

Special Article

Ketamine: an update on the first twenty-five years of clinical experience

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Summary

Key words

ANAESTHETICS, INTRAVENOUS: ketamine.

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Ketamine is a dissociative anaesthetic agent that has acquired a unique place in clinical practice. Since the first published report of its clinical use¹ an understanding of its anaesthetic, analgesic, and amnesic qualities has grown from extensive clinical and laboratory research. The initial experience with ketamine as a sole anaesthetic agent led to the recognition of unpleasant emergence reactions and cardiovascular stimulant properties, which limited its usefulness. However, supplementation with other drugs such as the benzodiazepines have reduced these side effects. Previous reviewers^{2,3} have detailed the early work on the pharmacology and clinical uses of ketamine. This review encompasses the more recent research on ketamine, and emphasizes human data. Ketamine's role in clinical anaesthesia is changing as a result of the evolving concepts of its mechanism of action and the advantages of alternative routes of administration.

Pharmacology

Ketamine [KETALAR®, KETAJECT®] is chemically related to phencyclidine (PCP) and cyclohexamine. It has a molecular weight of 238 and a pKa of 7.5. Although ketamine hydrochloride is water soluble, ketamine's lipid solubility is ten times that of thiopentone. The molecular structure (2-(O-chlorophenyl)-2-methylamino cyclohexanone) contains a chiral centre at the C-2 carbon of the cyclohexanone ring so that two enantiomers of the ketamine molecule exist: s(+)-ketamine and r(-)-ketamine. Commercially available racemic ketamine preparations contain equal concentrations of the two enantiomers. These enantiomers differ in anaesthetic potency, in the responses of the electroencephalograph (EEG), in effects on catecholamine reuptake, and possibly in the incidence of emergence reactions.

Pharmacokinetics

Ketamine has a high bioavailability following intravenous or intramuscular administration. First-pass metabolism and lower absorption necessitate higher dosages when

ketamine is administered by the oral or rectal routes (*vide infra*). Biotransformation takes place in the liver, and multiple metabolites have been described. The most important pathway involves N-demethylation by cytochrome P₄₅₀ to norketamine, an active metabolite with an anaesthetic potency one third that of ketamine. Norketamine (originally termed metabolite I in the earlier literature) is then hydroxylated and conjugated to water soluble compounds that are excreted in the urine. The cyclohexanone ring also undergoes oxidative metabolism. Earlier literature listed dehydronorketamine (metabolite II) as an important breakdown product of ketamine, but this compound is most likely an artifact of the chromatographic analysis, and not an important metabolite *in vivo*.⁴

Ketamine pharmacokinetics follow a three-term exponential decline. In unpremedicated patients, distribution half-life ($t_{1/2\pi}$) was 24.1 seconds, redistribution half-life ($t_{1/2\alpha}$) was 4.68 minutes, and elimination half-life ($t_{1/2\beta}$) was 2.17 hours.⁵ Pharmacokinetics were similar in children, except that absorption was more rapid following intramuscular administration, and higher concentrations of norketamine were present.⁶ Diazepam seems to inhibit the hepatic metabolism of ketamine, but etomidate does not.⁷

Pharmacodynamics

The pharmacodynamic effect of ketamine in humans is apparently due to the CNS activity of the parent compound. As CNS levels of ketamine decline by redistribution to the peripheral compartment, the CNS effects subside, although not as rapidly as would be predicted from its high lipid solubility.⁸ Decreased renal function, and the presence of active metabolites, do not prolong the drug's action. Tolerance and hepatic enzyme induction have been reported following chronic administration.

Both halothane and diazepam prolong the clinical anaesthetic effect of ketamine. However, it is not clear whether this is due to the synergistic effects of CNS depressant drugs, decreased ketamine clearance, or a combination of these factors. Diazepam causes an increase in plasma ketamine levels, but also a prolongation of $t_{1/2\alpha}$ and $t_{1/2\beta}$ in humans.

