] This may have implications in the management of patients with asthma.

Clinical studies have shown that the recovery time is reduced with *S*-(+)-ketamine

Key points

S-(+)-ketamine is more potent than its racemic mixture and has a faster recovery time; this has prompted reconsideration of the place of ketamine in anaesthetic practice.

Ketamine is a dissociative anaesthetic, which also provides profound analgesia. Pharyngeal and laryngeal muscular tone are maintained.

Ketamine should be considered for use as an anaesthetic agent in patients suffering haemodynamic compromise, for patients with active bronchospastic disease, and as an adjunct/supplement to regional or local anaesthesia.

The use of ketamine in pain relief is growing.

Ketamine plays a major role in field hospitals, in emergency retrieval, in developing countries, and in veterinary surgery.

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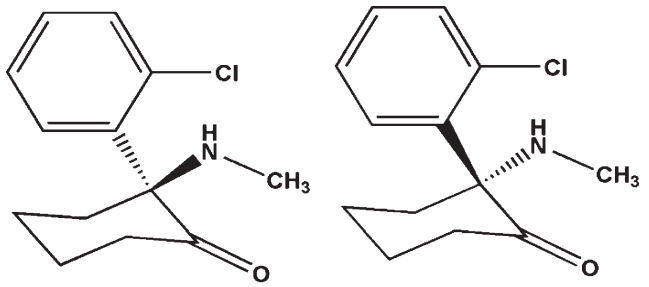

R-(–)- ketamine *S*-(+)- ketamine

Fig. 1 The optical isomers of ketamine

compared with the racemic mixture. The incidence of psychological side-effects is the same with each at equal plasma concentrations. However, because a smaller dose of *S*-(+)-ketamine is required for anaesthesia, there are less psychological side-effects. Coupled with the quicker recovery, patient acceptance of *S*-(+)-ketamine is greater. The *S*(+) enantiomer has been approved for clinical use in parts of Europe, although it is not available in the UK at the time of writing. *S*-(+)-ketamine is significantly more expensive than the generic, racemic ketamine.

CNS effects

Ketamine produces the so-called 'dissociative' anaesthetic state that has been described as functional and electrophysiological dissociation between the thalamo-neocortical and limbic systems. The EEG demonstrates a dominant theta activity with abolition of alpha rhythm. The unique clinical state produced by ketamine is typically a state of catalepsy in which the eyes remain open with a slow nystagmic gaze, whereas the corneal and light reflexes remain intact. Varying degrees of hypertonus and occasional purposeful movements unrelated to painful stimuli are noted in the presence of adequate surgical anaesthesia. Studies have demonstrated excitatory activity in both the thalamus and limbic systems without clinical evidence of seizure activity after ketamine administration. Thus, ketamine would be unlikely to precipitate convulsions in patients with seizure disorders and, in fact, experimental data suggest that ketamine has anticonvulsive and even neuroprotective properties.[4] Analgesia occurs at considerably lower blood concentrations than does the loss of consciousness. This is true for the racemic mixture and for *S*-(+)-ketamine.

Ketamine increases cerebral metabolism, cerebral blood flow (CBF), and intracranial pressure (ICP). The effect of *S*-(+)-ketamine on ICP is not yet known. The response of cerebral autoregulation to racemic ketamine has not yet been studied, but *S*-(+)-ketamine does not affect this autoregulation.[5] Pupillary dilatation, nystagmus, salivation, and lachrymation are common.

