Ketamine: Review of Its Pharmacology and Its Use in Pediatric Anesthesia

Stewart A. Bergman, DDS, MS
Baltimore College of Dental Surgery, Dental School, University of Maryland, Baltimore, Maryland

The management of the uncooperative pediatric patient undergoing minor surgical procedures has always been a great challenge. Several sedative techniques are available that will effectively alleviate anxiety, but short of general anesthesia, no sedative regimen is available that will enable treatment of the uncooperative child. Ketamine produces a unique anesthetic state, dissociative anesthesia, which safely and effectively enables treatment of these children. The pharmacology, proposed mechanisms of action, and clinical use of ketamine (alone and in combination with other agents) are reviewed and evaluated.

Key Words: Ketamine; Child patients; Limbic system NMDA receptor.

The anesthetic management of pediatric patients undergoing minor surgical procedures often is one of the most difficult problems faced by health care providers. This is especially true of anxious and fearful preschool children. Unlike adults, these children are not there of their own free will. Many are there as a result of sickness or injury and have no desire to participate in their treatment. They often have no prior experience and possess inadequate coping skills. As a consequence, many health care providers have resorted to pharmacological help in the management of these patients. Unfortunately, many of the techniques used provide added risk of injury to the patient and may greatly increase the cost of care. Many sedative techniques are available that will safely and effectively alleviate anxiety. Short of general anesthesia, however, no drugs have yet been developed that will enable treatment of the uncooperative child.

Ketamine, 2-(o-chlorophenyl)-2-(methylamino) cyclohexanone, a phencyclidine (PCP) and cyclohexamine derivative, was developed and introduced in the mid 1960s (Figure 1).[1] It produces a unique anesthetic state (dissociative anesthesia) characterized by a dissociation between the thalamocortical and limbic systems. Patients are usually unconscious and cataleptic or partially conscious but unable to respond purposefully to physical stimulation or verbal command, depending on dose. Their vital reflexes are generally intact but can be depressed. Therefore, by definition, ketamine produces a unique state somewhere between deep sedation and general anesthesia.

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Address correspondence to Dr Stewart A. Bergman, Professor of Oral-Maxillofacial Surgery, Baltimore College of Dental Surgery, Dental School, University of Maryland, 666 West Baltimore Street, Baltimore, Maryland 21201; SAB001@dental.umaryland.edu.

MECHANISM OF ACTION

The limbic system appears to be involved in the regulation of emotions (ie, fear, anger, pleasure, and contentment) (Table 1). It serves as a processing center receiving sensory input via the thalamus and brainstem and integrates it with highly processed sensory information (ie, visual, somatic sensory, and auditory information, and memories of past experience) from the sensory association cortex. It then invests the sensory experience with emotional significance and directly controls the regulatory centers (the hypothalamus and brainstem) that coordinate the visceral motor responses associated with these emotions. The autonomic nervous system, somatic motor system, and endocrine system mediate these responses. In addition, the limbic system plays a critical role in the development of short- and long-term memory. The sensory association areas of the cortex, components of the limbic system, and thalamus are directly depressed by ketamine. Consequently, higher central nervous system (CNS) centers are unable to receive or process sensory information, and its emotional significance cannot be assessed.[2] The result of ketamine administration is anesthesia, analgesia, suppression of fear and anxiety, and amnesia, which appear to be ideal for the uncooperative child patient.

Most of the pharmacologic effects of ketamine ap-

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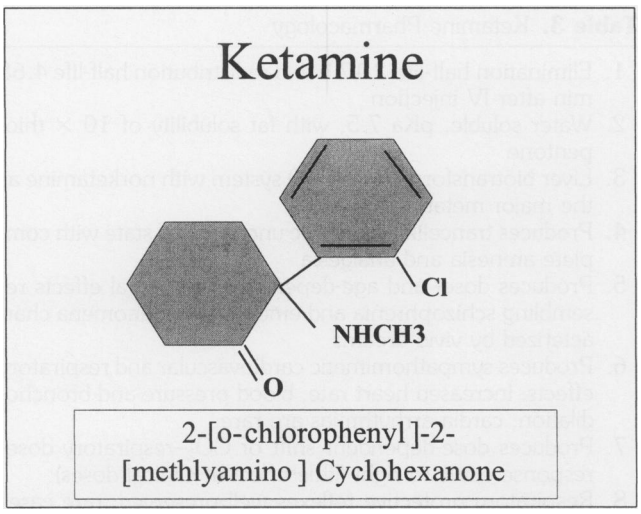

Figure 1. Chemical structure of ketamine; #2 carbon of cyclohexanone ring is optically active.

pear to be mediated by its interaction with *N*-methyl D-aspartate (NMDA) receptors (Table 2).[3] Ketamine is a noncompetitive antagonist at the NMDA receptor. The NMDA receptor is a cation-gated channel receptor permeable primarily to calcium and to a lesser extent to sodium and potassium (Figure 2). The NMDA receptor is one of several species of ion-gated receptors that bind to excitatory amino acids (EAA) of which glutamate, glycine, and aspartate are believed to be the major amino acids.[4] NMDA, a derivative of aspartic acid, binds selectively to the NMDA-receptor subtype (hence its name). Two non-NMDA EAA-receptor subtypes have been identified that are named after the agonistic amino acid derivatives that bind selectively, but not exclusively, to these receptors, the kainate and quisqualate (AMPA, amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid) receptors. Unlike the NMDA receptor, both of these receptors are ion-gated channel receptors for monovalent cations[4] (eg, Na^+ and K^+). A subspecies of quisqualate receptor does not appear to be linked to an ion-gated channel but rather to phospholipase C (PLC) via a G protein link.[5] PLC activation results in the conversion of phosphatidylinositol diphosphate (a membrane phospholipid) to inositol triphosphate (IP3) and diacylglycerol (DAG). Consequently, these receptors are sometimes referred to as metabotropic receptors. IP3 causes the release of intracellular calcium, and DAG activates protein kinase C. This results in activation of additional enzymes (ie, RAS-MAP kinases and calcineurin), eventually leading to promotion of RNA transcription and protein synthesis. This process is believed to be important in the development of long-term memory.[5]

These EAA receptors are located throughout the CNS, including the spinal cord, cerebellum, thalamus, basal ganglia, limbic system, and cortex. They are particularly important in cortico–cortical and cortical–subcortical interactions. For the most part, all species of

Table 1. Limbic System Functions

1. Regulation of emotions
2. Acts as processing center for sensory inputs from brainstem and thalamus
3. Integrates sensory information with highly processed sensory information from the sensory cortex and memories of past sensory experience
4. Invests sensory experience with emotional significance (ie, anger, joy, fear etc)
5. Controls regulatory centers mediating visceral motor responses associated with these emotions
6. Plays a critical role in development of long- and short-term memory

Table 2. Ketamine: Mechanisms of Action

1. Noncompetitive antagonist of the central nervous system NMDA receptors
   a. NMDA receptor is a calcium-gated channel receptor
   b. NMDA receptor agonists are excitatory amino acids: glutamic acid, aspartic acid, and glycine
   c. Agonist binding to receptor results in opening of ion channel and depolarization of the neuron
   d. NMDA receptor is involved in sensory input at the spinal, thalamic, limbic, and cortical levels
   e. Ketamine blocks sensory input and impairs limbic functions
2. Agonist at α- and β-adrenergic receptors
3. Antagonist at muscarinic receptors of the central nervous system
4. Blocks reuptake of catecholamines
5. Agonist at opioid sigma receptor