Analgesia from ketamine is associated with a plasma concentration of $0.15 \mu\text{g} \cdot \text{ml}^{-1}$ following intramuscular administration, and $0.04 \mu\text{g} \cdot \text{ml}^{-1}$ following oral administration. The difference in the analgesic plasma concentrations might be explained by a higher norketamine concentration following oral administration (probably from first-pass metabolism), which contributes to the analgesia. Awakening from ketamine anaesthesia takes place at plasma concentrations of 0.64 – $1.12 \mu\text{g} \cdot \text{ml}^{-1}$.⁹ Both sensory and motor block occur in humans using

high concentrations of ketamine for intravenous regional anaesthesia and subarachnoid block.^{10,11}

Mechanism of action

The anaesthetic state produced by ketamine was originally described as a functional and electrophysiological dissociation between the thalamocortical and limbic systems. Ketamine as the sole anaesthetic produces a cataleptic state with nystagmus and intact corneal and light reflexes. Hypertonus, purposeful movements and vocalization may occur.

Ketamine is a potent analgesic at subanaesthetic plasma concentrations, and its analgesic and anaesthetic effects may be mediated by different mechanisms. The analgesia may be due to an interaction between ketamine and central or spinal opiate receptors.¹²

N-METHYL-ASPARTATE RECEPTOR THEORY

N-methyl-aspartate (NMA) is an excitatory amine, and its receptors in mammalian brain are blocked by PCP and ketamine.^{13,14} The NMA receptors may represent a subgroup of the sigma opiate receptors ("the PCP site") that block spinal nociceptive reflexes.¹⁵ Ketamine also blocks NMA-induced seizures at high doses, and NMA-induced behavioural changes at lower doses in the rat model.¹⁶

Metaphit, a recently synthesized piperidine derivative, blocks the action of NMA by acetylating the receptors. It was hoped that metaphit might displace ketamine from NMA receptors and reverse ketamine anaesthesia. However, metaphit acts as an agonist/antagonist at the receptors, and does not reverse dissociative anaesthesia in the rat model.¹⁷

OPIATE RECEPTOR THEORY

Ketamine's affinity for opiate receptors is controversial, but this provides an attractive theory for its analgesic activity at central and spinal sites. Smith *et al.* showed that racemic ketamine displaced tritiated naloxone from rat brain opiate receptors *in vitro*, and that (+)ketamine was about twice as potent as (–)ketamine for this purpose.¹⁸ Finck and Ngai not only confirmed the above study, but also found similar stereospecific opiate receptor binding by (+)ketamine in guinea pig ileum *in vitro*.¹⁹ Cross-tolerance between the opiates and ketamine would also be expected if there is a common receptor. This has now been shown in two independent animal studies.^{20,21}

The opiate receptor theory would gain more credence if ketamine reversal by naloxone were proven in humans. Stella *et al.* reported that none of 68 adult patients premedicated with naloxone lost consciousness following the administration of ED₅₀ doses of ketamine.²² Amiot *et al.* repeated the doses used in the above study, but in

pregnant patients whose anaesthetic requirements may have been lower, and without a control group. They found no evidence of naloxone reversal of ketamine at a similar dosage.²³

MISCELLANEOUS RECEPTOR THEORY

Other neuronal systems may be involved in the antinociceptive action of ketamine, since blockade of noradrenaline and serotonin receptors attenuates the analgesic action of ketamine in animals.²⁴ Interaction of ketamine with sigma opiate receptors might be a plausible theory to explain dysphoric emergence reactions.²⁵

Ketamine also interacts with muscarinic cholinergic receptors in the CNS.²⁶ Ketamine decreased the average lifetime of single-channel currents activated by acetylcholine in an *in vitro* model.²⁷ This might help to explain ketamine's potentiation of neuromuscular blockade as well as its central effects.

Thus, centrally-acting anticholinesterase agents might be expected to reverse ketamine anaesthesia. However, the experimental data are contradictory.^{28,29} There is preliminary evidence that 4-aminopyridine might reverse the effects of both ketamine and the benzodiazepines.³⁰ The combination of 4-aminopyridine and physostigmine was also reported to reverse ketamine anaesthesia.³¹ Also, 4-aminopyridine releases acetylcholine at central and peripheral sites and it enhances neuromuscular transmission. The effects of 4-aminopyridine on NMA transmission are worthy of study.

Central nervous system effects

ELECTROENCEPHALOGRAPHIC EFFECTS

Ketamine induces consistent changes in the EEG. There is a reduction in alpha wave activity, while beta, delta and theta wave activity are increased.³² These changes were not significantly altered by diazepam.³³ Further discussion of EEG phenomena is included in the section on optical isomers of ketamine.

