Ketamine: A Controversial Drug for Neonates

Adnan T. Bhutta, MBBS, FAAP

Ketamine is widely used for anesthesia and analgesia in neonates and children. It provides potent sedation, analgesia, and amnesia, a short duration of action, supporting hemodynamic and respiratory stability. Noncompetitive antagonism of NMDA receptors produces its primary therapeutic effects, but it also alters receptor function at dopaminergic, serotonergic, cholinergic, and opioidergic sites. Recent interest in ketamine stems from its potential to block excitotoxic cell death, although concerns have been raised about anesthetic neurotoxicity in neonatal animal models. The development of ketamine, its clinical profile, toxic effects in the immature brain, and future applications in neonates and children are reviewed in this article.
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A Brief History of Ketamine

In 1957, Woodbridge spelled out the criteria for an ideal anesthetic: producing blockade of sensory, motor, autonomic, and cognitive functions.[1] The search for agents that produce such a state led to the development of a promising class of drugs called cyclohexylamines in the 1950s by the Parke-Davis pharmaceutical company.[2] The first compound to undergo clinical testing was Sernyl, better known as phencyclidine or PCP. Clinical studies with this compound showed severe and prolonged psychotomimetic effects in a large proportion of the patients.[3,4] In 1962, a PCP derivative was synthesized called 2(O-Chlorophenyl)-2-methylamino-cyclohexanone or CI-581, subsequently known as ketamine. This compound appeared more promising in animal studies, producing anesthesia and analgesia similar to phencyclidine but with a shorter duration of action and less propensity to produce convulsions.[5]

In 20 prison volunteers, Domino and coworkers showed that ketamine produced effective analgesia and anesthesia in doses of 1 to 2 mg/kg, with onset of effects at 1 minute, peak effects lasting 5 to 10 minutes, and electroencephalogram (EEG) changes for 1 to 2 hours. An increase in heart rate and systolic and diastolic blood pressure occurred, with slightly lower minute ventilation in the first minute. Nystagmus also occurred, with decreases in alpha waves, induction of theta waves on EEG, decreased primary complex in visual evoked responses (VER), and partially enhanced secondary complex.[6] Clinical studies using 1 to 2 mg/kg of ketamine for short procedures in 130 patients (29 patients were 2 years or younger) showed that ketamine provided adequate anesthesia, analgesia, and amnesia for more than 90% of patients while preserving protective airway reflexes. Patients recovered within 30 to 60 minutes after surgery. Side effects included slight increases in skeletal muscle tone, hallucinations in adult patients, with schizoid behavior in two patients. Ketamine produced a state resembling catalepsy, in which sensory input seemed to reach cortical sensory areas but was not perceived due to suppression of association areas. Thus, they termed the state induced by ketamine as "dissociative anesthesia," a term which remained in most future descriptions of this drug.[3]

Ketamine rapidly gained widespread acceptance due to its potent anesthetic and analgesic properties, short duration of action, and safe hemodynamic and respiratory profile. It was particularly useful for inducing anesthesia in children for surgical procedures inside or outside the operating room,[7] for battlefield emergencies,[8] and veterinary medicine.[9] Like other psychoactive agents, it also found its way into recreational drug use.[10,11] In 1999, it was classified as a schedule III drug to discourage its growing abuse.

The Biology of Ketamine

Pharmacology

Ketamine is marketed as a racemic 50:50 mixture of S(+)- and R(−)-ketamine enantiomers. It has a molecular weight of

Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR.
Address reprint requests to Adnan T. Bhutta, MBBS, FAAP, Pediatric Critical Care Medicine and Cardiology, Department of Pediatrics, University of Arkansas for Medical Sciences, Slot 512-3, 800 Marshall Street, Little Rock, AR 72202. E-mail: bhuttaadnant@uams.edu

Table 1 Pharmacokinetics of Ketamine in Children

	Age (yr)	WT (kg)	Dose (mg/kg)	T½ (min)	Vss (L/kg)	Cl (mL/min/kg)	AUC$_{0-\infty}$ (mg/mL/min)
Malinovsky, et al.[18]	4.8	18.6	3	125 ± 46	2.8 ± 1.2	22 ± 9.8	148.3 ± 55
Grant, et al.[17]	6.1	21.5	2	100 ± 19	1.9 ± 0.6	16.8 ± 3.3	NA