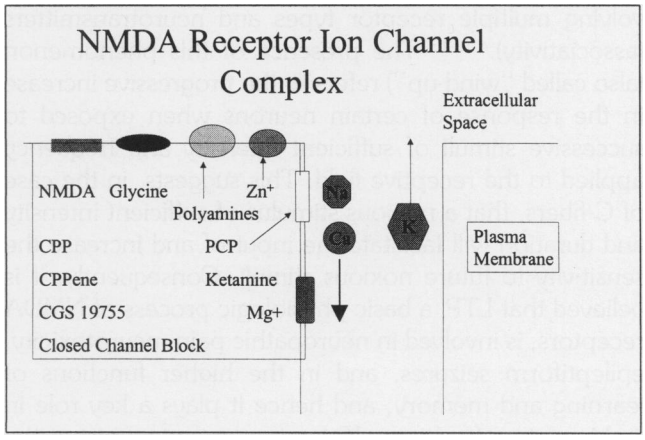

Figure 2. Schematic view of the NMDA-receptor ion channel. Agonists at the NMDA, glycine, and polyamine receptors all open the ion channel, resulting in depolarization. Antagonists at these receptors produce a closed-channel block. NMDA-receptor antagonists that bind to the phencyclidine receptor (ie, ketamine) produce an open-channel block. (Modified from Olney et al, 1995.)

EAA receptors are coupled together and are present at the same anatomic locations. EAA receptors do not exist in the peripheral nervous system.[6] The EAAs are believed to be the primary excitatory neurotransmitters of the CNS. They are present in the brain in high concentrations and are released from nerves following electrical stimulation.[7] EAA synaptic pathways appear to be involved in sensory input at the spinal, thalamic, limbic, and cortical levels.[8,9] EAA binding to their receptors causes opening of their respective channels, resulting in cell excitatory postsynaptic potentials (EPSPs) and eventual depolarizations when the resting neuronal membrane potential reaches firing level.[10] The NMDA receptors are postsynaptic receptors, which appear to transmit high-frequency signals, whereas the non-NMDA receptors appear to transmit low-frequency signals and are present at both pre- and postsynaptic locations.[4] In addition, EAA-mediated pathways display a phenomenon known as synaptic plasticity. That is, the sensitivity of NMDA receptors to opening their respective calcium-gated channels as a result of EAA neurotransmitter binding can be increased by the frequency of neuronal activation by the EAA. This phenomenon is called long-term potentiation (LTP) and results in sustained enhancement of synaptic transmission.[11] LTP has been shown to last for several days or even weeks.[4] LTP exhibits the properties of specificity, cooperativity, and associativity. LTP will only occur in those synaptic pathways in which there is tetanic (high-frequency) stimulation (specificity). LTP will only develop if the strength of stimulation exceeds a certain threshold. This requires synaptic input from multiple excitatory afferent fibers converging on a given neuron (cooperativity). Finally, cooperative interaction occurs heterosynaptically, involving multiple receptor types and neurotransmitters (associativity).[4,12,13] The presence of this phenomenon (also called "wind-up") refers to the progressive increase in the response of certain neurons when exposed to successive stimuli of sufficient intensity and frequency applied to the receptive field. This suggests, in the case of C-fibers, that a noxious stimulus of sufficient intensity and duration will facilitate the input of and increase the sensitivity to future noxious stimuli. Consequently, it is believed that LTP, a basic physiologic process of NMDA receptors, is involved in neuropathic pain, neurotoxicity, epileptiform seizures, and in the higher functions of learning and memory, and hence it plays a key role in limbic system functions. Ketamine, an antagonist at the NMDA receptor, would be expected to block or interfere with sensory input to higher centers of the CNS, with the emotional response to these stimuli, and with the processes of learning and memory.

Ketamine is a member of a chemically diverse group of compounds that are collectively called noncompetitive NMDA-receptor antagonists. All of these compounds bind to proteins that make up the ion channel of the NMDA receptor. This prevents the influx of Ca^{++} ions following EAA binding, thereby preventing depolarization. Ketamine and PCP, the benzomorphans (eg, cyclazocine and SKF 10,047 [*N*-allylnormetazocin), and morphine derivatives (eg, dextrorphan, dextromethorphan, and levorphanol) bind to the PCP site in the NMDA-receptor ion channel. These compounds also have effects at other receptor sites. They bind to the σ-receptor, which is distinct from the NMDA receptor. Ketamine and PCP also block acetylcholine muscarinic receptors of central neurons and may potentiate the effects of α-aminobutyric acid (GABA) synaptic inhibition.[3,14] Ketamine also acts as a weak agonist at opioid μ-receptors.[15] There is evidence that these compounds potentiate the effects of catecholamines by blocking the reuptake of these neurotransmitters.[4,16] It is the interaction at all these receptor sites that mediates the pharmacologic effects of ketamine.

Table 3. Ketamine Pharmacology

1. Elimination half-life 2.17 h and redistribution half-life 4.68 min after IV injection
2. Water soluble, pKa 7.5, with fat solubility of 10 × thiopentone
3. Liver biotransformation p450 system with norketamine as the major metabolite
4. Produces trancelike cataleptic unconscious state with complete amnesia and analgesia
5. Produces dose- and age-dependent behavioral effects resembling schizophrenia and emergence phenomena characterized by vivid dreams
6. Produces sympathomimetic cardiovascular and respiratory effects: increased heart rate, blood pressure and bronchodilation; cardia arrhythmias are rare
7. Produces dose-dependent shift of CO_2–respiratory dose-response curve to right (little effect at clinical doses)
8. Respiratory protective reflexes well preserved; rare cases of apnea and respiratory obstruction reported
9. Produces increased salivary and tracheobronchial secretions
10. Produces random head and extremity movements; skeletal muscle hypertonicity and rigidity reported at high doses

PHARMACOLOGY

Ketamine is water soluble with a pKa of 7.5, which permits nonirritating, intravenous, intramuscular, oral, intranasal, and rectal administration[17–22] (Table 3). It is 10 times more lipid soluble than thiopentone and can quickly cross the blood–brain barrier. Therefore, ketamine has relatively rapid onset of effect and recovery due to redistribution, similar to the thiobarbiturates. The onset of anesthesia/sedation, in one study, was 45 seconds after in-

travenous injection (2 mg/kg) and 4 minutes after intramuscular injection (3 mg/kg) with recovery times of 18 minutes and 25 minutes respectively.[17] After intravenous injection, the distribution half-life [t(½π)] was 24.1 seconds, redistribution half-life [t(½α)] was 4.68 minutes, and elimination half-life [t(½β)] was 2.17 hours.[23] Biotransformation takes place primarily in the liver. Multiple metabolites have been described. However, the most important pathway involves *N*-demethylation to norketamine by the cytochrome p450 enzyme system. Norketamine is an active metabolite with one third the anesthetic potency of ketamine.[24] Norketamine may enter multiple metabolic pathways leading to a multitude of compounds of which little is known of their pharmacologic activity. The majority of norketamine is hydroxylated and conjugated to form a water-soluble compound, which is readily secreted in the urine and to a much lesser extent in the feces.[25] Alternatively, the cyclohexanone ring can undergo oxidative metabolism to several minor metabolites the pharmacologic properties of which are little known. The pharmacokinetics is similar in children, except that absorption following intramuscular injection is more rapid and hepatic conversion to norketamine is more rapid. Hence higher concentrations of norketamine are measured.[26] Because of this, in addition to lower adsorption rates compared to intramuscular injection, oral and rectal administration is characterized by a significant first-pass effect necessitating higher doses.[19,22,27,28] Coadministration of drugs requiring hepatic metabolism will extend the half-life of ketamine by competing with hepatic enzymes. Consequently, combined use of benzodiazepines or barbiturates will prolong recovery time by about 30%.[29]