It is hard to draw objective conclusions regarding the anti-convulsant properties of ketamine. Although ketamine produces epileptiform EEG patterns in human limbic and thalamic regions, there is neither evidence that this affects cortical regions, nor that clinical seizures are likely to occur.³⁴ Animal data are particularly difficult to interpret, because of inter-species variations.

INTRACRANIAL PRESSURE

Many of the early studies of ketamine's effect on intracranial pressure (ICP) were conducted on spontaneously breathing subjects and were not controlled for changes in ICP due to hypercarbia.³⁵ Pfenninger *et al.* studied mechanically ventilated pigs with increased ICP,

and found no further increase in ICP with 0.5 or 2.0 mg · kg⁻¹ of IV ketamine.³⁶ It was also hypothesized in earlier studies, that ketamine increased ICP due to a direct cerebral vasodilatory action. However, Schwedler *et al.* injected ketamine directly into cerebral vessels, and found no effects on the vasculature.³⁷ Anterior fontanelle pressure, an indirect monitor of ICP, declined by 10 per cent in mechanically ventilated preterm neonates following 2 mg · kg⁻¹ of IV ketamine.³⁸

EMERGENCE PHENOMENA

The psychic emergence phenomena of ketamine have been described as floating sensations, vivid dreams (pleasant or unpleasant), hallucinations, and delirium. The phenomena are more common in patients over the age of 16 years, in females, in shorter operative procedures, in those receiving larger doses and with more rapid administration.² In a comparison of ketamine with thiopentone, in healthy unpremedicated volunteers, ketamine resulted in more abnormalities of mental status immediately after anaesthesia. However, these changes were not present by the following day.³⁹

Benzodiazepines have proven the most effective agents for the prevention of these phenomena.⁴⁰ Cartwright and Pingel found that midazolam significantly reduced the incidence of unpleasant dreams compared with diazepam.⁴¹ Toft and Romer compared ketamine-midazolam with ketamine-diazepam infusions, and found that ketamine-midazolam resulted in fewer emergence reactions and a shorter time to complete recovery.⁴²

Cardiovascular effects

A major feature that distinguishes ketamine from other intravenous anaesthetics is stimulation of the cardiovascular system. Numerous investigators have reported increases in heart rate, systemic arterial pressure, systemic vascular resistance, pulmonary arterial pressure, and pulmonary vascular resistance (PVR).⁴³ However, many of the earlier haemodynamic studies of ketamine were conducted on subjects spontaneously breathing room air, and were not controlled for the effects of respiratory depression or partial airway obstruction. In contrast, Balfors *et al.* assisted ventilation with an FiO₂ of 0.25 and found no significant change in PVR during ketamine administration in 16 adult patients.⁴⁴

MECHANISM

The mechanism of ketamine's cardiovascular effects is not well understood. A direct negative inotropic effect is usually overshadowed by central sympathetic stimulation. In an isolated dog heart preparation, Saegusa *et al.* demonstrated that high plasma concentrations of ketamine depressed contractile, but not pacemaker func-

tion.⁴⁵ Circulating catecholamine levels are increased at least partially by an inhibition of reuptake.⁴⁶ Central inhibition of catecholamine reuptake may also contribute to ketamine cardiovascular stimulation.

EFFECTS ON RHYTHM

The effect of ketamine on cardiac rhythm is also controversial. There are animal data (in cats) that suggest ketamine sensitizes the myocardium to the dysrhythmogenic effects of adrenaline.⁴⁷ However, ketamine reversed digitalis-induced dysrhythmias in dogs.⁴⁸ Cababbe and Behbahani reported two cases of serious dysrhythmias in plastic surgery patients who received 0.5 mg · kg⁻¹ of IV ketamine for sedation during infiltration of lidocaine solutions that contained adrenaline.⁴⁹

PREVENTION OF CARDIOVASCULAR STIMULATION

Numerous drugs have been shown to block the ketamine-induced cardiovascular stimulation, including α - and β -blocking agents, and verapamil.⁵⁰ Gold *et al.* demonstrated a dose-response relationship, using esmolol infusions to block the responses to ketamine and endotracheal intubation.⁵¹ Mayumi *et al.* showed that cervical epidural blockade blunted increases in HR and systolic blood pressure, probably secondary to a chemical cardiac sympathectomy.⁵²

