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REVIEWS

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Ketamine—Its Pharmacology and Therapeutic Uses

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CONTENTS

AN INCREASING INTEREST in intravenous anesthetic techniques has resulted from the availability of more efficacious intravenous agents, the rising cost of traditional volatile agents, and concern over anesthetic gas pollution in the operating room. Although the "ideal" intravenous anesthetic agent is yet to be developed, such an agent might possess the physical and pharmacological properties outlined in table 1. Originally, interest in such an intravenous anesthetic prompted the investigation of phencyclidine (CI-395, PCP, or Sernyl®) and its congener (CI-400, cyclohexamine). These drugs produced an adequate anesthetic state but long-lasting psychotomimetic activity during the postanesthetic period precluded their widespread clinical use.[1-3] Further research led to the clinical evaluation of ketamine (CI-581, Ketalar® or Ketaject®) which provided adequate surgical anesthesia, a rapid recovery and less prominent emergence reactions.[4] The ketamine molecule [2-(O-chlorophenyl)-2-methylamino cyclohexanone], which structurally resembles phencyclidine and cyclohexamine, has a molecular weight of 238, is water soluble, has a pK_a of 7.5,[5] and contains a chiral center producing two resolvable optical isomers or enantiomers (fig. 1). Although the racemic mixture (containing equal amounts of the two ketamine isomers) was approved for general clinical use in 1970, its clinical usefulness has been limited because of its cardiovascular-stimulating properties and high incidence of disturbing emergence reactions. In this review the authors will discuss the basic pharmacology of ketamine and its optical isomers and evaluate current clinical applications of this unique sedative, analgesic, and anesthetic drug.

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Basic Pharmacology

CENTRAL NERVOUS SYSTEM (CNS) EFFECTS

Ketamine produces a so-called "dissociative" anesthetic state which has been described as a functional and electrophysiological dissociation between the thalamoneocortical and limbic systems.[6] The unique *clinical* anesthetic state produced by ketamine has been characterized as a state of catalepsy in which the eyes remain open with a slow nystagmic gaze while corneal and light reflexes remain intact. Varying degrees of hypertonus and occasional purposeful movements unrelated to painful stimuli are noted in the presence of adequate surgical anesthesia. Judging the adequacy of anesthesia consists primarily of noting the presence or absence of purposeful responses to noxious stimuli. Minor CNS changes occur even after subanesthetic doses of ketamine.[7] These changes may interfere with one's ability to organize thoughts and understand the environment during emergence.

Early EEG studies by Domino *et al.*[4] reported depression of thalamo-neocortical pathways (producing hypersynchronous delta waves) and concomitant activation of the limbic system. Subsequent studies[8] have demonstrated excitatory activity in both the thalamus and limbic systems without clinical evidence of seizure activity following the administration of ketamine. Thus, although thalamic and limbic epileptiform patterns exist, there is no evidence that this seizure activity spreads to cortical

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TABLE 1. Physical and Pharmacological Properties of an Ideal Intravenous Anesthetic

1) Water-soluble, stable in solution, and long shelf-life
2) Nonirritating following im or iv administration
3) No hypersensitivity reactions
4) Rapid, smooth onset of action following im or iv administration
5) Minimal depression of cardiovascular and respiratory systems
6) Rapid degradation to inactive, nontoxic metabolities
7) Analgesia at subanesthetic levels
8) Rapid, smooth emergence (short elimination half-life) with minimal side-effects

areas.[9,10] In fact, Celesia *et al.*[11] found that natural sleep was a more potent stimulator of convulsions than ketamine in the epileptic patient. Thus, ketamine would be an unlikely agent to precipitate generalized convulsions in patients with seizure disorders and in fact, recent experimental data suggest that ketamine has anticonvulsant properties.[12]

Early observations suggested that analgesia following ketamine administration outlasted the period of anesthesia[13,14] and that this analgesic effect occurred even at subanesthetic doses of ketamine.[15-17] A number of experimental observations suggest explanations for its analgesic action. Massopust *et al.*[18] showed that ketamine produces a selective depressant effect on the medial thalamic nuclei. This observation was supported by the work of Sparks and colleagues,[19,20] who demonstrated that ketamine blocks afferent signals associated with the affective-emotional components of pain perception (*e.g.*, the spinoreticular tracts) without significantly impairing conduction of signals related to localization of somatic stimuli (*e.g.*, the spinothalamic tracts). Ohtani *et al.*[21] demonstrated a highly selective depression of nuclei involved in the transmission of impulses within the medial medullary reticular formation, a presumed relay station for the transmission of the affective-emotional components of nociception from the spinal cord to higher brain centers. Others[22-24] suggest that the analgesic action of ketamine may be explained in part by lamina-specific suppression of spinal cord activity. There is also evidence to suggest that ketamine binds stereospecifically to opiate receptors,[25-27] possibly competing with narcotic analgesics and endogenous morphine-like compounds for CNS and spinal cord receptor sites. However, other investigators have been unable to find evidence for an interaction between ketamine and opiate receptors.[28]

