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BRIEF REVIEW

Ketamine: A Review of Its Pharmacologic Properties and Use in Ambulatory Anesthesia

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The administration of intravenous agents is the most commonly used method in Canada and the United States to produce sedation or general anesthesia for dental procedures. Ketamine, a dissociative anesthetic, has several advantageous physical, pharmacokinetic, and pharmacodynamic properties. It can be used to induce anesthesia, sedation, analgesia, and amnesia. Ketamine can maintain functional residual capacity, induce bronchodilation, and avoid cardiovascular depression. However, adverse effects have been demonstrated, such as cardiovascular stimulation and unpleasant emergence phenomena, both of which may be modulated by supplementation with benzodiazepines. An increase in the use of ketamine for ambulatory anesthesia has recently been advocated. This review of the literature supports the use of ketamine as an effective agent for selected anesthetic procedures.

The intravenous route of drug administration is the most commonly used means to accomplish ambulatory anesthesia in dentistry in Canada and the United States. The goal of continually improving anesthetic care has fostered pursuit of the ideal intravenous agent, which would possess the properties outlined in Table 1.[1] Drugs such as the opioids, benzodiazepines, and barbiturates meet some, but not all, of these criteria. The phencyclidine derivative ketamine (Ketalar) appears to possess many of these desired properties. Although not widely used in the past, it is now being employed to an increasingly greater extent, including use in outpatient dental anesthesia.[2,3] Ketamine has a rapid, smooth onset of action and predictable duration of effect. Allergic reactions and pain and irritation upon parenteral administration are rarely observed. Although it exhibits many of the desired physical properties of an ideal agent,[1] does it have the ideal pharmacodynamic and pharmacokinetic profile? In particular, what are ketamine's effects on the central nervous system (CNS), respiratory system, and cardiovascular system? Since its introduction more than 25 yr ago, numerous clinical and laboratory investigations have been reported. This article briefly reviews the literature concerning the pharmacodynamics and pharmacokinetics of ketamine as well as its clinical applications for ambulatory anesthesia in dentistry.

PHARMACODYNAMIC PROFILE

Central Nervous System Effects

The pharmacodynamic actions of ketamine are summarized in Table 2. The major effects of ketamine administration involve the CNS. This agent produces a unique state that has been described as "dissociative anesthesia" and is characterized by profound analgesia, amnesia, and catalepsy. The dissociation component refers to a functional and electrophysiological separation of the thalamoneocortical and limbic systems. In this state it is believed that the brain fails to correctly transduce afferent impulses because of disruption in normal communications between the sensory cortex and the association areas. The result resembles catalepsy in which the eyes may remain open with slow nystagmus and intact corneal reflexes. Patients are generally noncommunicative though they may appear to be awake. Varying degrees of skeletal muscle hypertonus may be present. Nonpurposeful skeletal muscle movements may occur independently of surgical stimulation. Unlike the use of intravenous barbiturates for the induction of anesthesia, it is often difficult to assess a clear endpoint when ketamine is administered. Ketamine poses a unique problem when assessing the level of sedation or anesthesia because one cannot use eye signs, degree of muscle tone, or patient movement as indicators; keta-

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Table 1. Characteristics of an Ideal Intravenous Anesthetic Agent[a]

Physical Properties	*Pharmacokinetic Properties*	*Pharmacodynamic Properties*
Soluble in water	Rapid onset of action	Effective in inducing anesthesia
Stable in solution	Ability to titrate	Anxiolytic at subanesthetic doses
Absence of pain on injection	Predictable duration of effect	Analgesic at subanesthetic doses
Absence of postinjection irritation	Short elimination half-life	Amnestic at subanesthetic doses
		Minimal respiratory effects
		Minimal cardiovascular effects

[a] Adapted, in part, from White et al.[1]

mine's effects on these characteristics are not consistent with the classic signs of anesthesia.

Ketamine likely interacts with more than one type of pharmacologic receptor to produce its effects. The analgesia appears to be at least partially mediated by opioid receptors at brain, spinal, and peripheral sites. Ketamine binds preferentially to the mu, rather than the delta, opioid receptor.[4] A state of cross-tolerance to morphine has been demonstrated.[5] Ketamine has also been shown to interact with sigma/phencyclidine binding sites,[6] yet the analgesic effect appears to be specific to the established opioid receptor sites.[7] The sigma/phencyclidine component may mediate the dysphoria that can be induced by ketamine.