The benzodiazepines are the most efficacious agents for attenuating the cardiovascular effects of ketamine. Diazepam, midazolam, and flunitrazepam are all effective for this purpose.⁵³ Midazolam is water-soluble, very similar to ketamine in its pharmacokinetic behaviour, and has become a common adjunct to ketamine anaesthesia.⁵⁴

The interaction with other anaesthetic agents, including the potent volatile agents, either diminishes or abolishes ketamine's cardiovascular stimulant effects. Dobson showed that the combination of ketamine and thiopentone greatly reduced ketamine-induced cardiovascular stimulation.⁵⁵

ISCHAEMIC HEART DISEASE

In the patient with ischaemic heart disease, the cardiovascular stimulant effects of ketamine might precipitate myocardial ischaemia. Studies in dogs indicated that ketamine as a sole agent increased coronary blood flow and myocardial oxygen consumption.^{56,57} However, clinical studies of ketamine-diazepam anaesthesia for cardiac surgical patients indicate haemodynamic stability.⁵⁸⁻⁶⁰

The choice of neuromuscular blocking agent is important in the patient with ischaemic heart disease. The vagolytic action of pancuronium resulted in more rapid tachycardia when administered with ketamine, than a ketamine-vecuronium combination.⁶¹

CARDIOVASCULAR EFFECTS IN CHILDREN AND NEONATES

Ketamine is frequently used in children with congenital heart disease. The acute haemodynamic effects of ketamine in children undergoing cardiac catheterization were studied by Morray *et al.*⁶² Two minutes following 2 mg · kg⁻¹ of IV ketamine, there were minor haemodynamic changes, not associated with any difference in intracardiac shunting, PaCO₂ or PaO₂. Following IV ketamine, 2 mg · kg⁻¹, Hickey *et al.* found no change in pulmonary vascular resistance index, systemic vascular resistance index, or cardiac index in 14 intubated infants who were ventilated mechanically.⁶³ There was no difference between infants with preexisting elevations in PVR, and those with normal PVR.

Greeley *et al.* compared the effects of anaesthetic induction with 1M ketamine, 6 mg · kg⁻¹, with halothane/nitrous oxide (70 per cent) on arterial oxygen saturation measured by digital pulse oximetry.⁶⁴ They studied children who were prone to hypercyanotic episodes. Both induction techniques were associated with increased arterial oxygen saturation. Laishley *et al.* similarly found ketamine to be a safe induction agent in patients with cyanotic congenital heart disease, although ketamine was associated with increased HR.⁶⁵

Anaesthetic induction in the preterm neonate is frequently complicated by hypotension. In a comparison of IV and inhalational induction techniques, ketamine, 2 mg · kg⁻¹, resulted in a significantly lower incidence of hypotension than fentanyl, 20 μ g · kg⁻¹, halothane 0.5 per cent, or isoflurane 0.75 per cent.⁶⁶ While ketamine resulted in an average 16 per cent decrease in systolic arterial pressure, this returned to preinduction values after skin incision in both the ketamine and fentanyl groups. In a haemodynamic study of spontaneously breathing neonatal lambs, Burrows *et al.* found no significant cardiovascular changes with IV ketamine, 1 mg · kg⁻¹ or 2 mg · kg⁻¹.⁶⁷

Respiratory effects

Ketamine is a mild respiratory depressant. Bourke *et al.* found dose-related respiratory depression with incremental doses of ketamine.⁶⁸ They found that ketamine alone caused the CO₂-response curve to shift to the right, but did not change the slope of the curve. The respiratory depression caused by ketamine is similar to that caused by opiates, and dissimilar from most sedative-hypnotics and anaesthetics, because the slope of the CO₂-response curve is not affected. This evidence suggests that opiate receptors play a role in the respiratory depressant effects of ketamine.