Ketamine affects CNS neurotransmitter systems, including interactions with cholinergic receptors of the muscarinic type[25] and brain acetylcholinesterase.[29] Acetylcholine turnover rates were found to be reduced in the rat caudate nucleus and hippocampus during ketamine anesthesia,[30] suggesting that acetylcholine utilization may be related to ketamine-induced electrophysiologic changes in these subcortical structures. The clinical relevance of such experimental observations to analgesia or other neuropharmacological effects of ketamine awaits further clarification. However, several investigators have reported that the centrally-active anticholinesterase physostigmine antagonizes the sedative and anesthetic actions of ketamine while not affecting its analgesic properties.[31-33] Others have found that physostigmine is unable to reverse the CNS effects produced with anesthetic doses of ketamine.[34] Interestingly, Agoston *et al.*[35] recently reported that 4-aminopyridine, a potent antagonist of nondepolarizing myoneural blocking drugs, enhanced the rate of recovery from ketamine-diazepam anesthesia.

POSTANESTHESIA EMERGENCE REACTIONS

The psychic sensations reported during emergence from ketamine anesthesia have been characterized as alterations in mood state and body image, dissociative or extracorporeal (out-of-body) experiences, floating sensations, vivid dreams or illusions, "weird trips," and occasional frank delirium.[36] The vivid dreams and visual illusions usually disappear immediately upon wakening, although recurrent illusions (flashbacks) have been reported several weeks after ketamine administration in adults[37] and children.[38,39]

Recent cerebral glucose utilization studies in animals indicate that ketamine produces depressive action on the inferior colliculus (a primary acoustic relay nucleus) and the medial geniculate (a visual relay nucleus).[40,41] It would appear that psychic emergence reactions occur secondary to ketamine-induced depression of these auditory and visual relay nuclei, leading to misperception and/or misinterpretation of and auditory and visual stimuli. Furthermore, the loss of skin and musculoskeletal sensations results in a decreased ability to feel gravity, thereby producing a sensation of bodily detachment or floating in space.[42] Despite many statements in the literature to the contrary, there is no evidence that covering the eyes during the operative and postoperative periods or allowing patients to emerge in a quiet area alters the incidence of emergence reactions.[43] In fact, we would emphasize the importance of both preoperative and postoperative discussions with the patient regarding the expected effects of ketamine and its common side-effects (*e.g.*, vivid dreaming, floating sensations, dizziness, and

S,(+)-Ketamine hydrochloride R,(−)-Ketamine hydrochloride

FIG. 1. Absolute configuration of ketamine isomers.

blurred vision). In our experience this has reduced the incidence of unpleasant emergence sequelae irrespective of the adjunctive agent used.

The psychic disturbances following ketamine vary in incidence from less than 5 per cent[44,45] to greater than 30 per cent.[36,46-48] Various factors associated with a higher incidence of emergence reactions include: age (less than 10 per cent incidence of unsatisfactory anesthesia and/or emergence reactions in patients less than 16 years old *vs.* 24–34 per cent in patients greater than 16 years old);[49] sex (females greater than males); subjects who normally dream; large doses of ketamine (>2 mg/kg, iv); rapid iv administration (>40 mg/min);[43,50-52] or a history of personality problems.[53] In a controlled study, Garfield *et al.*[54] concluded that ketamine has the property of producing auditory, visual, proprioceptive and confusional illusions in common with other general anesthetics; however, the incidence was significantly higher with ketamine. When compared to a general anesthetic regimen including thiopental, nitrous oxide and halothane, the degree of postoperative anxiety was found to be no greater in patients who only received ketamine.[54] A comparison of the psychological changes in children after either ketamine or halothane/nitrous oxide anesthesia revealed no significant differences.[55]

A variety of premedicants and adjunctive agents have been evaluated in attempts to prevent the untoward emergence reactions following ketamine anesthesia. Atropine premedication prior to ketamine administration has been shown to increase the frequency of unpleasant dreams.[50,56] Similarly, droperidol may increase the occurrence of vivid dreams when used as a premedicant,[46,50,57,58] although it was originally reported to reduce the incidence of adverse emergence reactions.[59] Furthermore, even though droperidol may reduce the total dosage of ketamine, patients receiving droperidol tended to be significantly less alert, less responsive, and more disoriented during the recovery period.[60] Several investigators have reported a decrease in the incidence of posthypnotic emergence phenomenon when ketamine was used in conjunction with sedative-hypnotics (*e.g.*, thiopental)[61] or other general anesthetics (*e.g.*, halothane, enflurane and nitrous oxide).[62,63]