Ketamine contains a chiral center at the C-2 carbon of the cyclohexanone ring so that 2 enantiomers exist, S(+) ketamine and R(−) ketamine (Figure 1). Commercially available racemic ketamine preparations (such as Ketalar) contain equal concentrations of the 2 enantiomers. The dextro-S(−)-isomer of ketamine has approximately three- to fourfold the potency of the levo-R(−)-isomer that correlates with the binding affinity of the isomers to the PCP site.[30,31] The S(+)-isomer appears to be cleared more rapidly than the R(−)-isomer, resulting in a shorter duration of effect and more rapid recovery.[32] Equipotent doses of the S(+)-isomer and the racemate appear to have similar effects on physiologic parameters.[33] There is evidence to suggest that the R(−)-isomer produces a higher rate of emergence reactions and more agitated behavior than the S(+)-isomer.[34] Emergence phenomena have been described as floating sensations, vivid dreams (both pleasant and frightening), hallucinations, and delirium. These emergence phenomena appear to occur more frequently in adults (30–50%) than in children (5–15%), in women more than in men, and at higher doses of ketamine.[34] It is well documented that

NMDA Receptor Hypofunction Hypothesis

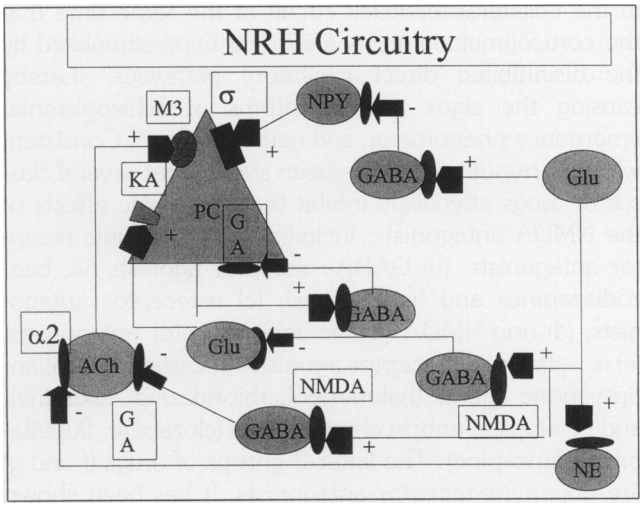

Figure 3. There are 3 excitatory inputs to the corticolimbic pyramidal neurons (PC) mediated by 3 neurotransmitters: acetylcholine (muscarinic M3 receptor), glutamate (kainic acid excitatory amino acid receptor) and neuroprotein Y (σ-receptor). Hypofunction of the NMDA receptor disinhibits all 3 excitatory inputs, resulting in dysfunction and injury to these neurons. (Modified from Olney et al, 1995.)

phencyclidine and (to a lesser extent) ketamine produce behavioral effects resembling schizophrenia in healthy adults and exacerbate symptoms in schizophrenic patients.[35] These patients experience the altered sensory perception, bizarre and impoverished thought and speech, impaired attention, and disrupted memory characteristic of schizophrenia. It is believed that these dose-related effects of phencyclidine and ketamine are due to their antagonism at the NMDA receptor.

Olney et al have put forth the NMDA-receptor hypofunction hypothesis, which appears to explain the behavioral effects seen following administration of NMDA-receptor antagonists (Figure 3).[36] Simply stated, hypofunction of the NMDA receptor can induce dysfunction and injury of corticolimbic neurons by a disinhibition principle. Similar neurons have been found in the thalamus, basal forebrain, and brainstem. The EAA glutamate acting at NMDA receptors on GABA and norepinephrine neurons maintains tonic inhibition over the multiple convergent excitatory pathways to corticolimbic neurons via GABAa and α_2-adrenergic receptors. Excitatory inputs to these neurons are mediated by 3 neurotransmitters, acetylcholine (a muscarinic agonist), a σ-receptor agonist, and a non-NMDA glutamate (kainic acid) receptor agonist. All 3 excitatory pathways are disinhibited when NMDA receptors are blocked. In addition, the corticolimbic neurons provide negative feedback by collaterals to GABA-ergic neurons via a gluta-

mate NMDA-receptor–mediated synapse. An NMDA-receptor antagonist, therefore, would abolish inhibition in the collateral feedback circuit at the same time that the corticolimbic neurons are being hyperstimulated by the disinhibited direct excitatory pathways, thereby causing the signs and symptoms of schizophrenia, emergence phenomena, and neurotoxicity.[37] Consistent with this hypothesis, it has been shown that several classes of drugs effectively inhibit the neurotoxic effects of the NMDA antagonists, including (a) muscarinic receptor antagonists, (b) GABAa receptor agonists (ie, benzodiazepines and barbiturates), (c) σ-receptor antagonists, (d) non-NMDA (kainic acid) receptor antagonists, (e) α_2-adrenergic receptor agonists, (f) certain typical antipsychotic agents (haloperidol, thioridazine, loxapine), and (g) atypical antipsychotic agents (clozapine, flupefiapine, olanzapine). The latter 2 groups of drugs (f and g) are dopamine-receptor antagonists. It has been shown that dopamine inhibits glutamate release from glutamergic neurons.[38,39] Dopamine hyperactivity, therefore, will lead to NMDA-receptor hypofunction due to reduced glutamate release and development of schizophrenic symptoms. Blockade of dopaminergic receptors with the antipsychotic drugs will reverse this effect. Consistent with this hypothesis, it has been shown that concomitant administration of the benzodiazepines is most effective in preventing emergence phenomena produced by ketamine.[40–42] The combination of ketamine–midazolam was reported to be more effective than ketamine–diazepam in reducing emergence reactions and had less effect in prolonging recovery.[43]

Furthermore, it has been shown by Farber et al that fetal rats and postnatal rats younger than 1.5 months (corresponding to puberty in these animals) are totally insensitive to the neurotoxic action of the NMDA antagonists. Between puberty and full adulthood, these animals gradually become fully sensitive to NMDA-receptor antagonist toxicity.[44] This age-dependent sensitivity is consistent with human studies that demonstrate a much lower incidence of emergence reactions in children than in adults following ketamine anesthetics.[34] Olney et al postulate that the neurocircuitry necessary for NMDA-receptor hypofunction effects may not be fully developed until after puberty.[36]