RESPIRATORY PATTERN

Three recent studies have examined the effects of keta-

mine on respiratory pattern and functional residual capacity. Morel *et al.* administered IV ketamine, $1 \text{ mg} \cdot \text{kg}^{-1}$, over five minutes to unpremedicated volunteers.⁶⁹ They reported periods of increased ventilation interspersed with periods of apnoea, with no net change in expired CO_2 . Mankikian *et al.* administered IV ketamine, $3 \text{ mg} \cdot \text{kg}^{-1}$, followed by an infusion of $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to patients who breathed spontaneously through endotracheal tubes.⁷⁰ They reported maintenance of functional residual capacity, minute ventilation, and tidal volume, with an increase in the contribution of the intercostal (relative to diaphragmatic) contribution to tidal volume. Functional residual capacity is also preserved in young children during ketamine anaesthesia.⁷¹

HYPOXIC PULMONARY VASOCONSTRICTION

There is evidence to suggest that ketamine does not inhibit hypoxic pulmonary vasoconstriction.⁷² Rees and Gaines found no difference between ketamine and enflurane in terms of oxygenation or shunt fraction in humans during one-lung anaesthesia.⁷³ Weinreich *et al.*, and Rees and Howell demonstrated the use of ketamine infusions in humans for pulmonary surgery requiring one-lung anaesthesia.^{74,75} Rogers and Benumof found that halothane and isoflurane did not lower PaO_2 during one-lung ventilation in ketamine- or methohexitone-anaesthetized patients, and there were no significant differences between the ketamine and methohexitone groups.⁷⁶

BRONCHODILATION

The bronchodilator effects of ketamine have been evident since the early clinical studies. Ketamine is as effective as halothane or enflurane in preventing bronchoconstriction in an experimental canine model.⁷⁷ It is likely that circulating catecholamines are the cause of ketamine's bronchodilatory effects, because propranolol will block the protective effects of ketamine in the canine model. Ketamine has been used in the treatment and emergency intubation of paediatric patients with status asthmaticus.⁷⁸⁻⁸⁰

AIRWAY MAINTENANCE

Ketamine generally preserves airway patency and respiratory function. Nevertheless, there are rare reported cases of pulmonary aspiration, prolonged apnoea⁸¹ and arterial hypoxaemia.⁸² Salivary and tracheo-bronchial secretions are increased by ketamine, and a prophylactic antisialagogue is required. Glycopyrrolate and atropine are equally effective for reducing these secretions during ketamine/diazepam anaesthesia.⁸³

Optical isomers

After initial animal research showed potential advantages

for (+)ketamine, human research with the ketamine enantiomers commenced. (+)Ketamine produced more effective anaesthesia than the racemate or (-)ketamine. More psychic emergence reactions occurred after (-)ketamine than the racemate or (+)ketamine.⁸⁴

In a more recent study, White *et al.* found that (+)ketamine was approximately four times as potent as (-)ketamine. (+)Ketamine and the racemate produced similar EEG changes, but (-)ketamine produced a lesser degree of EEG slowing. The lesser degree of EEG response to (-)ketamine seemed to correlate with its lower hypnotic and analgesic potency, and its lower affinity for opiate receptors.⁸⁵

Other pharmacologic effects

NEUROMUSCULAR BLOCKADE

Although ketamine alone produces an increase in skeletal muscle tone, it enhances the action of neuromuscular blockers such as succinylcholine and d-tubocurarine. The effect of ketamine on pancuronium neuromuscular blockade is controversial, but a recent study in monkeys showed a dose-related depression of thumb twitch with increasing doses of ketamine in the presence of pancuronium.⁸⁶ Cronnelly *et al.*⁸⁷ proposed that ketamine decreases the sensitivity of the motor end plate, while Marwaha⁸⁸ reported that ketamine initially potentiates, and then blocks the twitch response to direct muscle stimulation.

ENDOCRINE/METABOLIC RESPONSE

A recent study compared ketamine with thiopentone-halothane anaesthesia in patients undergoing pelvic surgery. Prior to the start of surgery, blood glucose, plasma cortisol, and heart rate were increased in the ketamine group. However, there were no endocrine, metabolic, or haemodynamic differences between the two groups after the start of surgery.⁸⁹

EFFECTS ON INTRAOCULAR PRESSURE

The effects of ketamine (with atracurium) on intraocular pressure (IOP) were recently reviewed and studied by Badrinath *et al.*⁹⁰ They found that IOP decreased significantly after anaesthetic induction, but before intubation. Following intubation, IOP returned to the preinduction control level and remained stable. Ketamine was not superior to thiopentone or etomidate for this purpose.