Benzodiazepines appear to be the most efficacious in attenuating the psychic actions of ketamine during the emergence period. Diazepam (0.15–0.3 mg/kg, iv) has been reported to significantly decrease the incidence of dreams and to eliminate postoperative illusions when administered prior to induction of ketamine anesthesia.[64,65] In terms of its ability to attenuate emergence sequelae, others have reported diazepam to be equally effective whether administered at the outset or at the completion of the procedure.[46,66] Although diazepam is highly effective in preventing vivid emergence reactions and delirium following ketamine, a high incidence of floating sensations, dizziness and dreaming has been reported even in the presence of diazepam.[67]

Of the currently available benzodiazepines, lorazepam (2–4 mg, po or iv) is reported to be the most effective in preventing unpleasant dreams and emergence sequelae after ketamine.[68,69] The enhanced effectiveness of lorazepam may be related to its ability to produce more effective and longer-lasting amnesia than diazepam.[70-72] A more recently introduced benzodiazepine, flunitrazepam, 0.03 mg/kg, iv, also attentuates the emergence sequelae associated with ketamine anesthesia.[73-75] Unfortunately all currently available benzodiazepines are insoluble in water and possess long elimination half-life values. Thus, they produce a high incidence of phlebitis and contribute to a prolonged recovery when used as adjuncts to ketamine. A new shorter-acting benzodiazepine, midazolam, appears to offer several potential advantages since this water-soluble agent prevented dreaming and emergence sequelae when used as an adjunct to ketamine for induction of general anesthesia.‡

Cardiovascular Effects

Ketamine produces a dose-related rise in the rate-pressure product (often in excess of 100 per cent) with a transient rise in the cardiac index but without significantly altering the stroke index.[76,77] Initially, the cardiostimulatory effects of ketamine were thought to be due to increased sympathetic nervous system activity, with enhanced norepinephrine release secondary to depression of baroreceptor reflex activity.[78] Subsequent studies[79,80] have shown that the cardiovascular stimulation associated with ketamine was not altered by direct baroreceptor nerve stimulation, while ketamine blocked the bradycardia produced by stimulation of the depressor nerve, suggesting that the origin of ketamine-induced cardiovascular stimulation is unrelated to baroreceptor desensitization. Traber *et al.*[81] suggested that the sympathomimetic effects of ketamine might be mediated within the CNS because ganglionic blockade and thoracic epidural block were capable of ablating its cardiostimulatory properties (even though adrenergic-blocking drugs were unable to completely block the pressor response to ketamine). In fact, when ketamine is injected directly into the cerebral circulation, an immediate increase in blood pressure, heart rate, and cardiac output is produced and these effects can be markedly attenuated by prior administration of pentobarbital.[82] Based on this study and others,[83,84] it is felt that ketamine produces its sympathomimetic actions *primarily* by direct stimulation of CNS structures.

‡ White PF: Unpublished data.

In the absence of autonomic control, ketamine has direct myocardial depressant properties.[85,86] *In vitro*, ketamine produced a dose-dependent decrease in the rate and force of myocardial contraction which was not altered by pretreatment with atropine, phentolamine, or propranolol.[87-89] Furthermore, the ketamine-induced myocardial depression is antagonized by hypothermia.[87,90]

The effect of ketamine on the cardiac rhythm is controversial. There is evidence to suggest that ketamine has the ability to sensitize the myocardium to catecholamines and thereby enhance the arrhythmogenicity of epinephrine;[91,92] however, these same investigators have demonstrated a transient dose-related antiarrhythmic effect of ketamine. In animal studies, ketamine abolished epinephrine-induced arrhythmias by prolonging the relative refractory period[77,78] and was capable of reversing digitalis-induced arrhythmias.[93]

The cardiovascular effects of ketamine are not confined to actions on CNS centers and the heart. Several investigators have suggested that ketamine has both inhibitory and excitatory effects on the peripheral sympathetic nervous system.[94-95] Juang *et al.*[96] demonstrated that ketamine depressed smooth muscle contraction in response to preganglionic stimulation, while producing a transiently increased contraction in response to postganglionic stimulation, suggesting an effect at the level of the sympathetic ganglia. The effects of ketamine on postganglionic adrenergic neurons include inhibition of intraneuronal uptake of catecholamines, *i.e.*, a cocaine-like effect[90,95,97,98] and a dose-dependent inhibition of extraneuronal norepinephrine uptake.[99,100]

Recent studies have demonstrated that ketamine directly dilates vascular smooth muscle while causing sympathetically mediated vasoconstriction.[101,102] The net effect is that systemic vascular resistance is not significantly altered by ketamine.[86,103] Even though ketamine increases coronary blood flow, it may be insufficient to meet the metabolic demands of the myocardium produced by the increase in the rate-pressure product and cardiac work.[104,105] A recent study[106] found no change in myocardial oxygen extraction with ketamine administration because the increase in coronary blood flow was accompanied by a comparable rise in myocardial oxygen consumption.