238 and pKa of 7.5.[12] It is a highly lipophilic compound that distributes rapidly from the systemic circulation. The brain-to-plasma ratio for ketamine in rats is estimated to be 6.5:1.[13] In humans, up to 47% of ketamine is bound to plasma proteins. The free fraction of ketamine determines the rate of diffusion to a site of action.[14] Ketamine undergoes N-demethylation by CYP2B6, 2C9, and 3A4 to its primary active metabolite, norketamine, with a minor inactive metabolite, dehydroxynorketamine, generated by direct oxidation. Norketamine is 1/3 to 1/5 as potent as ketamine but may provide prolonged analgesia.[15] Ketamine exhibits a high intrinsic clearance, with plasma clearance dependent on hepatic blood flow and extensive first-pass metabolism when given orally.[16]

Limited pharmacokinetic data for ketamine in children are mainly derived from two studies evaluating the disposition of ketamine following intravenous, intramuscular, rectal, and nasal administration in children undergoing surgery.[17,18] The concentration-time profiles were consistent between the two studies, with a two-compartment model showing the best fit for each data set. Subjects in Malinovsky's study received 3 mg/kg of intravenous ketamine ($n = 8$), with ketamine concentrations greater than 2000 ng/mL at 5 and 10 minutes. In Grant's study, subjects ($n = 4$) received 2 mg/kg intravenous ketamine, with average concentrations at 5 and 15 minutes being 2000 and 960 ng/mL, respectively (Table 1).

Beyond these two reports, there are limited data evaluating ketamine concentrations in infants and toddlers who received intravenous ketamine. A case report by Cederholm and coworkers describes the use of continuous ketamine infusions in a 14-month-old patient with 50% body surface area burns.[19] Over 21 days of ketamine infusion, its plasma clearance averaged 32.1 mL/min/kg (range 21.5-44 mL/min/kg). Preterm neonates ($n = 16$) receiving 0.5, 1, or 2 mg/kg of intravenous ketamine for tracheal suction, showed mean concentrations of 103, 189, and 379 ng/mL, respectively, measured at 15 minutes after the ketamine dose. All subjects had detectable ketamine concentrations at 12 hours following these doses (limit of quantitation 20 ng/mL), but no pharmacokinetic assessment was conducted in this study.[20]

Ketamine analgesia in adults was associated with plasma levels of 150 ng/mL after an IM dose and 40 ng/mL after an oral dose. Awakening from anesthesia occurred at plasma concentrations ranging from 640 to 1120 ng/mL in the same age group.[12]

The S-enantiomer of ketamine appears to have a favorable cardiovascular profile and neuroprotective effects.[21] The dose required for S(+)-ketamine is less than that required for the racemic mixture with fewer side effects and shorter recovery time,[22,23] prompting the replacement of racemic ket-amine with S(+) ketamine in some European countries. It can be administered via IV, IM, or rectal routes for anesthesia and has been administered via caudal epidurals to augment peri-operative analgesia in children.[22]

Mechanisms of Action

Animal studies using autoradiography and human studies using positron emission tomography (PET) show that ketamine induces the maximum increase in metabolic activity in the cortical and subcortical structures associated with the limbic system.[24-30] Interestingly, at subanesthetic doses, where the analgesic effect is more prominent, metabolic activity of these regions is decreased.[30]

At a cellular level, ketamine is widely known to be an N-methyl D-aspartate (NMDA) receptor antagonist, although its interactions with other receptors are being increasingly recognized. Glutamate receptors play essential roles in synaptogenesis and neuronal survival,[31,32] but they are also central to cell death induced by excitotoxicity.[32-35] Ketamine is a low-affinity, use-dependent, noncompetitive antagonist of NMDA receptors.[36-38] The blockade is use-dependent in that the rates of onset and the recovery from blockade are increased by applying NMDA agonists.[39] Using a patch clamp technique to investigate NMDA-activated currents from cultured mouse hippocampal neurons, Orser and coworkers observed that ketamine inhibits the NMDA receptor by two distinct mechanisms. First, it blocks the open channel and thereby reduces channel mean open time; second, by binding to the closed receptor, it decreases the frequency of channel opening by an allosteric mechanism (see Fig. 1). Low concentrations of ketamine predominantly caused closed-channel blockade, whereas both open and closed channel blockade occurred at higher ketamine concentrations.[39] Ketamine concentration-based differences in the mechanism of NMDA receptor blockade also have clinical implications, with the analgesic properties of ketamine apparent at low levels and anesthetic effects apparent at much higher concentrations.[39]

Nicotinic acetylcholine receptors (nAChRs) have been implicated in attention, arousal, and analgesia, and their blockade could play a role in the hypnosis, amnesia, analgesia, and autonomic regulation.[40] Multiple in vitro studies have shown that ketamine inhibits nAChRs, and that the preservative, benzathonium chloride, used in commercial preparations of ketamine also inhibits nAChRs.[40]