Table 1 Pharmacokinetics of ketamine[2]

Volume of distribution	3 litre kg^{-1}
Onset of action (i.v.)	30 s
Bioavailability	
i.m.	93%
intranasal	25–50%
oral	20–25%
Protein binding	20–50%
Distribution half life	10 min
Elimination half life	2–3 h
Site of metabolism	Liver: cytochrome P_{450}
Metabolites	Norketamine, dehydronorketamine

Table 2 Comparison of the effects of *S*-(+)- and *R*-(−)-ketamine (ratios)

Ketamine	*S*(+)	*R*(−)
NMDA affinity	4	1
Plasma concentration	1	1
Cerebral concentration	1	1
Elimination rate	1	0.8–1
Anaesthetic potency	3	1
Side-effects	Similar to racemic mixture	

Emergence reactions

Psychic sensations after ketamine emergence can be alterations in mood state and body image, floating sensations, vivid dreams or illusions, and occasional frank delirium. These dreams and illusions usually disappear on full wakening. However, it is important to discuss with patients these anticipated effects of ketamine. The incidence of psychic effects is approximately 5–30%. A higher incidence is associated with factors such as increasing age, female gender, patients who normally dream, rapid intravenous administration, and large doses. Ketamine has been observed to activate psychoses in patients with schizophrenia. However, it has not been implicated in long-term psychotic reactions in patients without known psychiatric disease. Premedication can attenuate psychic reactions: midazolam (0.07–0.1 mg kg^{-1}), diazepam (0.15–0.3 mg kg^{-1}), and lorazepam (2–4 mg) i.v. have been shown to be effective. The incidence is also decreased when used in conjunction with other sedative hypnotics and general anaesthetics.

Cardiovascular effects

Ketamine has a unique combination of cardiovascular effects. Its administration is usually associated with tachycardia, increased blood pressure, and increased cardiac output. The exact mechanism of this centrally mediated sympathetic response is still not known. However, in the absence of autonomic control, ketamine has a direct myocardial depressant effect, which is usually overridden by this central response. *S*-(+)-ketamine in equal doses produces similar haemodynamic side-effects. It is possible to reduce the undesirable cardiovascular effects by giving ketamine as a continuous infusion and use of a benzodiazepine.

Respiratory effects

Ketamine has minimal effect on central respiratory drive, although a transient decrease in ventilation can occur after bolus administration. Ketamine is a bronchial smooth muscle relaxant, so it has a special role in intractable asthma. It improves pulmonary compliance and is as effective as halothane in preventing bronchospasm. But the *S*(+) enantiomer may not be as useful as the racemate for reasons mentioned earlier.

Ketamine increases salivary secretions, which can produce potential problems in children by causing upper airway obstruction. Although swallowing, cough, sneeze, and gag reflexes are relatively intact with ketamine, silent aspiration can occur. Laryngospasm is frequently cited as an adverse effect of ketamine, but it is rarely observed. Frequently, sonorous respirations mistaken for laryngospasm are actually because of airway positioning, and such breathing problems can be managed simply by repositioning the patient's head. True laryngospasm during ketamine sedation is usually caused by stimulation of the vocal cords by instrumentation or secretions. Secretions can be reduced by giving glycopyrrolate premedication.

Effects on other systems

Ketamine has not been shown to have any adverse effects on hepatic and renal systems. Intraocular pressure is slightly increased after ketamine administration.

Ketamine produces an increase in muscle tone and sometimes muscle spasms, although it has been safely used in myopathies and malignant hyperthermia. Variable effects on uterine tone have been reported. Other effects include emesis, transient rash, and agitation.

Presentation, dosage, and routes of administration

The commercial racemic solution of ketamine is a mixture of *R* (−) and *S*(+) isomers in equal amounts, available as 10, 50, and 100 mg ml^{-1} with a preservative, benzathonium hydrochloride. The optical isomer *S*-(+)-ketamine is available in 5 and 25 mg ml^{-1} concentrations (not licensed in the UK, presently).

Ketamine can be administered i.v., i.m., orally, nasally, rectally, and the preservative-free solution epidurally. International licensed routes of administration vary; in the UK, it is licensed for i.m. and i.v. use. The dose depends on the route of administration and the desired therapeutic effect.

A benzodiazepine may be administered either orally (diazepam 10–30 mg, lorazepam 2–5 mg) 60–90 min before induction or smaller doses i.v. immediately before induction.