Another effect of ketamine that sets it apart from other parenteral anesthetics is its stimulatory effect on the cardiovascular system, despite a direct negative inotropic effect. It causes an increase in cardiac rate and in systemic and pulmonary vascular resistance, resulting in increased systemic and pulmonary blood pressure.[33,45,46] The concomitant administration of clonidine, a α_2-catecholamine receptor agonist that blocks the release of norepinephrine by sympathetic nerves, significantly reduces the sympathomimetic effects of ketamine.[47] Continuous infusion of esmolol, a β_1-receptor blocker, reduced the ionotropic and chronotropic effects on the heart in a dose-dependent manner.[48] Finally, cervical epidural local anesthetic blocks significantly blunted increases in cardiac rate and blood pressure.[49] There is also some evidence that ketamine has a direct adrenergic effect by binding directly to α- and β-adrenergic receptors.[50] These observations strongly suggest that the sympathomimetic effects of ketamine are due to a combination of centrally mediated increased sympathetic nervous system stimulation, a possible direct effect, and the effect of ketamine in blocking the reuptake of catecholamines. As with emergence phenomena, benzodiazepines have been reported to dampen the sympathomimetic effects of ketamine because of their central GABA-ergic inhibitory effects.[40,51,52] Cardiovascular stability has been reported in cardiac surgery patients under anesthesia induced by ketamine and diazepam or midazolam.[53,54] However, Marlow et al reported significant increases in heart rate and blood pressure following intubation of primarily hypertensive patients after induction of anesthesia with ketamine and midazolam.[55]

The effect of ketamine on cardiac rhythm is controversial. Several investigators have reported enhancement of myocardial sensitivity to catecholamines,[56–58] while others reported a decreased arrhythmogenic potential.[59,60] This suggests that ketamine produces a direct antiarrhythmic effect on the myocardium and an indirect arrhythmogenic effect by inducing a sympathomimetic effect. Clinical experience has demonstrated that cardiac dysrhythmias have rarely occurred under ketamine anesthesia.[61]

Ketamine is a mild respiratory depressant. Ketamine, in a dose-related manner, causes a shift of the CO_2 dose-response curve to the right but does not change the slope of the curve.[62] Respiratory drive to CO_2 may be depressed as much as 15 to 22%.[63] This effect is similar to that of opioids and unlike that of other parenteral sedative hypnotics, which also alter the slope of the curve. In one study, ketamine was administered intravenously at 3 mg/kg, followed by continuous infusion of 20 μg/kg/min.[64] Following induction, patients were intubated and allowed to breathe room air. Functional residual capacity, minute volume, and tidal volume were all maintained. Similar results have been reported in children.[63] Thus respiratory stimulation to hypercarbic drive remains intact at clinical doses but can be significantly depressed at higher doses. In addition, it has been shown that spontaneous respiration and muscular tone of the tongue and pharynx is well maintained. The protective airway reflexes, including coughing, sneezing, and swallowing, are not depressed.[65,66] Hence, endotracheal intubation is often unnecessary. However, rare cases of apnea, airway obstruction, and pulmonary as-

piration have been reported.[67–70] Ketamine, when used in combination with midazolam for pediatric anesthesia, has caused significant hypoxia.[71] Hence, close monitoring of patients by individuals capable of providing respiratory support is essential.

Salivary and tracheobronchial secretions are increased by ketamine. Ketamine has been shown to have antimuscarinic effects and to induce centrally mediated increased sympathomimetic effects.[14] Both of these effects would tend to decrease salivary flow. The mechanism responsible for the observed increased salivary flow, therefore, is believed to be centrally mediated. The superior salivatory nucleus receives excitatory afferent stimulatory inputs from several afferent neurons (ie, lingual and chorda tympani nerves) and from the cerebral cortex, which is believed to mediate conditioned reflexes.[72] In addition, several animals (eg, dog and rat) that control body temperature by hypersalivation also have inputs from the thermal centers of the anterior hypothalamus.[73] Ketamine appears to produce hypersalivation by stimulating cortical centers that have afferent inputs to the superior salivatory nucleus. The use of an antisialagogue (eg, glycopyrrolate or atropine) is recommended; these are equally efficacious in preventing secretions.[74] Ketamine is reported to be a potent bronchodilator. Asthmatic patients given ketamine have decreased bronchospasm and airway resistance.[75,76] The mechanism of this response is due to a combination of drug-induced increase in sympathetic stimulation, a direct smooth-muscle dilating effect, and decreased centrally mediated vagal outflow.

Ketamine produces epileptiform electroencephalogram patterns in the human limbic and thalamic regions, suggesting that ketamine is a proconvulsive agent. However, there is no evidence that ketamine effects cortical regions nor that clinical seizures are more likely to occur.[29] NMDA-receptor agonists have been shown, by increasing intracellular calcium, to either induce seizures or to lower the threshold of seizures to such stimuli as hypoxia.[77,78] As an NMDA-receptor antagonist, ketamine therefore would be expected to have anticonvulsant activity. Recent studies have suggested that ketamine is both anticonvulsant and neuroprotective.[7,79,80] However, because of species variation, animal data is difficult to interpret.[81] Consequently, the controversy over whether ketamine is a proconvulsant or anticonvulsant persists.

Ketamine has been reported to produce skeletal muscle hypertonicity and rigidity. In addition, many patients demonstrate random head or extremity movements unrelated to noxious stimulation. However, in most cases the severity of these phenomena has not been great enough to interfere with the procedure being performed.[2] The effect on muscle tonicity is dose related. Opisthotonus, generalized extensor spasm, has been reported after administration of 14 mg/kg and 19 mg/kg.[82] Both of these doses of ketamine are considerably greater than that used clinically. Ketamine has also been reported to increase the effect of muscle relaxants such as succinylcholine, *d*-tubocurarine, and pancuronium.[83,84]

The effect of ketamine on intraocular pressure remains controversial. Several authors report increases in intraocular pressure,[85–89] whereas others report no change in intraocular pressures.[90,91] The reason for this discrepancy is probably the fact that multiple factors may influence intraocular pressure. Intraocular pressure is under the dynamic balance of aqueous humor production by the ciliary body, the rate of elimination via the canal of Schlemm, the regulation and control of choroidal blood volume, the extraocular muscle tone, and the volume of vitreous humor. Dilation of choroidal blood vessels, relaxation of intraocular smooth muscle, and increased tension of extraocular muscles all tend to increase intraocular pressure. Ketamine is known to produce sympathomimetic effects via both central and peripheral mechanisms. Several investigators have reported increases in aqueous humor catecholamines in both humans and animals under ketamine anesthesia associated with an increase in intraocular pressure.[88,92–94] Ketamine is now most frequently used in combination with either a benzodiazepine or propofol that significantly obtunds the sympathomimetic effect. Norbury reported a significant decrease in intraocular pressure when ketamine was used in combination with flunitrazepam.[95] Cugini,[96] who administered ketamine in combination with droperidol and diazepam, reported similar results.

PEDIATRIC CLINICAL STUDIES

Cotsen et al[17] reported the clinical results of the safety and efficacy of ketamine anesthesia/sedation for 211 children between the ages of 3 days and 10 years who underwent short radiologic interventional procedures. One hundred fourteen patients were administered 2 mg/kg ketamine with 0.01 mg atropine intravenously (IV), and 97 patients were given 3 mg/kg ketamine with 0.02 mg/kg atropine intramuscularly (IM). The average induction time for the IV group was 45 seconds, and average induction time for the IM group was 4 minutes. Sedation was considered excellent in 191/211 (91%) of the patients. The sedation was considered light in the remaining 20 patients, but the procedures were still able to be performed. Pulse oximetry O_2 saturation was greater than 95% throughout the procedure in 200/211 (95%) patients. Transient desaturation below 95%, which was rapidly corrected by airway manipulation and supplemental oxygen via nasal cannula or face mask, occurred in 11

patients. Apnea occurred in 1 7-week-old patient born prematurely after 32 weeks gestation. Assisted ventilation was required for several respirations, and the patient promptly recovered. No patients required tracheal intubation. Only minor cardiovascular changes were noted in all patients. The average recovery time, after completion of the procedure, was 18 minutes for the IV group and 25 minutes for the IM group.