Ketamine was found to increase pulmonary artery pressures in dogs.[107] Similarly, in patients, ketamine markedly elevates pulmonary artery pressure and right ventricular stroke work secondary to increased pulmonary vascular resistance.[108] Thus, ketamine is probably contraindicated in patients with minimal right ventricular reserve (*e.g.*, pulmonary emboli and pulmonary hypertension). In patients without cardiopulmonary disease, ketamine produced a 40 per cent increase in pulmonary vascular resistance, a secondary increase in right heart work, and a transient 20 per cent increase in the intrapulmonary shunt.[103]

In experimental hemorrhagic and septic shock, Wong and Jenkins[109] demonstrated a significant increase in both systolic and diastolic blood pressure after ketamine. Furthermore, while cardiac output was increased in endotoxic shock, it was unchanged in hemorrhagic shock. Longnecker and Sturgill[110] reported a higher survival rate in hypotensive rats anesthetized with ketamine than halothane. However, Weiskopf *et al.*[111] using a graded hemorrhage dog model, found that although continuous ketamine anesthesia was more effective in maintaining the cardiovascular system, it produces a greater base deficit and larger increases in arterial lactate concentration than the volatile anesthetic agents.

Critically ill patients occasionally respond to ketamine with an unexpected drop in blood pressure which may result from the inability of the sympathomimetic actions of ketamine to counterbalance its direct myocardial depressant and vasodilatory effects. Waxman *et al.*[112] observed occasional decreases in cardiac and pulmonary performance when ketamine was used for induction of anesthesia in critically ill and acutely traumatized patients. Furthermore, others have demonstrated that general anesthetics block the cardiovascular-stimulating properties of ketamine such that significant cardiovascular depression can be produced when ketamine is used during halothane or enflurane anesthesia.[62,113]

Using ketamine and thiopental as part of a balanced anesthetic technique decreases the degree of cardiac stimulation produced by ketamine.[114] Others have shown that ketamine-induced cardiovascular stimulation and the concomitant rise in plasma free norepinephrine levels may be significantly decreased by premediation with diazepam (0.2–0.5 mg/kg, iv).[115-117] Although lorazepam is more effective than diazepam in preventing emergence reactions, it is unable to block the cardiovascular stimulation produced by ketamine.[118] Of the newer benzodiazepines, flunitrazepam[119] and midazolam§ appear to be the most effective in attenuating the cardiostimulatory properties of ketamine. Nevertheless, the clinical significance of ketamine-induced cardiovascular stimulation in patients without hypertension, coronary artery disease, or cerebral vascular disease is yet to be established.

Ketamine produces an increase in cerebrospinal fluid (CSF) pressure which appears related to an increase in cerebral blood flow secondary to cerebral vasodilation and a rise in systemic blood pressure.[120,121] Hence, ketamine should probably be avoided in patients with abnormal CSF flow dynamics or other intracranial pathology. Case reports have described ketamine-induced apnea secondary to medullary compression resulting

§ White PF: Unpublished data.

from increased intracranial pressure.[122,124] The increase in cerebral blood flow produced by ketamine is blunted effectively by prior administration of either thiopental[125] or diazepam.[126]

Pulmonary Effects

In patients spontaneously breathing room air, ketamine, 2 mg/kg, iv, given as a rapid bolus injection produced significant reductions in Pa_{O_2} lasting from 5–10 minutes.[127] In contrast, premedicated patients (diazepam 10–15 mg, im) spontaneously breathing room air who received ketamine, 2 mg/kg, iv, over 60 seconds showed no significant change in either Pa_{O_2} or $C(a\text{-}v)_{O_2}$.[128] Furthermore, when an infusion of ketamine, 1 mg/kg, iv, was administered during vaginal deliveries, no significant changes were noted in either maternal or infant arterial blood gas values.[129] The respiratory response to CO_2 challenge is maintained during ketamine anesthesia.[130] Thus, ketamine does not produce significant respiratory depression except in those situations when it is given as a rapid iv infusion. Furthermore, Lumb *et al.*[131] found consistently lower shunt fractions and higher Pa_{O_2} values when a continuous infusion of ketamine was compared to halothane during one-lung anesthesia in dogs.