It has been suggested that ketamine's site of action involves the N-methyl-D-aspartate (NMDA) receptor. These receptors play a major role in the transmission of sensory information and are thought to mediate the excitation of neurons in the CNS secondary to interactions with excitatory amino acid neurotransmitters. NMDA inhibition produces catalepsy, consistent with the effect of ketamine administration. Ketamine has been shown to be a potent noncompetitive NMDA antagonist, and it is suggested that this may be the mechanism for its anesthetic and behavioral effects.[8]

In addition to its other effects, ketamine potentiates the effect of neuromuscular blocking drugs in a dose-dependent manner.[9] The mechanism may include interaction with muscarinic cholinergic receptors.[10–12] Although ketamine can activate epileptiform foci in patients with known seizure disorders,[13] it paradoxically appears to possess anticonvulsant properties.[14,15]

Emergence phenomena have been the most frequently reported adverse effects of ketamine. These reactions are described as a feeling of floating, vivid dreams, hallucinations, and delerium.[16] The reported incidence varies from less than 5% to greater than 30%.[16–19] These reactions appear more commonly in patients over the age of 16 yr, in females, and following brief procedures. They also appear to be related to the dose and rate of drug administration.[20] The use of benzodiazepines has been advocated to reduce these reactions,[21] as discussed below.

Ketamine potently vasodilates cerebral blood vessels, increasing cerebral blood flow by 62%[22] to 80%.[23] This, in turn, is responsible for documented increases in intracranial pressure in patients with compromised intracranial compliance.[24] This effect is reduced if diazepam, midazolam, or thiopental is administered before the ketamine.[25] Nevertheless, increased cerebrospinal fluid pressure contraindicates the use of ketamine.

Respiratory Effects

The administration of ketamine results in unusual respiratory effects when compared with other anesthetic agents. In spontaneously breathing patients, administration of most general anesthetic drugs causes an immediate decrease in the functional residual capacity (FRC), which results in an increase in the arterial-alveolar oxygen difference.[26] As lung volume decreases during expiration, the small, thinned-wall airways in the dependent regions of the lungs have a tendency to collapse. The volume at which airway closure occurs is defined as the closing capacity. The effect of FRC maintenance is to ensure inflation of these dependent portions of the lungs. This is particularly important in children, as the closing capacity is closer to the FRC than it is in

Table 2. Pharmacodynamic Effects of Ketamine

Central Nervous System	*Respiratory System*	*Cardiovascular System*
Anesthesia	Maintenance of FRC	Increase in cardiac output
Analgesia	Bronchodilation	Increase in heart rate
Amnesia	Stimulation of secretions	Increase in blood pressure
Emergence phenomena	Mild depression	

adults. In children, small decreases in FRC can result in airway closure during normal tidal breathing, which can produce ventilation-perfusion abnormalities clinically seen as a drop in oxygen saturation. Ketamine appears to be unique in its ability to maintain FRC upon induction of anesthesia,[27,28] thereby decreasing the chances of intraoperative hypoxemia.[26,29]

During ketamine anesthesia in spontaneously breathing patients, the minute ventilation may be maintained at the same level as in the awake state.[30] Moreover, there may be minimal changes in gas exchange and an absence of atelectasis and shunting. It appears that, because skeletal muscular tone is maintained during ketamine anesthesia (unlike the case with the volatile agents), atelectasis or changes in ventilation-perfusion and FRC do not occur. With spontaneously breathing patients, unlike mechanically ventilated patients, the anesthesiologist has minimal control over these changes due to the inability to supply positive airway pressure. This is important in dental anesthesia, as changes in any of these parameters can result in a decrease in oxygen saturation.

Ketamine's overall effect on respiration is a matter of controversy. Studies have demonstrated ketamine to be both a respiratory stimulant[31] and a respiratory depressant.[32] However, only the study showing ketamine to be a respiratory depressant appeared to properly assess the ventilatory response. Ketamine has other beneficial effects on the respiratory apparatus, including increased lung compliance and decreased airway resistance. The mechanism supporting these effects is not currently understood. Bronchodilation induced by ketamine is not affected by histamine, acetylcholine, potassium chloride, propranolol, or indomethacin, each of which would implicate a specific system influencing bronchial tone.[33] Ketamine may possess calcium-channel blocking properties mediated by a dose-dependent inhibition of extracellular calcium transport.[34]

Ketamine is reported to be a safe agent for the asthmatic patient because it can protect against bronchospastic attacks and resolve symptoms of acute asthma present at the time of induction.[35,36] It has even been used successfully by continuous infusion for the treatment of asthma unresponsive to conventional approaches.[37,38] The use of ketamine in spontaneously breathing patients with a history of asthma would therefore appear to be indicated, although specific studies to support this have not been performed to date.