EFFECTS ON COAGULATION

Atkinson *et al.* have shown that intramuscular ketamine irreversibly inhibits the aggregation of platelets in baboons.⁹¹ The inhibition may be similar to that produced by aspirin. However, there was no increased bleeding from the experimental animals' exposed carotid arteries, and

no bleeding times were performed. Heller *et al.* found no significant haemostatic changes in humans undergoing ketamine/midazolam anaesthesia.⁹²

Clinical uses

Epidural and intrathecal ketamine

The recent popularity of epidural and intrathecal opiates, and ketamine's proposed interaction with opiate receptors, have generated several investigations into the efficacy of epidural and intrathecal ketamine. Theoretically, ketamine should not have the occasional severe respiratory depressant side-effects associated with epidural or intrathecal morphine. A preliminary study showed no neurotoxic effects in baboons injected intrathecally with preservative-containing ketamine.⁹³ Following this, there was a report of patients with intractable cancer pain, who obtained relief lasting 30 minutes to over six hours following epidural ketamine.⁹⁴

The series of clinical studies of epidural ketamine that followed are difficult to interpret because many of the authors' conclusions are based on uncontrolled experimental data. Islas *et al.* claimed potent analgesia from 4 mg of epidural ketamine in a study of 50 patients.⁹⁵ In another study comparing intramuscular ketamine, 30 mg, epidural ketamine, 10 mg, and epidural ketamine, 30 mg, the investigators claimed a good analgesic effect. However, even in the 30 mg epidural dose group, 46 per cent of the patients required supplemental analgesia within 24 hours.⁹⁶ In a study of 40 patients who received epidural ketamine, 15 mg, analgesia began at five minutes and lasted an average of four hours. However, there was also a ten per cent incidence of psychotomimetic reactions.⁹⁷

In two studies comparing epidural ketamine with epidural morphine, morphine was the more potent and longer-acting analgesic.^{98,99} The study of Kawana *et al.* is the only double-blinded, controlled comparison of epidural ketamine and morphine published to date.

The only human study of intrathecal ketamine for surgical anaesthesia (50 mg in 3 ml five per cent dextrose with 0.1 mg adrenaline) reported good motor and sensory blockade, but of limited duration (mean 58 minutes). However, motor blockade did not occur without adrenaline, and higher dermatomal levels of blockade were associated with CNS side-effects.¹⁰⁰

Oral and rectal ketamine

The analgesic effects of 0.5 mg·kg⁻¹ ketamine administered orally versus intramuscular administration of the same dose were studied by Grant *et al.*¹⁰¹ Onset of analgesia was delayed with oral ketamine (30 minutes), and was associated with a lower serum level (40 ng·ml⁻¹) compared with the intramuscular dose (15 minutes and

150 ng·ml⁻¹, respectively). The levels of norketamine were also higher in those receiving oral ketamine. The authors attribute these results to first-pass metabolism, and propose that norketamine contributed to the analgesic effect. Morgan and Dutkiewicz reported the case of a three-year-old child who received oral ketamine, 1 mg·kg⁻¹, as an analgesic for daily burn dressing changes for ten days.¹⁰²

Rectal ketamine, 8.7 mg·kg⁻¹, was administered to children for the induction of anaesthesia, and loss of consciousness took place after 7 to 15 minutes. Peak serum concentrations were reached at 40 minutes and there was a high level of norketamine, similar to the results with oral ketamine.¹⁰³ Malaquin administered rectal ketamine, 10 mg·kg⁻¹, to children, with onset of action at nine minutes, and peak effect at 25 minutes.¹⁰⁴ Cetina compared oral and rectal ketamine in children, and recommended rectal ketamine, 15 mg·kg⁻¹, combined with droperidol, 0.0125 mg·kg⁻¹, for induction of anaesthesia.¹⁰⁵

Obstetrics

The initial experience with standard IV doses (2 mg·kg⁻¹) of ketamine in parturients for vaginal delivery was notable for a high incidence of maternal complications and neonatal depression. However, using lower IV doses of ketamine (0.2–1.0 mg·kg⁻¹), these problems were markedly reduced. In a study comparing low spinal anaesthesia and IV ketamine, 1 mg·kg⁻¹, maternal and neonatal arterial blood gases were not significantly different.¹⁰⁶ In an acidotic fetal lamb model, ketamine anaesthesia preserved fetal organ perfusion, and did not worsen the acidosis.¹⁰⁷