In vitro studies have also shown that Ketamine blocks the high-affinity state of the D2-dopamine receptor.[41] This high-affinity blockade may explain its psychomimetic effects, seen during emergence, and may also explain the catalepsy seen during peak anesthetic effects. At subanesthetic concentra-
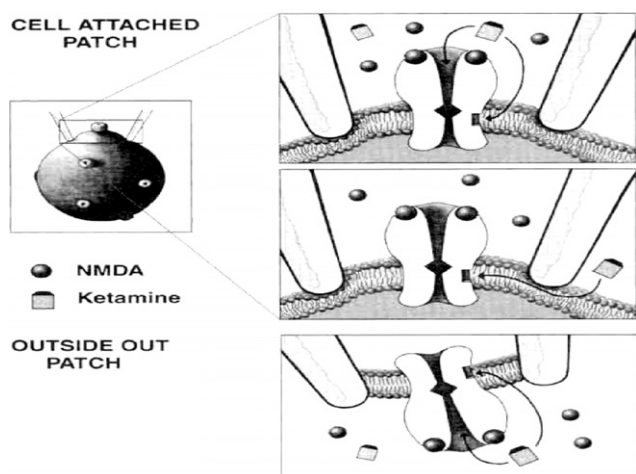
Figure 1 Schematic representation of NMDA receptor activity. It is proposed that ketamine may interact with the receptor at two potentially distinct sites: one site located within the channel pore and a second site associated with a hydrophobic domain of the protein. The binding of the agonist to the receptor is assumed to modify the binding of ketamine to both sites. Binding of ketamine at the site associated with the channel pore would decrease channel-open time, whereas binding to the membrane-associated site does not require the channel to be in the open state.[39]

tions, ketamine stimulates the high-affinity D2 receptor and causes incorporation of GTP into the cell, whereas at anesthetic concentrations, it inhibits the D2 receptor, leading to catalepsy.[42] Similarly, in vitro evidence shows that ketamine is a serotonin 5-HT$_2$ receptor agonist,[43] suggesting that it may inhibit multiple G-protein-linked receptors such as the adrenergic, muscarinic, and opiate receptors.[44]

Lastly, ketamine also has antiinflammatory effects. Decreased TNF-α, interleukin 6 (IL-6), and IL-8 levels, as well as stabilization of neutrophil activation, reducing the release of inflammatory mediators, have been observed in vitro, in animal models, and in patients receiving ketamine.[45-49] In addition, the NMDA antagonistic effect of ketamine was found to be neuroprotective in animal models.[50-54] The exact mechanism by which ketamine exerts its antiinflammatory effect remains unclear, although ketamine suppresses NF-κB expression[55-58] and NF-κB plays a central role in the proinflammatory response.[59]

Therapeutic Uses of Ketamine

Anesthesia/Sedation

Ketamine has a well established role in pediatric anesthesia and it is routinely used for induction and maintenance of anesthesia.[60] The usual dosage of Ketamine is 0.5 to 2 mg IV or 4 to 5 mg IM. The cardiovascular stability observed with ketamine has made it a popular induction agent in pediatric anesthesia for children with heart disease.[61] It is also commonly used for conscious sedation in pediatric emergency departments, endoscopy suites, catheterization laboratories, and radiology suites.[62-66]

Continuous infusions of ketamine are used in the intensive care unit, as an adjunct to other agents, to provide sedation during mechanical ventilation.[67,68] In particular, children requiring ventilation for status asthmaticus are preferentially sedated with ketamine due to its bronchodilatory effect.[69] A double-blinded, randomized, placebo-controlled trial for low-dose ketamine infusion for 2 hours in the emergency department did not provide any incremental benefits over standard therapy.[70]

Analgesia

Preoperative analgesia with ketamine decreases the central sensitization to painful stimuli, reducing morphine requirements in the first 24 hours as well as postoperative nausea and vomiting.[71,72] In neonates, 1 mg/kg of ketmine reduces the pain induced by tracheal suctioning, but does not attenuate the concomitant heart rate or blood pressure changes.[20] Oral formulation of ketamine (10 mg/kg) provides effective analgesia and sedation for burn dressing changes in children.[73]

Ketamine use is also being explored for chronic pain in adults,[74] although there is only one published case report on similar use in a child.[75] Ketamine administered by rectal, subcutaneous, transdermal, and intranasal routes for treatment of chronic pain or in battlefield emergencies is also reported.[76]