While ketamine is reported to maintain laryngeal tone and reflexes, there are reported cases of pulmonary aspiration.[39] Ketamine is a potent stimulator of salivary and tracheobronchial secretions, and diligent suction of the oral cavity is required in the nonintubated patient to decrease the possibility of coughing and aspiration and to prevent laryngospasm. The antimuscarinic agents glycopyrrolate and atropine are equally effective in reducing these secretions.[40]

Cardiovascular Effects

Ketamine differs from most anesthetic agents in that it appears to stimulate the cardiovascular system, producing increases in heart rate, cardiac output, and blood pressure.[29,31,32,41] The mechanism for this effect is not well understood, as ketamine has been shown to depress myocardial contractility directly.[42] The observed cardiovascular stimulation can be blocked by α- and β-adrenoceptor antagonists as well as by the calcium-channel blocker verapamil.[42,43] The clinical effect of ketamine's direct negative inotropic effect is likely masked by an induction of central sympathetic stimulation.[41] Alternatively, ketamine's ability to increase circulating catecholamine concentrations, putatively by inhibiting neuronal reuptake, may also override the negative inotropism.[44] Benzodiazepines are reported to attenuate these effects.[45]

The sympathomimetic effects would be expected to increase myocardial oxygen demand, and therefore ketamine is contraindicated in patients with significant ischemic heart disease.[46] Furthermore, ketamine's cardiovascular-stimulating effects would contraindicate use in patients where an elevation of blood pressure should be avoided, such as those with a history of significant hypertension or cerebrovascular accident.

Cardiac dysrhythmias are uncommon following ketamine administration, although some animal studies suggest that ketamine sensitizes the myocardium to the dysrhythmogenic effects of epinephrine.[47] At present, there is no definitive information on the effect of ketamine on heart rhythm.

Due to its cardiovascular effects, particularly its ability to maintain arterial blood pressure, ketamine has been advocated for use in young patients with cyanotic congenital heart disease, hypovolemic patients, and those in cardiogenic shock.[48,49] In children with cyanotic congenital heart disease, the amount of oxygen that can be taken up by the lung is related to the pulmonary blood flow. Ketamine has been used to decrease right-to-left intracardiac shunting, thus maximizing the pulmonary blood flow and the arterial oxygen tension (PaO_2).

PHARMACOKINETIC PROFILE

Ketamine may be administered by the intravenous, intramuscular, oral, and rectal routes without signs of irritation. Peak plasma concentrations have been reported to occur within 1 min following intravenous administration, within 5 to 15 min following intramuscular injection, and 30 min after oral administration.[50,51] Absorption of rectal keta-

mine in children has been reported to peak at 45 min,[52] although in one study, induction of anesthesia occurred within 6 min.[53] Plasma concentrations of the metabolite norketamine are notably higher than ketamine itself following oral administration.[50]

Initially, ketamine is distributed to highly perfused tissues, including brain, to achieve levels four to five times that in plasma. Subsequently, anesthetic action is terminated by redistribution from these vessel-rich tissues to less well-perfused tissues. Ketamine has high lipid solubility and low plasma protein binding (12%), which facilitates rapid transfer across the blood-brain barrier. The distribution half-life approximates 10 min.