Intravenous ketamine offers certain advantages in the rapid-sequence induction of the parturient for Caesarean section. In comparison with thiopentone, ketamine is advantageous for hypovolaemic patients (e.g., abruptio placenta, placenta praevia) or patients with bronchospasm. Dich-Nielsen and Holasek reported their satisfactory experience with 100 Caesarean section patients, using primarily ketamine.¹⁰⁸ Comparing ketamine, 1 mg·kg⁻¹, with thiopentone, 4 mg·kg⁻¹, there were no differences in neonatal PaO₂, acid-base balance, or Apgar scores.¹⁰⁹ Schultetus *et al.* used the same doses of ketamine and thiopentone as above, and found that ketamine better attenuated the haemodynamic response to laryngoscopy and intubation, with no difference in neonatal outcome.¹¹⁰ Ketamine, 1 mg·kg⁻¹, also was more effective than thiopentone, 4 mg·kg⁻¹, or a ketamine (0.5 mg·kg⁻¹)/thiopentone (2 mg·kg⁻¹) combination in preventing intraoperative awareness.¹¹¹

It was claimed that ketamine anaesthesia resulted in decreased blood loss during first trimester abortions, due

to an increase in uterine tone. However, a recent study comparing ketamine-midazolam with methohexitone found no difference in blood loss.¹¹²

Teratologic effects of ketamine have been demonstrated in rats.¹¹³ A generalized degenerative effect was dependent on the dose and duration of treatment. However, no human data on ketamine teratogenicity are available.

Paediatric radiation therapy and burned patients

Ketamine is useful in maintaining sedation and immobility in paediatric patients requiring repeated radiation therapy.^{114,115} These early reports noted that tolerance to IV and IM ketamine developed with repeated administration. Byer and Gould reported the case of an 11-week-old infant whose ketamine requirement increased 250 per cent by the 13th treatment.¹¹⁶

Burned patients require frequent painful procedures. The use of ketamine analgesia in burn units is remarkable for the development of tolerance with repeated administration. The possibility of using oral or rectal ketamine should be investigated further, especially in patients with extensive burns, where intravenous access is limited.

Outpatient anaesthesia

The trend towards more ambulatory surgery has fostered an interest in ketamine because of its acceptably short duration of action and postoperative analgesic effects. Unfortunately, supplemental agents administered to decrease the incidence of psychic emergence phenomena (e.g., benzodiazepines) also prolong recovery time. White reported that continuous infusions of ketamine (as a supplement to nitrous oxide) were preferable to bolus administration in outpatient anaesthesia.¹¹⁷ However, fentanyl infusions led to more rapid emergence than ketamine infusions in a followup study.¹¹⁸

Critically ill patients

The role of ketamine for the induction and maintenance of anaesthesia in patients with hypovolaemia, pericardial tamponade, constrictive pericarditis, and cardiogenic shock is well documented. In the battlefield or catastrophic setting, ketamine might be advantageous, considering the likelihood of encountering hypovolaemic patients. Bion compared low-dose ketamine and pentazocine infusions for analgesia, and found that ketamine better preserved arterial blood pressure and respiratory rate, although pentazocine provided better anxiolysis.¹¹⁹ Jago *et al.* used ketamine anaesthesia with heavy papaveretum premedication, and found that emergence sequelae were very common in the battlefield setting.¹²⁰ Restall *et al.* utilized a fixed combination intravenous infusion of ketamine, midazolam, and vecuronium with satisfactory results, and have recommended it for military surgery.¹²¹

Cardiac surgery

The use of ketamine in cardiac surgery has been largely overshadowed by high-dose narcotic techniques during the last ten years. However, in a randomized, prospective comparison of high-dose fentanyl with diazepam-ketamine anaesthesia for single-valve replacement and myocardial revascularization, the following results were found: ketamine-diazepam anaesthesia was associated with decreased postoperative fluid and vasopressor requirements, decrease pulmonary shunt fraction, and shorter intensive care unit stay. Both techniques resulted in a stable intraoperative haemodynamic picture.¹²²

Miscellaneous topics

Ketamine has been used uneventfully in patients with previous episodes of malignant hyperthermia. Postoperatively, there were no complications and no significant changes in creatine phosphokinase levels.¹²³ However, a fatal case of malignant hyperthermia has been reported following a ketamine anaesthetic for a diagnostic muscle biopsy in a five-year-old child.¹²⁴

A case of diabetes insipidus induced by a ketamine infusion was reported in a patient receiving ketamine for chronic pain. The condition responded to intranasal desmopressin acetate, and resolved on discontinuation of the ketamine infusion.¹²⁵

Summary

In nearly 25 years of clinical experience, the benefits and limitations of ketamine analgesia and anaesthesia have generally been well-defined. The extensive review of White *et al.*² and the cardiovascular review of Reves *et al.*⁴³ are broad in their scope and have advanced the understanding of dissociative anaesthesia. Nevertheless, recent research continues to illuminate different aspects of ketamine pharmacology, and suggests new clinical uses for this drug.