Pruit et al reported on the results of administering 3 mg/kg ketamine, 0.05 mg/kg midazolam, and 0.005 mg/kg glycopyrrolate IM to 37 children of both sexes between the ages of 12 months to 7 years who were to undergo oral-maxillofacial surgical procedures of 30 to 45 minutes duration in the emergency department.[61] An additional 1 mg/kg ketamine was administered IM if there was inadequate sedation. Twenty-six patients (70%) were rated as cooperative or sleeping with an average onset of 4.8 minutes (range, 3–10 minutes) after injection. The remaining 11 patients were crying or fighting intermittently. However, the surgical procedure was able to be completed for 6 of these patients without need for additional ketamine. The remaining 5 patients were given an additional 1 mg/kg IM within 10 minutes after the initial injection. Two of the children became completely cooperative, 2 were more tranquil, and 1 was unaffected. Sinus tachycardia was seen in most children, but no dysrhythmias were noted on continuous electrocardiogram monitoring. On average, there was an 18% increase in pulse rate. Respiratory rate also increased an average of 13% without any evidence of airway obstruction or laryngospasm; the O_2 saturation was greater than or equal to 96% in all cases. Two children (5%) developed emesis during recovery, but none did during the surgical procedure. One had clear liquids 30 minutes prior to drug administration, and the other experienced emesis after being discharged. Neither patient experienced any adverse effects, airway compromise, or aspiration as result of the emesis. Hypersalivation was observed in 4 patients (10%), 1 of whom required suctioning. Muscular hypertonicity and random movements were observed in 1 (3%) and 5 patients (14%), respectively. Holding the patient's head or using light restraints easily controlled the random movements. Finally, a transient hyperemic rash that did not require any intervention was seen in 4 patients (10%). The time from injection of drugs to discharge following recovery averaged 76 minutes (range, 50–120 minutes). Mild agitation was observed in 10 patients during recovery, and 1 patient had moderate agitation. However, no patient reported experiencing hallucinations or delirium. Ataxia was seen in all patients.

Similar results were reported in a smaller emergency-room based study.[97] Patients that varied in age from 6 months to 6 years were given ketamine 4 mg/kg and atropine 0.01 mg/kg IM. All patients were adequately sedated, according to the surgeon's evaluations. The onset of adequate sedation following drug administration was 3 to 4 minutes, average duration was 71 to 93 minutes, and time to recovery and discharge was 75 to 96 minutes. Heart rate increased an average of 24 beats/min, systolic blood pressure increased 12 mmHg, and diastolic blood pressure increased 7 mmHg. Respiratory rate was unchanged, and no patients required airway support or supplemental O_2. One patient experienced postoperative emesis, and 1 patient had bad dreams.

In another recent study,[98] 68 patients, ranging in age from 4 months to 17 years of age, were sedated for 350 procedures (74 lumbar punctures, 97 bone marrow aspirations or biopsies, 95 imaging studies, and 84 radiotherapy sessions). All were acceptably sedated and allowed the planned procedure to be performed. At least 90% were judged to be optimally sedated, as determined by both the parents and medical staff. In this study, patients were initially administered midazolam 0.05 mg/kg to 0.1 mg/kg IV with a maximum single dose of 2 mg and a total dose of 4 mg. This was followed 2 to 5 minutes later with 1.0 to 2.0 mg/kg ketamine IV. An additional 0.5 to 1.0 mg ketamine IV was administered, as needed, to a maximum total dose of 6 mg/kg. An antisialagogue was not administered. No serious complications were encountered; no patient required intubation, bag or mask ventilation, or pharmacologic reversal of dissociative anesthesia. Cardiac parameters were relatively stable. Systolic blood pressure increased on average 10 mmHg, and diastolic blood pressure increased 5 mmHg, associated with an increase in heart rate of 10 to 15 beats/min. Respiratory rates decreased on average 3 to 4 breaths per minute. Pulse oximetry demonstrated a 2 to 6% decrease in O_2 saturation in 70% (245/350) of the patients. This occurred within 1 to 2 minutes after ketamine administration and returned to baseline within another 1 to 2 minutes. Decreasing the frequency or dose of ketamine administered attenuated this effect. Four patients (1%) experienced a significant drop in O_2 saturation below 85% that required interruption of the procedure and stimulation of the patient to correct the hypoxia. All patients developed increased oral secretions, several requiring oral suctioning. A transient macular rash was noted in 12% of the patients. However, none developed urticaria, wheezing, or any sign of laryngeal obstruction. Only 2 patients experienced agitation during recovery, and 2 patients reported transient sleep disturbances. Emesis occurred in 8 (3%) of 276 patients who did not have lumbar punctures. All emesis occurred during the recovery period when the patients were awake. After completion of the procedure, recovery time varied between 15 and 120 minutes, with 70% of patients recovering in less than 30 minutes.

Ketamine has also been successfully used via the nasal

route of administration, either used alone or in combination with midazolam. In one study, 30 children requiring dental treatment were randomly assigned to 1 of 3 groups. Group 1 received 3mg/kg ketamine; group 2 received midazolam 0.4 mg/kg, and group 3 received either 1.5 or 1.0 gg/kg sufentanil. All drugs were administered intranasally.[21] Sedation was evaluated utilizing a 10-point scale, with 1 being hysterical or untreatable, 5 being ideal sedation, and 10 being obtunded and desaturated, requiring airway management. Midazolam produced acceptable sedation with a mean sedation score of 4. Desaturation below 90% SaO_2 by pulse oximetry was not observed. Ketamine also provided adequate sedation with a mean sedation score of 4, but 2 children experienced brief periods of desaturation below 90%. Sufentanil 1.5 mg/kg produced much more deeply sedated children, with a mean sedation score of 7. There was a high incidence of desaturation below 80%. In addition, recovery time was significantly longer than the other 2 agents. The 1 mg/kg sufentanil doses produced results similar to the other 2 agents. Similar acceptable results were reported by Diaz, who administered 3mg/kg intranasally, and by Louon, who administered 5 mg/kg ketamine plus 0.56 mg/kg midazolam intranasally.[20,99]

Several studies have reported successful use of ketamine alone and in combination with midazolam administered via the oral route.[19,27,28] The dose of ketamine varied from 5 to 12.5 mg/kg. Most children were rated as having good to excellent sedation. Amnesia was more reliably produced when ketamine was administered. Ketamine also produced superior anxiolysis and analgesia than midazolam alone. However, significant respiratory depression was reported at the higher doses of ketamine, especially when midazolam was used in combination with ketamine.