Biotransformation of ketamine into multiple metabolites occurs in the liver.[54] The most important pathway involves N-demethylation by cytochrome p450 to norketamine, an active metabolite with an anesthetic potency approximately one-third that of ketamine. Norketamine is then hydroxylated and conjugated to water-soluble compounds that are excreted in urine. Because of the high first-pass effect, oral administration results in increased concentrations of norketamine, as stated above, and could hypothetically result in prolonged anesthetic action due to this active metabolite. Hepatic clearance is characterized by a high intrinsic extraction ratio of 0.9 and therefore should be sensitive to changes in blood flow to the liver. Concurrent administration of diazepam can prolong the plasma half-life of ketamine and its metabolites due to inhibition of hepatic metabolism.[55]

Elimination is primarily by the kidney, with only a small percentage recovered in the urine as the unchanged drug.[56] The elimination half-life is approximately 2 hr, which is secondary to the combination of rapid clearance and large volume of distribution.[51] It has been reported that children eliminate ketamine at approximately twice the rate as do adults.[57]

CLINICAL APPLICATIONS

Ketamine has been used for a wide range of procedures, including preoperative and intraoperative sedation, single-agent anesthesia, balanced anesthesia, regional anesthesia, spinal anesthesia, and postoperative analgesia. Ketamine has been widely accepted as a preoperative agent to reduce anxiety and facilitate induction of general anesthesia.[49,53,58,59] Inhalational or intravenous induction of general anesthesia is often unacceptable for children, necessitating the use of adequate premedication. Intramuscular administration of low doses of ketamine has been used successfully in children, with one study demonstrating that administration of 2 mg/kg resulted in a rapid onset of dissociation, averaging 2.7 min.[58] Although this technique was found to be rapid, safe, and predictable, recovery and discharge times were prolonged when compared with the administration of an inhalational agent alone. Orally administered ketamine can provide a degree of sedation similar to that of intramuscular morphine but with the potential advantages of ease of administration and high patient acceptance.[48]

Other techniques that have been investigated include ketamine administered rectally at a dose of 10 mg/kg for induction of general anesthesia following midazolam and atropine premedication.[60] Loss of consciousness occurred after 9 to 15 min, and anesthesia was then maintained with intermittent boluses of intravenous ketamine. No adverse effects were reported other than delayed awakening. Ketamine also appears to have potential as a regional anesthetic agent in the upper extremity[61] and epidurally.[62–64]

Ketamine has been assessed as a means of achieving postoperative analgesia in children who received halothane anesthesia.[65] Analgesia was found to be satisfactory when ketamine was administered intravenously, 1 mg/kg, at the end of the procedure. Halothane blocked the normal cardiovascular stimulation produced by ketamine, further evidence of ketamine's ability to affect sympathetic outflow, since halothane is a known sympatholytic. Recovery was not delayed, and emergence was reported to be superior to the standard halothane recovery.

In the past, there was concern that ketamine might induce malignant hyperthermia (MH) reactions. The concern stemmed from ketamine's ability to increase circulating catecholamines, which was considered a possible trigger of MH. Ketamine, however, did not induce MH reactions in susceptible swine, leading to the conclusion that the anesthetic agent is safe to use in the MH-susceptible individual.[66] This conclusion is consistent with the recommendations of the Malignant Hyperthermia Association of the United States.[67]

For use as a general anesthetic agent, ketamine is administered at a dose of 1 to 2 mg/kg intravenously or 5 to 10 mg/kg intramuscularly. For use in sedation or analgesia only, the suggested doses are 200 to 750 μg/kg intravenously (followed by 5 to 20 μg/kg/min as a continuous infusion) or 2 to 4 mg/kg if given intramuscularly.[68]

Use with Benzodiazepines

Emergence phenomena have been the most frequently reported adverse effects of ketamine. Use of benzodiazepines has been suggested as a means to decrease emergence problems by their amnestic and dream-altering properties. Originally, diazepam and lorazepam were recommended, but these have been gradually replaced by midazolam.[69,70] Midazolam significantly reduces the incidence of unpleasant dreams[71] and provides a more rapid

recovery than does diazepam.[72] This finding reflects diazepam's much longer elimination half-life.

The combined use with benzodiazepines has the advantage of providing increased sedation and anxiolysis. Ketamine has been compared with fentanyl as an adjunct for diazepam- and nitrous oxide-induced outpatient sedation. While there was no difference in unfavorable emergence reactions, amnesia was greater in patients who received ketamine.[73–75]

Midazolam in combination with low-dose ketamine has been used for outpatient cosmetic surgical procedures.[76] Intraoperative and postoperative problems were minimal when midazolam was administered at a dose of 0.03 to 0.05 mg/kg over a 2-min period followed by ketamine 0.5 to 1.0 mg/kg over a 30-sec interval. Additional small doses of ketamine and midazolam were given to decrease responses to painful stimuli and to maintain an adequate level of sedation. This study is relevant to dental anesthesia in that it relied on local anesthesia to prevent pain, thereby decreasing patient stimulation and reducing the required dose of anesthetic agent. This approach is the same as that commonly used in ambulatory dental anesthesia.