The identification of the N-methylaspartate receptor gives further support to the concept that ketamine's analgesic and anaesthetic effects are mediated by separate mechanisms. The stereospecific binding of (+)ketamine to opiate receptors *in vitro*, more rapid emergence from anaesthesia, and the lower incidence of emergence sequelae, make (+)ketamine a promising drug for future research.

Clinical applications of ketamine that have emerged recently, and are likely to increase in the future, are the use of oral, rectal, and intranasal preparations for the purposes of analgesia, sedation, and anaesthetic induction. Ketamine is now considered a reasonable option for anaesthetic induction in the hypotensive preterm neonate. The initial experience with epidural and intrathecal ketamine administration has not been very promising but the data are only

preliminary in this area. The use of ketamine in military and catastrophic settings is likely to become more common.

The clinical availability of midazolam will complement ketamine anaesthesia in several ways. This rapidly metabolized benzodiazepine reduces ketamine's cardiovascular stimulation and emergence phenomena, and does not have active metabolites. It is dispensed in an aqueous medium, which is usually non-irritating on intravenous injection, unlike diazepam. The combination of ketamine and midazolam is expected to achieve high patient acceptance, which never occurred with ketamine as a sole agent.

Finally, it is necessary to point out the potential for abuse of ketamine.¹²⁶ While ketamine is not a controlled substance (in the United States), the prudent physician should take appropriate precautions against the unauthorized use of this drug.

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Résumé

Pendant presque 25 ans d'expérience clinique, les bénéfices et les limitations de l'anesthésie à la kétamine ont été généralement bien définis. Les revues extensives de White *et al.*² ainsi que celles de Reeves *et al.*⁴³ ont énormément aidé à comprendre l'anesthésie dissociative. Néanmoins, des études récentes continuent à nous éclairer sur les différents aspects de la pharmacologie de la kétamine et suggèrent de nouvelles utilisations cliniques de cette drogue. L'identification du récepteur du N-Méthyl-Aspartate amène une preuve que l'anesthésie et l'analgésie à la kétamine ont chacune un mécanisme d'action différent. La liaison stéréospécifique de la (+) kétamine aux récepteurs opiacés *in vitro*, l'émergence plus rapide de l'anesthésie, et une incidence plus basse de séquelles lors de l'émergence, rend la (+) kétamine une drogue prometteuse pour des recherches futures. Les applications cliniques de la kétamine qui ressortent récemment, et qui probablement augmenteront dans le futur sont reliées à l'utilisation orale, rectale et intra-nasale de la kétamine pour des fins d'analgésie, de sédation ou induction anesthésique. La kétamine est actuellement considérée comme une option raisonnable pour l'induction anesthésique chez les nouveau-nés prématurés en hypotension. L'expérience initiale avec la kétamine en injection épidurale et intrathécale ne fut pas prometteuse et les données sont encore préliminaires dans ce domaine. L'utilisation de la kétamine dans les catastrophes et les manœuvres militaires va probablement être plus fréquente. La disponibilité clinique du midazolam va compléter l'anesthésie à la kétamine de plusieurs

façons. Cette benzodiazépine est rapidement métabolisée. Elle réduit la stimulation cardiovasculaire de la kétamine ainsi que les phénomènes d'émergence sans avoir des métabolites actifs. Elle est disponible sous une forme aqueuse et n'est pas irritante lors de l'injection intra-veineuse comme le diazépam. La combinaison de la kétamine et du midazolam sera bien acceptée par les patients contrairement à ce qui arrive quand on utilise la kétamine seule. Finalement, il est nécessaire de mentionner la possibilité d'abus de la kétamine.¹²⁶ Alors que la kétamine n'est pas une substance contrôlée (aux États-Unis) la prudence suggère aux médecins de prendre des précautions appropriées contre son utilisation non-autorisée.