In early clinical studies, an increase in pulmonary compliance and a decrease in airway resistance and bronchospasm was noted following administration of ketamine to patients with reactive airway disease.[132,133] *In vitro* bronchial smooth muscle studies with ketamine demonstrated muscle relaxation, antagonism of the spasmogenic effects of carbachol and histamine, and a potentiation of the antispasmodic effects of epinephrine.[134,135] Moreover, propranolol blocked the relaxant effect of epinephrine but not that of ketamine, suggesting that *in vitro* ketamine acts at sites other than beta-receptors. Ketamine was found to be as effective as halothane or enflurane in preventing experimentally induced bronchospasm in dogs.[136] The ability of ketamine to antagonize antigen-induced bronchospasm might be related in part to its vagolytic and direct smooth muscle relaxant effects. However, the major component *in vivo* appears to be related to ketamine's sympathomimetic properties since the protective effect against antigen-induced bronchospasm is lost in the presence of beta-adrenergic blockade.

Salivary and tracheal-bronchial mucus gland secretions are increased by ketamine, necessitating prophylactic administration of an antisialogogue. Despite alleged retention of the protective pharyngeal and laryngeal reflexes,[137] tracheal soiling and aspiration has been reported following induction of anesthesia with ketamine.[138,139] Clearly, one should *not* assume that the use of ketamine obviates the need for careful airway management and/or endotracheal intubation in all situations.

Miscellaneous Pharmacologic Effects

Ketamine frequently produces an increase in skeletal muscle tone[4] and occasionally muscle spasms,[140] although it has been used safely in patients with myopathies¶ and malignant hyperthermia.[141,142] In the rat phrenic nerve-hemidiaphragm preparation, ketamine has been shown to increase indirectly evoked twitch tension but produced no effect on directly stimulated skeletal muscle.[143,144] However, a more recent study reported that ketamine produces neuromuscular effects by a direct postsynaptic action, initially potentiating and then blocking the twitch response elicited by direct muscle stimulation.[145] These data suggest that ketamine may interfere with calcium binding or its fluxes and thereby contribute to the initial potentiation and subsequent depression of twitch tension. These actions might explain ketamine's enhancement of the neuromuscular actions of succinylcholine, *d*-tubocurarine, and pancuronium.[144,146,147]

The reduction in blood loss which has been reported when ketamine is used as an induction agent for first trimester abortions,[148] may be related to its ability to increase both uterine tone as well as the intensity of uterine contractions.[149,150] In parturients, ketamine has been reported to have variable effects on uterine tone and contractility.[151-154] Oats *et al.*[155] found that ketamine was able to induce contractions equal to ergometrine, when administered during the first trimester of pregnancy, but exerted no effect in the third trimester. Although ketamine had no effect on basal uterine tone in the parturient, Marx *et al.*[156] reported that ketamine produces dose-related changes in uterine activity in the term pregnant uterus. Analgesic doses of ketamine (0.2–0.4 mg/kg, iv) produced no significant effects, while larger induction doses (>1 mg/kg, iv) produced increases in the intensity of uterine contractions.

Ketamine has reportedly been used safely in a patient with acute intermittent porphyria.[157] Nevertheless, it can increase ALA synthetase activity in animals and therefore should be used with caution in patients with porphyria.[158]

Ketamine produces only a mild elevation in blood glucose (12 per cent) compared to that produced by halothane (55 per cent) or thiopental (72 per cent).[159] Serum free fatty acids are decreased by ketamine (13 per cent) in contrast to halothane and thiopental which produce 59 per cent and 34 per cent increases, respectively.[159] Thyroxine (T4) levels are not altered by ketamine; however, T3 levels are reduced.[160] Therefore, the dose-dependent hypothermia produced by ketamine in rats at ambient temperatures[161] may be due to decreased heat

¶ Lees, DE, Emma P, Hittner K, et al: The safety of ketamine in pediatric neuromuscular disorders. Int Anesth Res Soc 53rd Congress, p 75, 1979.