Induction of anaesthesia: 0.5–1.5 mg kg^{-1} i.v. or 4–10 mg kg^{-1} i.m.
Maintenance of anaesthesia: 10–30 μg kg^{-1} min^{-1} via i.v. infusion.

Sedation and analgesia: 0.2–0.75 mg kg^{-1} i.v. or 2–4 mg kg^{-1} i.m, followed continuous infusion of 5–20 μg kg^{-1} min^{-1} with or without supplemental oxygen.

Clinical applications

Despite its unique features, ketamine remains outside the realm of routine clinical use because of its unwanted psychomimetic effects. However, with the development of *S*-(+)-ketamine, its wide range of use is being rediscovered (Table 3).

Sedation

Ketamine is appropriate for children undergoing procedures in isolated situations. Emergence reactions in children are less intense, so it can be used for both sedation and general anaesthesia in procedures such as cardiac catheterization (with caution in patients with raised pulmonary vascular resistance), radiotherapy, radiological investigations, and burns dressings. Unfortunately, there is no information as to how many times ketamine can be used safely, even though it is often used repeatedly in the same individual. Generally, subanaesthetic doses are required for minor procedures. Ketamine is often combined with premedication (e.g. benzodiazepines) to reduce the dose requirement and emergence reactions, and an antisialogogue (e.g. glycopyrrolate) to reduce salivary secretions.

In both adults and children, ketamine can be used as a supplement (i.v. or i.m.) during regional anaesthesia. It can also be given via the epidural route as an adjunct to a local anaesthetic to extend the duration of analgesia. Low-dose ketamine has also been used along with propofol to improve the quality of sedation.

NMDA antagonists prevent the induction of central sensitization to painful stimuli. Ketamine is the only NMDA antagonist available; studies have demonstrated that small-dose perioperative administration of ketamine results in reduced postoperative opioid requirements[6] (40–60% on an average). Ketamine-treated patients also experienced less post operative nausea and vomiting.[6]

Induction and maintenance

Ketamine has been extensively used in burns units for dressing changes, debridement, and skin grafting procedures in children and adults. Low-dose ketamine (l.5–2.0 mg kg^{-1} i.m) in these patents seems to have a rapid onset of action and produce good operating conditions, amnesia, and satisfactory analgesia with a rapid recovery. However, patients requiring repeated administration may develop tolerance.

High-risk patients with cardiorespiratory disorders (excluding ischaemic heart disease) represent prime candidates for ketamine anaesthesia. Extensive experience with ketamine in paediatric cardiac catheterizations has shown it to be highly effective with fewer catheter-associated arrhythmias than other general

Table 3 Indications and contra indications

Indications
Aged and poor risk patients
Shock and cardiovascular instability.
Severe dehydration.
Respiratory failure or bronchospasm.
Severe anaemia.
Major thoracoabdominal procedures.
Cardiac tamponade and constrictive pericarditis.
Obstetric patients
Rapid sequence induction
Severe hypovolaemia.
Acute haemorrhage.
Acute bronchospasm.
Low dose for analgesia
Supplement regional technique.
Transient analgesia at the time of delivery.
Adjunct to local or regional anaesthesia
Low dose for sedation and analgesia during the procedure.
Supplement for inadequate block.
Outpatient surgery
Paediatric anaesthesia
Diagnostic and therapeutic procedures.
Induction of anaesthesia.
Caudal analgesia.
Adult anaesthesia
Brief surgical procedures.
Supplement local or regional technique.
Diagnostic and therapeutic procedures.
Reactive airway disease
Intractable bronchial asthma.
COPD with bronchospasm.
Patients with thermal injuries
Debridement and skin grafting.
Dressing changes.
Postoperative analgesia
As an adjunct with morphine PCA.
Recovery room.
Intensive care units.
Procedural sedation in intensive care
Paediatric cannulation, central lines.
Adult central lines, endoscopies, dressing changes.
Developing countries and field hospitals
Chronic pain
For patients in whom airway management may be difficult
Unstable cervical spine.
Trapped casualties.
Contra indications
A high predisposition to laryngospasm or apnoea (e.g. active pulmonary infection, patients younger than 3 months).
Severe cardiovascular disease, such as angina, heart failure, or malignant hypertension (because of cardiostimulant effects of ketamine, although this is controversial).
CSF obstructive states (e.g. severe head injury, central congenital or mass lesions).
Intraocular pressure pathology (e.g. glaucoma, acute globe injury).
Previous psychotic illness (potential activation of psychoses)
Hyperthyroidism or thyroid medication use (possibility of severe tachycardia or hypertension).
Porphyria (possibility of triggering a porphyric reaction).