Finally, ketamine has also been successfully administered via the rectal route of administration. Lokken reported a crossover study in which children between the ages of 1 and 7 were given either ketamine in combination with midazolam (1.0 mg/kg ketamine plus 0.3 mg/kg midazolam) or 0.3 mg/kg midazolam alone.[22] Sedation was rated as good to excellent in 16/24 children who received midazolam alone versus 18/24 with ketamine added. However, the investigators reported that ketamine provided improved amnesia, anxiolysis, and significant analgesia. Similar results were reported by Van Der Bijl, who administered 0.3 mg/kg midazolam plus 5 mg/kg ketamine.[100]

It is apparent from the results of these recent studies and from the experience with ketamine reported in the literature over the past 35 years that ketamine is both safe and effective as a pediatric dissociative anesthetic/sedative agent. Especially when combined with a low dose of a benzodiazepine (ie, midazolam) and an antisialagogue (ie, glycopyrrolate or atropine), ketamine provides excellent anxiolysis, dissociative anesthesia, and analgesia while reducing the incidence and severity of dysphoric reactions and hypersecretion. Ketamine, even when combined with midazolam and an antisialagogue, can be administered via both enteral and parenteral routes, obviating the need for IV access. This makes it a versatile, safe, and efficacious agent that cannot be matched by any other in treating the fearful, uncooperative pediatric patient. Dissociative anesthesia is achieved rapidly, using either the IM or IV route of administration, and recovery time to discharge after drug administration varies from 30 to 120 minutes. After induction, maintenance of anesthesia can be achieved by continuous infusion of 1 to 2 mg/kg/h instead of incremental doses of 0.5 to 1.0 mg/kg.[101] Nasal, oral, and rectal administration has also been shown to provide effective sedation. The incidence and severity of adverse events is remarkably low. However, significant hypoxic events have been reported, although all responded rapidly to appropriate intervention and none required tracheal intubation. Other frequent adverse events include postoperative emesis, agitation during recovery, and occasional bad dreams. Therefore, continuous monitoring and vigilance by personnel trained in the administration of deep sedation and general anesthesia is essential to

Table 4. Protocols for the Administration of Ketamine for Pediatric Sedation/Dissociative Anesthesia

Method	*Dose*
Nasal administration[a]	Midazolam 0.5 mg/kg Atropine 0.02 mg/kg Ketamine 5.0 mg/kg
Oral administration[b]	Ketamine 5–10 mg/kg in small-volume elixir
Rectal administration[b]	Midazolam 0.30 mg/kg Ketamine 5 mg/kg Atropine 0.02 mg/kg[c]
Intramuscular administration[d]	Midazolam 0.05 mg/kg Atropine 0.01 mg/kg Ketamine 3.0 mg/kg
Intravenous administration	Midazolam 0.05–0.10 mg/kg[e] Atropine 0.01 mg/kg Ketamine 1.0–2.0 mg/kg[f]

[a] Dilute to 2 mL with saline, and administer 1 mL in each nares; allow 15 min for onset of sedation.

[b] Allow 30 min for onset of sedation.

[c] Optional.

[d] An additional 1.0 mg/kg of Ketamine may be injected if dissociative anesthesia is inadequate within 10 min of initial dose; allow 5–10 min for onset of dissociative anesthesia.

[e] To onset sedation (maximum single dose of 2 mg; maximum total dose of 4 mg).

[f] An additional 0.5–1.0 mg/kg may be added if dissociative anesthesia is inadequate (maximum single dose of 2 mg). Instead of incremental doses of 0.5–1.0 mg/kg, a continuous infusion of 1–2 mg/kg/h may also be used for maintenance.

permit early detection of complications and the institution of effective remedial steps (Table 4).

REFERENCES

1. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic in man. *Clin Pharmacol Ther.* 1965;6:279–291.
2. White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic uses. *Anesthesiology.* 1982;56:119–136.
3. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by *N*-methyl-aspartate. *Br J Pharmacol.* 1983;79:565–575.
4. Collingridge GL, Singer W. Excitatory amino acid receptors and synaptic plasticity. *Trends Pharmacol Sci.* 1990; 11:290–296.
5. Brambilla R, Gnesutta N, Minichiello L, et al. A role for the Ras signaling pathway in synaptic transmission and long-term memory. *Nature.* 1997;390(6657):281–286.
6. Cotman CW, Monaghan DT, Ottersen OP, Storm-Mathisen J. Anatomic organization of excitatory amino acid receptors and their pathways. *Trends Neurosci.* 1987;10:273–280.
7. Sagratella S. NMDA antagonists: antiepileptic-neuroprotective drugs with diversified neuropharmacological profiles. *Pharmacol Res.* 1995;32:1–13.
8. Farb CR, LeDoux JE. NMDA and AMPA receptors in the lateral nucleus of the amygdala are postsynaptic to auditory thalamic afferents. *Synapse.* 1997;27:106–121.
9. Hatfield T, Gallagher M. Taste-potentiated odor conditioning: impairment produced by infusion of an *N*-methyl-D-aspartate antagonist into basolateral amygdala. *Behav Neurosci.* 1995;109:663–668.
10. Herrling PL, Morris R, Salt TE. Effects of excitatory amino acids and their antagonist on membrane and potential of cat caudate neurons. *J Physiol.* 1983;339:207–222.
11. Bashir ZI, Alford S, Davies SN, Randall AD, Collingridge GL. Long-term potentiation of NMDA receptor-mediated synaptic transmission in the hippocampus. *Nature.* 1991;349(6305):56–58.
12. Li H, Weiss SR, Chuang DM, Post RM, Rogawski MA. Bidirectional synaptic plasticity in the rat basolateral amygdala: characterization of an activity-dependent switch sensitive to the presynaptic metabotropic glutamate receptor antagonist 2*S*-alpha-ethylglutamic acid. *J Neurosci.* 1998;18:1662–1670.
13. Izquierdo I, Medina JH. Correlation between the pharmacology of long-term potentiation and the pharmacology of memory. *Neurobiol Learn Mem.* 1995;63:19–32.
14. Durieux ME. Inhibition by ketamine of muscarinic acetylcholine receptor function. *Anesth Analg.* 1995;81:57–62.
15. Smith DJ, Pekow GM, Martin LL, Coalgate B. The interaction of ketamine with the opiate receptor. *Life Sci.* 1980;26(10):789–795.
16. Lundy PM, Lockwood PA, Thompson G, Frew R. Different effects of ketamine isomers on neuronal and extraneuronal catecholamine uptake mechanisms. *Anesthesiology.* 1986;64:359–363.
17. Cotsen MR, Donaldson JS, Uejima T, Morello FP. Efficacy of ketamine hydrochloride sedation in children for interventional radiologic procedures. *Am J Roentgenol.* 1997; 169:1019–1022.
18. Lu DP, Lu GP, Reed JFR. Safety, efficacy, and acceptance of intramuscular sedation: assessment of 900 dental cases. *Compendium.* 1994;15:1348, 1350, 1352, 1362.
19. Alderson PJ, Lerman J. Oral premedication for paediatric ambulatory anaesthesia: a comparison of midazolam and ketamine. *Can J Anaesth.* 1994;41:221–226.
20. Louon A, Reddy VG. Nasal midazolam and ketamine for paediatric sedation during computerised tomography. *Acta Anaesthesiol Scand.* 1994;38:259–261.
21. Abrams R, Morrison JE, Villasenor A, Hencmann D, Da Fonseca M, Mueller W. Safety and effectiveness of intranasal administration of sedative medications (ketamine, midazolam, or sufentanil) for urgent brief pediatric dental procedures. *Anesth Prog.* 1993;40:63–66.
22. Lokken P, Bakstad OJ, Fonnelop E, et al. Conscious sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. *Scand J Dent Res.* 1994;102:274–280.
23. Domino EF, Domino SE, Smith RE. Ketamine kinetics in unmedicated and diazepam premedicated subjects. *Clin Pharmacol Ther.* 1984;36:645–653.
24. Ebert B, Mikkelsen S, Thorkildsen C, Borgbjerg FM. Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *Eur J Pharmacol.* 1997;333:99–104.
25. Adams JD, Baillie TA, Trevor AJ, Castagnoli N. Studies on the biotransformation of ketamine—identification of metabolites produced in vitro in rat liver microsomal preparations. *Biomed Mass Spectrom.* 1981;8:527–538.
26. Grant IS, Nimmo WS, McNicol LR, Clements JS. Ketamine disposition in children and adults. *Br J Anaesth.* 1983; 55:1107–1111.
27. Qureshi FA, Mellis PT, McFadden MA. Efficacy of oral ketamine for providing sedation and analgesia to children requiring laceration repair. *Pediatr Emerg Care.* 1995;11:93–97.
28. Roelofse JA, Joubert JJ, Swart LC, Stander I, Roelofse PG. An evaluation of the effect of oral ketamine and standard oral premedication in the sedation of paediatric dental patients. *J Dent Assoc S Afr.* 1996;51:197–201.
29. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth.* 1980; 36:186–197.
30. Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J. Differential psychopathology and patterns of cerebral glucose utilization produced by (*S*)- and (*R*)-ketamine in healthy volunteers using positron emission tomography (PET). *Eur Neuropsychopharmacol.* 1997;7:25–38.
31. Zeilhofer HU, Swandulla D, Geisslinger G, Brune K. Differential effects of ketamine anantiomer on NMDA recep-