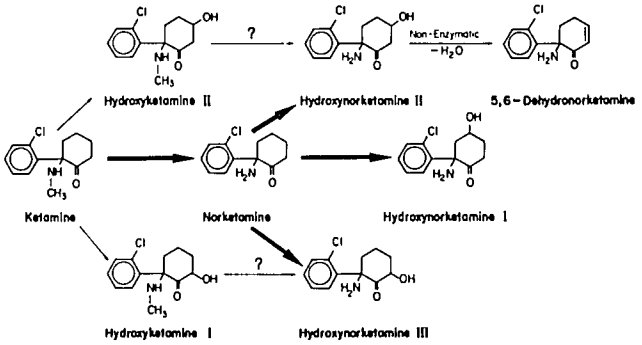

FIG. 2. Biotransformation of ketamine.

production as well as increased heat loss secondary to cutaneous vasodilation.

Initial studies indicated that ketamine increased plasma renin activity,[162] an effect which was attenuated by prior treatment with antihypertensive agents.[163] However, recent studies[164] demonstrated no change in renin activity during ketamine anesthesia, even though the pressor response to angiotension I and II was accentuated when compared to that produced under halothane anesthesia. In addition, ketamine produces an activation of the pituitary-adrenal axis,[165,166] with adrenal release of catecholamines[167] and corticosteroids.[168] During deep ketamine anesthesia inhibition of this pituitary activation was reported,[169] although intense and prolonged stimulation was noted upon emergence.

BIODISPOSITION, PHARMACOKINETICS, AND DRUG INTERACTIONS

Ketamine is metabolized extensively by hepatic drug-metabolizing enzyme systems and although some biotransformation pathways are well-established, others remain postulated. A recently advanced scheme of ketamine metabolism is presented in figure 2.[170] A major pathway of biotransformation involves N-demethylation of ketamine via cytochrome P-450 enzymes to form norketamine (metabolite I) which can then be hydroxylated at one or more positions in the cyclohexanone ring to form hydroxy-norketamine compounds, which in turn can be conjugated to more water-soluble glucuronide derivatives. Ketamine can also undergo ring hydroxylation without prior N-demethylation but quantitatively, this pathway appears to be of minor importance. The hydroxylated metabolites of norketamine are unstable at high temperatures, undergoing thermal dehydration to form a cyclohexenone oxidation product, dehydronorketamine, which has been designated "metabolite II" in much of the past literature on ketamine metabolism. Adams *et al.*[170] have evidence that this compound results artifactually from the gas chromatographic method[171] used by most investigators for analysis of ketamine and its metabolites.

Following its intravenous administration, less than 4 per cent of a dose of ketamine can be recovered from urine as either unchanged drug or norketamine and only 16 per cent appears as hydroxylated derivatives.[172] Fecal excretion accounts for less than 5 per cent of an injected dose of ketamine.[173] The precise composition of the balance of metabolites of ketamine that are eliminated is not clear, but it is presumed that the major components are glucuronide derivatives of the various hydroxylated intermediates.

Only minimal attention has been given to the possible pharmacological effects of the different metabolites of ketamine. In animal studies, norketamine appears to be from one-fifth to one-third as potent as ketamine as an anesthetic,[174,175] but nothing is known concerning other metabolites. It would be of interest to ascertain if other identified metabolites have either cardiovascular or CNS actions that contribute to adverse effects of the parent drug. Alternatively, certain metabolites could be devoid of such effects while retaining therapeutically useful analgesic or anesthetic properties.

The pattern of biodisposition of ketamine is in some ways analogous to that of the short-acting barbiturates such as thiopental, which it resembles in terms of its rapid onset of action, relatively short duration of hypnotic effects, and its high lipid solubility. Peak plasma levels are achieved within one minute following intravenous administration of ketamine to animals and within five minutes following intramuscular injection.[176,177] Initially, ketamine is distributed to highly perfused tissues, including the brain, to achieve levels four to five times that of the plasma.[5,177,178] Subsequently, the drug is redistributed from vessel-rich tissues to less well-perfused tissues.

In experiments to determine relationships between the effects of ketamine and its biodisposition, it was shown that the duration of hypnosis was not affected by either the induction or inhibition of drug-metabolizing enzymes[5,178] or decreases in renal clearance of the drug.[179] This suggests that redistribution of ketamine from the brain to other tissues is primarily responsible for termination of its hypnotic or anesthetic effects. Hepatic metabolism is important for the ultimate clearance of ketamine from the body and may be a factor in terminating postanesthetic effects of the drug. Pharmacokinetic studies of ketamine in humans, using a two-compartment model system,[172,180] demonstrate that the initial distribution phase of intravenous ketamine from the central compartment (plasma) to peripheral tissue compartments occurs with a half-life ($t_{1/2}$) of 7 to 11 minutes. The elimination phase, which reflects both metabolic and excretory processes, occurs with a half-life ($t_{1/2}$) of be-

tween 2 and 3 hours. Using a continuous infusion technique, Idvall *et al.*[77] reported an elimination $t_{1/2}$ of 79 minutes.