anaesthetics. Ketamine might be deleterious in patients with limited right ventricular functional reserve and increased pulmonary vascular resistance.

In patients with reactive airway disease, ketamine (racemate) can be useful as it produces bronchodilation and profound analgesia allowing administration of an increased inspired oxygen concentration.

Ketamine, if combined with a benzodiazepine or a benzodiazepine with an opioid, attenuates unwanted tachycardia, hypertension, and also postoperative psychomimetic reactions. This technique produces minimal haemodynamic perturbations, profound analgesia, dependable amnesia, and uneventful recovery.

Ketamine as an adjunct

Preservative-free ketamine has been added to caudal bupivacaine to improve the duration of analgesia, without affecting the analgesic intensity.[7] Interest in this use of ketamine is growing and, in a recent survey, 32% of the UK paediatric anaesthetists reported their use of epidural ketamine.[8]

Neurosurgery

Historically, it has been believed that ketamine is contraindicated in patients with increased ICP, but reports of neuroprotective and even neuroregenerative effects have generated research into this topic.[4] Ketamine may prevent abnormal calcium ion fluxes or glutamate accumulation through its interaction with NMDA receptors. The increase in CBF after ketamine administration is less than the increase in $CMRO_2$. *S*-(+)-ketamine reduced or maintained cerebral metabolism in most regions of the brain (experimental studies).[9] Ketamine may yet prove to have a place in neurosurgery.

Immunofunction

Although ketamine has little effect on vascular endothelium, studies have demonstrated a significant reduction in leucocyte activation during hypoxaemia or sepsis.[10] Ketamine suppresses pro-inflammatory cytokine production in human whole blood *in vitro*. In a study of the different isomer effects on isolated guinea pig hearts, *S*-(+)-ketamine was effective in reducing neutrophil adhesion, whereas *R*-(−)-ketamine had a negative effect by worsening the coronary vascular fluid leakage into the surrounding tissue. A reduction in cellular adhesion by ketamine has been demonstrated both on leucocytes and platelets. Further clinical studies are required to clarify the above findings.

Recreational misuse and legal status

Available in some places as K, Special K, Vitamin K, or Lady K, ketamine enjoys recreational popularity. It appears to be the latest futile attempt to cleanse Blake's 'doors of perception' by chemical means. Most commonly, it comes as a powder, but can also be obtained in liquid and tablet form. It can be insufflated (snorted, also known as 'taking bumps') or placed in beverages. Some individuals feel paralysed after taking illicit ketamine and may not be able to speak without slurring. When consumed in larger doses, it can produce the 'K-hole' effect, that is a state of wildly dissociated experiences in which other worlds or dimensions that

are difficult to describe in words are said to be perceived, all the while being completely unaware of one's individual identity or the outside world.

In the UK, ketamine has recently been classified as a controlled drug and from January 1, 2006, ketamine has been labelled as a class-C drug under the Misuse of Drugs Act 1971. Other class-C drugs include cannabis, tranquilizers, and anabolic steroids.

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Please see multiple choice questions 26–29