Other Potential Clinical Applications

Experimental evidence using animal models of hypoxia–ischemia and traumatic brain injury showed promising results with the application of NMDA blockade, where large doses of ketamine after injury resulted in decreased neuronal death.[52,77-81] Neuroprotective effects also occurred in neonatal rodent models of inflammatory pain in which a preemptive, clinically relevant dose of ketamine (5 mg/kg) administered before daily formalin injections in postnatal day 1 to 4 (P1–P4) animals ameliorated the increased cell death occurring in animals who received formalin injections without ketamine.[82]

Redmond and coworkers showed that neurologic injury during hypothermic circulatory arrest during cardiac surgery is mediated through glutamate excitotoxicity and suggested a role for glutamate antagonists as neuroprotective agents. Although animal studies using NMDA antagonists have been promising,[83,84] a randomized, controlled trial in adults comparing S(+)-Ketamine to remifentanil did not show any neuroprotection in cognitive testing 10 weeks after cardiopulmonary bypass surgery.[85] No trials have been reported in neonates or children.

Adverse Effects of Ketamine

Systemic adverse effects like laryngospasm, respiratory depression, increased respiratory secretions, and emesis have been reported in children.[63] We will limit our discussion to its adverse effects on the brain.

Psychomimetic Effects

The psychomimetic effects of ketamine are usually described as emergence reactions after clinical use, leading to its increased popularity as a "club drug."[86] Chronic ketamine use causes changes in the dorsolateral prefrontal cortex similar to those seen in patients with schizophrenia,[87] justifying its use to develop animal models of schizophrenia. Cotreatment with benzodiazepines may decrease these emergence reactions, but two double-blind randomized trials in children failed to show any benefit of midazolam with ketamine.[88,89] Therapeutic effects of longer-acting benzodiazepines, timed for peak effects during emergence from ketamine, remain to be investigated.

Intracranial Hypertension

Increased intracranial pressure (ICP) in patients with reduced intracranial compliance was reported with ketamine.[90-92] A systematic review of the literature, however, suggests that this observation may be unfounded. Randomized or nonrandomized control or cohort studies in patients with traumatic brain injury or brain tumor or aneurysm show that ketamine increases cerebral blood flow and ICP in spontaneously breathing volunteers. Under conditions of controlled ventilation, however, ketamine does not increase ICP, suggesting previous reports of increased ICP may have occurred secondary to hypoventilation and hypercarbia. Compared with sedation with opioids, a greater cerebral perfusion pressure is maintained with ketamine sedation and the need for vasopressors is reduced. During anesthesia, ketamine does not reduce cerebral blood flow or impair autoregulation.[21]

Neurotoxicity

A raging controversy exists with regard to anesthetic neurotoxicity caused by ketamine. Four hours after a single subcutaneous dose of ketamine 40 mg/kg, Olney and coworkers observed the presence of pathological vacuolation of neurons in the cingulate and retrosplenial regions in adult female rats, reversible within a 24-hour period. These changes were not seen with lower doses of 5, 10, and 20 mg/kg of ketamine.[93] In 1999, these investigators published another landmark study showing that repeated ketamine doses (20 mg/kg × 7 doses over 9 hours) and other NMDA antagonists increased neuroapoptosis in the developing brain of P7 rats.[94] Both in vitro and in vivo rodent and primate models independently confirmed these findings,[95-97] showing that both brain immaturity and prolonged exposures were necessary to produce neuroapoptotic cell death.

While examining these results, however, clinicians must closely explore the relevance of these animal models to the clinical use of ketamine. Specifically, the clinical use of ketamine is usually followed by a surgical or procedural stress. Such stressful stimuli can cause excessive glutamate release, which is blocked by the preemptive use of ketamine[82]; but no such stimulus was present in these models. Additionally, the doses used in these animal models resulted in plasma ketamine levels 7 to 10 times higher than those produced by clinical doses of ketamine. Furthermore, the developmental age of the rodent models used in these studies corresponded to a 16- to 22-week-old fetus. Therefore, the applicability of these models to clinical scenarios is limited.

Conclusions

Ketamine is a widely used anesthetic in neonates and children due to its rapid onset of action, short duration of action, effective anesthetic and analgesic properties, and relatively safe respiratory and hemodynamic profile. It is a noncompetitive NMDA receptor antagonist, and this property offers the intriguing possibility of using this agent to minimize neuronal cell death caused by as trauma, hypoxia, or ischemia. The possibility of hallucinations, increased ICP, and neuronal death in an immature brain after the administration of repeated high doses of the agent have limited its further use. The preponderance of evidence, however, favors its continued clinical use and the need for further research into expanding its potential clinical applications.

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