At the termination of the ketamine-induced anesthetic state, a large fraction of the ketamine administered remains in body tissues in unchanged form and this may have significance with respect to cumulative effects and the potential for drug interactions. Halothane has been shown to slow distribution and redistribution of ketamine and to inhibit its hepatic metabolism,[177] both actions contributing to a prolongation of the CNS effects of the drug. In animal studies, ketamine caused a dose-dependent decrease in halothane anesthetic requirement, and even at subhypnotic doses ketamine elicited prolonged decreases in halothane MAC.[175] Agents used as adjuvants in anesthesia, including diazepam and secobarbital, have been shown to prolong the elimination half-life of ketamine and to delay recovery from ketamine anesthesia.[181] When given intravenously during induction, diazepam caused an increase in ketamine plasma levels and a decrease in its clearance rate,[180] effects which are presumed to reflect inhibition of hepatic metabolism of ketamine by the benzodiazepine. Other premedications have been reported to prolong recovery from the anesthetic effects of ketamine.[182] On the other hand, nitrous oxide has been shown to significantly reduce the dosage of ketamine required for surgical anesthesia and to shorten the recovery period.[183] It is not clear whether such drug interactions are based on changes in the biodisposition of ketamine or if they reflect pharmacodynamic factors.

The chronic administration of ketamine to laboratory animals results in an increase in activity of hepatic drug-metabolizing enzymes, including those responsible for metabolism of ketamine itself.[178] By increasing the levels of cytochrome P-450, NADPH reductase and the rate of metabolism of Type I substrates, ketamine resembles phenobarbital.[184] The "self-inductive" effects of chronic ketamine administration increases the activity of enzymes involved in its own metabolism and could modify responses to repeated administration fo the drug. Such a mechanism could explain, at least in part, the reported occurrence of tolerance to the analgesic effects of ketamine that occur in burn and radiotherapy patients following repeated exposures to the drug.[17,185-187] Moreover, certain effects of ketamine on animal behavior are subject to rapid "acute" tolerance[188] or to tolerance that develops after only a single prior exposure to the drug.[189] These latter alterations in drug response are unlikely to result from changes in metabolism or biodisposition of the drug. Finally, ketamine maintains self-administration behavior in a manner similar to CNS depressant drugs[190] and not surprisingly, several cases of ketamine abuse have been reported.[191-193]

Optical Isomers of Ketamine

All of the studies of ketamine cited above concern the drug in its racemic form, though a chiral center at C_2 of the cyclohexanone ring permits the existance of two resolvable optical isomers or enantiomers, which when studied by physical chemistry techniques have absolute configurations of S(+)-ketamine hydrochloride and R(−)-ketamine hydrochloride, respectively.** The individual optical isomers of a number of psychoactive compounds, including hallucinogens,[194] amphetamines,[195] narcotics,[196] and sedative-hypnotics[197] are well-established to differ in pharmacological properties. Thus, it is not surprising that the individual ketamine isomers would have the potential for differences in their neuropharmacological effects. In rats, the (+)-enantiomer of ketamine was shown to have a higher therapeutic index, expressed as LD_{50} over ED_{50} (hypnosis), than the racemate or (−)-ketamine and at equihypnotic doses the (+)-enantiomer caused less stimulation of locomotor activity than (−)-ketamine.[198] The relative pharmacological properties of the optical isomers of ketamine have also been compared in mice.[199] In these studies, (+)-ketamine was shown to be three times more potent than (−)-ketamine as an analgesic, and 1.5 times more potent in terms of its hypnotic effects. More importantly, at equianalgesic doses the (+)-isomer caused less excitation than (−)-ketamine. Such neuropharmacological differences are quantitative, but recently it has been possible to demonstrate important qualitative differences between the two ketamine isomers. In rats, (−)-ketamine increased the rate of schedule-controlled responding behavior in a dose-dependent manner, while (+)-ketamine did not increase response rate at any dose, acting solely as a depressant of such behavior.[200] Observations of this type at the animal level, provided the incentive for a comparative study of the ketamine isomers in surgical patients.[36] To assess the intraoperative and postoperative effects of the isomers compared to the racemic mixture as sole anesthetics, equianesthetic doses of racemic ketamine (2 mg/kg), (+)-ketamine (1 mg/kg) or (−)-ketamine (3 mg/kg), were administered intravenously in a randomized, double-blind manner to 60 healthy patients undergoing elective outpatient procedures. The (+)-isomer of ketamine was judged to produce more effective anesthesia than either the racemate or (−)-isomer (95 *vs.* 75 *vs.* 68 per cent, respectively). Quantification of verbal responses in the postanesthetic period suggested that more psychic emergence reactions occurred after administration of (−)-ketamine than the racemic compound or (+)-ketamine (occurrence of 53 *vs.* 15 *vs.* 5 per cent, respectively). Furthermore, the patients

** Woolf TF, Castagnoli N, Trevor AJ, et al: Unpublished data.

given (−)-ketamine demonstrated more agitation than those given the racemate or (+)-ketamine. Although it is of a preliminary nature, this double-blind study disclosed differences in anesthetic potency, physical side-effects, the incidence of postanesthetic emergence phenomena, and patient anesthetic preference between the two optical isomers of ketamine.