The combination of ketamine with diazepam or midazolam in one syringe for the purpose of controlled infusion was shown to be compatible, with no change in color, separation, precipitation, or change in pH.[77] The relevance of these findings is that infusions appear to provide the most controlled means of providing balanced anesthesia. The use of continuous intravenous infusions of anesthetic and analgesic drugs is associated with fewer intraoperative side effects and shorter recovery times than the intermittent bolus technique.[78]

Use in Dental Anesthesia

In dental anesthesia, ketamine is often used as a supplement in low doses that would not induce general anesthesia if given alone. Bennett[2] introduced an adaptation to this approach by referring to ketamine "dissociative-sedation." This technique involves administering ketamine as a sole agent by low-dose intravenous infusion for the management of the difficult pediatric patient. Infusion allows for maintenance of steady, low blood concentrations of ketamine. The aim is to provide analgesia and amnesia at a subanesthetic level. Patients were reported to remain conscious and cooperative, with satisfactory analgesia and postoperative amnesia. However, Bennett's statement that the use of supplemental oxygen is not a requirement because of ketamine's "respiratory-stimulating" properties is not fully substantiated. In addition, the safety of this form of sedation has not been demonstrated to be greater than any other form of intravenous sedation. It would be valuable to perform a double-blind study comparing this technique with other standard intravenous sedation methods.

Low-dose ketamine has also been compared with methohexital in regard to quality of anesthesia for oral surgery procedures.[79] When administered with diazepam, meperidine, and nitrous oxide, ketamine was effective in minimizing pain and anxiety related to injection of local anesthetic. While of interest, this investigation failed to demonstrate a clear benefit for the use of ketamine compared with methohexital.

Use of rectal ketamine for premedication prior to general anesthesia has been assessed in pediatric dental patients.[80] In this study, a dose of 5 mg/kg produced satisfactory anxiolysis and sedation 30 min after administration, similar to that found with 0.3 mg/kg rectal midazolam. However, ketamine was associated with a greater incidence of adverse reactions, such as visual disturbances, salivation, and crying, among others.

CONCLUSION

Ketamine has a number of specific advantages and disadvantages, as listed in Table 3. However, its role in ambulatory dental anesthesia is not entirely clear. While possessing many desirable properties, its adverse effects, primarily emergence problems, have limited its use. Ketamine would appear to be of benefit for the uncooperative pediatric or mentally handicapped patient. It is clearly a useful anesthetic agent for the asthmatic patient due to its bronchodilating properties. When administered intramuscularly, either at low doses to facilitate mask induction or higher doses as the sole induction agent, ketamine has proved to be effective. Its rapid, predictable onset and relatively short duration of action make it ideal in these patient groups. Its use as a sole anesthetic agent by low-dose continuous intravenous infusion requires more con-

Table 3. Clinical Profile of Ketamine

Advantages	*Disadvantages*
Analgesia at subanesthetic doses	Emergence phenomena
Amnesic	Cardiovascular stimulation
FRC maintained	Mild respiratory depression
Laryngeal reflexes only slightly depressed	Stimulation of oral secretions
Rapid, smooth onset	Not easily titratable
Predictable duration of action	
Nontoxic metabolites	
Water soluble	
Stable in solution	
Nonirritating after injection	
Allergic reactions very rare	

trolled studies to establish both its effectiveness and safety. The use of benzodiazepines to attenuate ketamine's adverse reactions, however, is clearly substantiated. Since the ideal intravenous anesthetic is not yet available, combining two relatively short-acting intravenous drugs possessing complementary pharmacologic properties, such as ketamine and midazolam, is logical. Further research is required to confirm that this combination could provide an optimal sedation technique for both children and adults.

Traditionally, the use of intravenous agents in dental anesthesia has been operator-specific, with little scientific basis upon which to draw. In a survey of 264 clinicians, Dionne and Gift identified 82 different drug combinations used for intravenous sedation.[81] The often-heard statement that small doses of multiple drugs present less risk than large doses of single agents has yet to be confirmed scientifically. Establishment of an intravenous technique that involves few agents, and is safe and effective, may be realized by combining midazolam with ketamine. Clearly, more research in this area is required.

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