tor currents in cultured neurons. *Eur J Pharmacol.* 1992;213: 155–158.

32. Adams HA, Bauer R, Gebhardt B, Menke W, Baltes-Gotz B. Total IV anesthesia with *S*-(+)-ketamine in orthopedic geriatric surgery. Endocrine stress reaction, hemodynamics and recovery. *Anaesthesist.* 1994;43:92–100.

33. Geisslinger G, Hering W, Thomann P, Knoll R, Kamp HD, Brune K. Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. *Br J Anaesth.* 1993;70:666–671.

34. White PF, Ham J, Way WL. Pharmacology of ketamine isomers in surgical patients. *Anesthesiology.* 1980;52:231.

35. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry.* 1994;51:199–214.

36. Olney JW, Farber MD, Nuri B. Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry.* 1995; 52:998–1007.

37. Sharp FR, Butman M, Koistinaho J, et al. Phencyclidine induction of the hsp 70 stress gene in injured pyramidal neurons is mediated via multiple receptors and voltage gated calcium channels. *Neuroscience.* 1994;62:1079–1092.

38. Rowlands GC, Roberts PJ. Activation of dopamine receptors inhibits calcium dependent glutamate release from cortico-striatal terminals in vitro. *Eur J Pharmacol.* 1980;62: 241–247.

39. Maura G, Carbone R, Raiteri M. Release-regulating D-2 dopamine receptors are located on striatal glutamatergic nerve terminals. *J Pharmacol Exp Ther.* 1988;247:680–684.

40. Cartwright PD, Pingel SM. Midazolam and diazepam in ketamine anesthesia. *Anaesthesia.* 1984;59:439–442.

41. Mattila MA, Larni HM, Nummi SE, Pekkola PO. Effect of diazepam on emergence from ketamine anaesthesia. A double-blind study. *Anaesthesist.* 1979;28:20–23.

42. Freuchen I, Ostergaard J, Kuhl JB, Mikkelsen BO. Reduction of psychotomimetic side effects of Ketalar (ketamine) by Rohypnol (flunitrazepam). A randomized, double-blind trial. *Acta Anaesthesiol Scand.* 1976;20:97–103.

43. Toft P, Romer U. Comparison of midazolam and diazepam to supplement total intravenous anaesthesia with ketamine for endoscopy. *Can J Anaesth.* 1987;34:466–469.

44. Farber NB, Price MT, Labruyere J, Fuller TA, Olney JW. Age dependency of NMDA antagonist neurotoxicity. *Soc Neurosci Abstracts.* 1992;18:1148.

45. Jacobson JD, McGrath CJ, Smith EP. Cardiorespiratory effects of induction and maintenance of anesthesia with ketamine–midazolam combination, with and without prior administration of butorphanol or oxymorphone. *Am J Vet Res.* 1994;55:543–550.

46. Appel E, Dudziak R, Palm D, Wnuk A. Sympathoneuronal and sympathoadrenal activation during ketamine anesthesia. *Eur J Clin Pharmacol.* 1979;16:91–95.

47. Munro HM, Sleigh JW, Paxton LD. The cardiovascular response to ketamine: the effects of clonidine and lignocaine. *Acta Anaesthesiol Scand.* 1993;37:75–78.

48. Gold MI, Brown M, Coverman S, Herrington C. Heart rate and blood pressure effects of esmolol after ketamine induction and intubation. *Anesthesiology.* 1986;64:718–723.

49. Mayumi T, Dohi S, Takahashi T. Cardiovascular effects of ketamine in humans with cervical or lumbar epidural blockade. *Anesthesiology.* 1985;62:39–43.

50. Bevan RK, Rose MA, Duggan KA. Evidence for direct interaction of ketamine with alpha 1- and beta 2-adrenoceptors. *Clin Exp Pharmacol Physiol.* 1997;24:923–926.

51. Kumar SM, Kothary SP, Zsigmond EK. Plasma free norepinephrine and epinephrine concentration following diazepam–ketamine induction in patients undergoing cardiac surgery. *Acta Anaesth Scand.* 1978;22:593–600.

52. Soltis RP, Cook JC, Gregg AE, Sanders BJ. Interaction of GABA and excitatory amino acids in the basolateral amygdala: role in cardiovascular regulation. *J Neurosci.* 1997; 17:9367–9374.

53. Jackson APF, Dhadphale PR, Callaghan ML. Haemodynamic studies during induction of anaesthesia for open heart surgery using diazepam and ketamine. *Br J Anaesth.* 1978;50:375–377.

54. Tuman KJ, McCarthy RJ, Ivankovich AD. Perioperative hemodynamics using midazolam–ketamine for cardiac surgery. *Anesth Analg.* 1988;67:s238.

55. Marlow R, Reich DL, Neustein S, Silvay G. Haemodynamic response to induction of anaesthesia with ketamine/midazolam. *Can J Anaesth.* 1991;38:844–848.

56. Hamilton JT, Bryson JS. The effect of ketamine on transmembrane potentials of Purkinje fibers of the pig heart. *Br J Anaesth.* 1974;46:636–642.

57. Bednarski RM, SRA, Majors LJ. Reduction of the ventricular arrhythmogenic dose of epinephrine by ketamine administration in halothane-anesthetized cats. *Am J Vet Res.* 1988;49:350–354.

58. Cabbabe EB, Behbahani PM. Cardiovascular reactions associated with the use of ketamine and epinephrine in plastic surgery. *Ann Plast Surg.* 1985;15:50–56.

59. Koehntop DE, Liao JC, Van Bergen FH. Effects of pharmacologic alterations of adrenergic mechanisms of cocaine, tropolone, aminophylline, and ketamine on epinephrine-induced arrhythmias during halothane–nitrous oxide anesthesia. *Anesthesiology.* 1977;46:83–93.

60. Aya AG, Robert E, Bruelle P, et al. Effects of ketamine on ventricular conduction, refractoriness, and wavelength: potential antiarrhythmic effects—a high-resolution epicardial mapping in rabbit hearts. *Anesthesiology.* 1997;87:1417–1427.

61. Pruitt JW, Goldwasser MS, Sabol SR, Prstojevich SJ. Intramuscular ketamine, midazolam, and glycopyrrolate for pediatric sedation in the emergency department [see comments]. *J Oral Maxillofac Surg.* 1995;53:13–17; discussion 18.

62. Bourke DL, Malit LA, Smith TC. Respiratory interactions of ketamine and morphine. *Anesthesiology.* 1987;66: 153–156.

63. Hamza J, Ecoffey C, Gross JB. Ventilatory response to CO_2 following intravenous ketamine in children. *Anesthesiology.* 1989;70:422–425.

64. Mankikian B, Cantineau JP, Sartene R. Ventilatory pattern of chest wall mechanics during ketamine anesthesia in humans. *Anesthesiology.* 1986;65:492–499.

65. Green SM, Nakamura R, Johnson NE. Ketamine sedation for pediatric procedures. Part I: A prospective series. Part II: Review and implications. *Ann Emerg Med.* 1990;19: 1024–1046.

66. Drummand GB. Comparison of sedation with midazolam and ketamine: effects on airway muscle activity. *Br J Anaesth.* 1996;76:663–667.

67. Green SM, Rothrock SG. Transient apnea with intramuscular ketamine [letter; comment]. *Am J Emerg Med.* 1997;15:440–441.

68. van Wijhe M, Stricker BHC, Rejger VS. Prolonged apnoea with ketamine. *Br J Anaesth.* 1986;58:573–574.

69. Penrose BH. Aspiration pneumonia following ketamine induction for general anesthesia. *Anesth Analg.* 1972; 51:41–43.

70. Litman RS. Apnea and oxyhemoglobin desaturation after intramuscular ketamine administration in a 2-year-old child [letter; comment]. *Am J Emerg Med.* 1997;15:547–548.

71. Roelofse JA, Roelofse PG. Oxygen desaturation in a child receiving a combination of ketamine and midazolam for dental extractions. *Anesth Prog.* 1997;44:68–70.

72. Ishizuka K, Murakami T. Cortically evoked responses of superior salivary nucleus neurons in the cat. *Proc Finn Dent Soc.* 1989;85:355–359.

73. Furuyama F, Murakami M, Oiwa T, Nishino H. Differences in thermal salivation between the FOK rat (a model of genotypic heat adaptation) and 3 other rat strains. *Physiol Behav.* 1998;63:787–793.

74. Morgansen F, Mueller D, Valentin N. Glycopyrrolate during ketamine/diazepam anaesthesia. *Acta Anaesthesiol Scand.* 1986;30:332–336.

75. Corssen G, Gutierrez J, Reves JG. Ketamine in the anesthetic management of asthmatic patients. *Anesth Analg.* 1972;81:588–596.

76. Strube PJ, Hallam PL. Ketamine by continuous infusion in status asthmaticus. *Anaesthesia.* 1986;41:1017–1019.

77. Chen CH, Chen AC, Liu HJ. Involvement of nitric oxide and *N*-methyl-D-aspartate in acute hypoxic altitude convulsion in mice. *Aviat Space Environ Med.* 1997;68:296–299.

78. Matsumoto I, Davidson M, Wilce PA. Polyamine-enhanced NMDA receptor activity: effect of ethanol. *Eur J Pharmacol.* 1993;247:289–294.

79. Church J, Zeman S, Lodge D. The neuroprotective action of ketamine and MK-801 after transient cerebral ischemia in rats. *Anesthesiology.* 1988;69:702–709.

80. Pfenninger E, Himmelseher S. Neuroprotection by ketamine at the cellular level: Review [in German]. *Anaesthesist.* 1997;46(suppl 1):47–54.

81. Kugler J, Doenicke A. Ketamine—anticonvulsive and proconvulsive actions. *Anaesthesist.* 1994;43(suppl 2):S2–S7.

82. Radnay PA, Badola RP. Generalized extensor spasm in infants following ketamine anesthesia. *Anesthesiology.* 1973;39:459–460.

83. Cronnelly R, Dretchen KL, Sokoll MD, Long JP. Ketamine myoneural activity and interaction with neuromuscular blocking agents. *Eur J Pharm.* 1973;22:17–22.

84. Tsai SK, Lee C. Ketamine potentiates nondepolarizing neuromuscular relaxants in a primate. *Anesth Analg.* 1989; 68:5–8.

85. Corssen G, Hoy JE. A new parenteral anesthetic CI 581: its effect on intraocular pressure. *J Pediatr Ophthalmol.* 1967;4:20–21.

86. Yoshikawa K, Murai Y. The effect of ketamine on intraocular pressure in children. *Anesth Analg.* 1971;50:199–202.

87. Adams AK. Ketamine in paediatric ophthalmic practice. *Anaesthesia.* 1973;28:212–213.

88. Cooper RL, Constable IJ, Davidson L. Aqueous humor catecholamines. *Curr Eye Res.* 1984;3:809–813.

89. Schaffer J, Lindner J, Piepenbrock S. Propofol, isoflurane and neuroleptanesthesia. Ophthalmic surgery in geriatric patients. *Anaesthesist.* 1993;42:149–156.

90. Peuler M, Glass DD, Arens JF. Ketamine and intraocular pressure. *Anesthesiology.* 1975;43:575–578.

91. Ausinsch B, Rayburn RL, Munson ES. Ketamine and intraocular pressure in children. *Anesth Analg.* 1976;55: 773–775.

92. Antal M, Mucsi G, Faludi A. Ketamine anesthesia and intraocular pressure. *Ann Ophthalmol.* 1978;10:1281–1284, 1289.

93. Bar-llan A, Pessah NI. On the use of ketamine in ocular pharmacological studies. *J Ocul Pharmacol.* 1986;2: 335–344.

94. Gallar J, Liu JH. Stimulation of the cervical sympathetic nerves increases intraocular pressure. *Invest Ophthalmol Vis Sci.* 1993;34:596–605.

95. Norbury A, Rocke AD, Brock-Utne JG, Mackenzie R, Welsh N, Downing JW. Balanced total intravenous anaesthesia and intraocular pressure. *Anaesth Intensive Care.* 1981;9: 255–259.

96. Cugini U, Lanzetta P, Nadbath P, Menchini U. Sedation with ketamine during cataract surgery. *J Cataract Refract Surg.* 1997;23:784–786.

97. Petrack EM, Marx CM, Wright MS. Intramuscular ketamine is superior to meperidine, promethazine, and chlorpromazine for pediatric emergency department sedation. *Arch Pediatr Adolesc Med.* 1996;150:676–681.

98. Parker RI, Mahan RA, Giugliano D, Parker MM. Efficacy and safety of intravenous midazolam and ketamine as sedation for therapeutic and diagnostic procedures in children [see comments]. *Pediatrics.* 1997;99:427–431.

99. Diaz JH. Intranasal ketamine preinduction of paediatric outpatients. *Paediatr Anaesth.* 1997;7:273–278.

100. Van Der Bijl P, Roelofse JA, Stander IA. Rectal ketamine and midazolam for premedication in pediatric dentistry. *J Oral Maxillofac Surg.* 1991;49:1050–1054.

101. Hartvig PJ. Postoperative analgesia and sedation following pediatric cardiac surgery using a constant infusion of ketamine. *J Cardiothorac Vasc Anesth.* 1993;7:148–153.