The fact that the individual optical isomers of ketamine do differ in their pharmacological properties suports the suggestion that the CNS effects of these compounds are exerted, at least in part, via interactions with specific receptors, although the precise nature of such "target" molecules awaits further elucidation. However, certain of the neuropharmacological differences may also result from variations between otical isomers of ketamine in terms of metabolism and biodisposition. For example, following administration of equimolar quantities of the separate isomers, they are subjected to metabolism at different rates.[198,199] The N-demethylated compound, (+)-norketamine, has been shown to accumulate in the brain tissues of laboratory animals to a greater extent than (−)-norketamine. In contrast, the ring-hydroxylated metabolites of (−)-ketamine reach brain levels three times higher than similar metabolites of the (+)-isomer. Since these individual metabolites have yet to be studied in terms of their neuropharmacological effects, it remains possible that they may be implicated in certain of the previously described CNS effects of ketamine.

Clinical Applications

Anesthesia for Burn Patients

Ketamine has been used extensively in burn units for dressing changes, debridements and skin grafting procedures in children[201,202] and adults.[13] Low-dose ketamine (1.5–2.0 mg/kg, im) is alleged to have a rapid onset of action and to produce good operating conditions, amnesia, and satisfactory analgesia with a rapid recovery and reestablishment of routine activities.[17] However, an apparent tolerance to ketamine developed in all patients receiving more than two exposures to ketamine, and the dose had to be increased progressively in patients receiving repeated administration. Ketamine, 4.0–6.0 mg/kg, im, produced excellent surgical conditions for eschar excision.[187] The "rapid recovery" from ketamine allowed for a minimal delay in resuming nutritional intake. Mild emergence reactions manifested by excitment and/or illusions were noted in about 10 per cent of these unpremedicated burn patients.

Anesthesia for the Aged and Critically Ill

Ketamine has been useful in critically ill patients where a period of hypotension or apnea could be life-threatening. Unfortunately, it is difficult to extract objective and meaningful data from many of these uncontrolled clinical reports. When ketamine has been used in a critically ill patient population, it has been reported to provide good surgical anesthesia with a greater margin of safety than "conventional" anesthesia, with a low incidence of side-effects and postoperative complications.[44,77,203–205] Vaughan and Stephen[206] utilized ketamine in thoracic and abdominal surgical procedures in elderly, poor risk patients and reported hemodynamic stability and rapid emergence with a low incidence of unpleasant dreams (4 per cent). Ketamine has been regarded by some as advantageous for patients in hemorrhagic shock,[207–209] while others have disputed its usefulness in this situation.[112,210] Induction of ketamine anesthesia in patients who were hypovolemic secondary to acute hemorrhage caused no change or a slight increase in blood pressure and heart rate, in contrast to the marked pressor response following its administration to normovolemic subjects. In patients who had been in borderline or actual shock for several days, induction of anesthesia with ketamine produced a marked depressor response and possible maldistribution of systemic blood flow.[112] It is possible that prolonged preoperative stress diminishes the usual cardiovascular stimulation produced in response to ketamine, thereby unmasking its direct myocardial depressant properties.

Interesting case reports regarding the successful use of ketamine to treat severe bronchospasm refractory to conventional bronchodilators have appeared in the anesthesia literature.[211,212] Ketamine produces an increase in pulmonary compliance and a reduction in airway resistance in patients with asthma.[132,133] Ketamine was found to be effective in treating bronchospasm occurring during halothane anesthesia.[132] Because of its salutary effects on airway resistance, ketamine may be the agent of choice for rapid induction of anesthesia in patients with reactive airway disease. Furthermore, ketamine is a reasonable alternative to enflurane or isoflurane in patients without significant cardiovascular diseases who are receiving parenteral bronchodilators at the time of surgery. Finally, ketamine would be advantageous in those situations where a high inspired oxygen concentration is required to maintain adequate tissue oxygenation, (*e.g.*, severe anemia).

Obstetrical Anesthesia

Early studies utilizing ketamine for analgesia during routine vaginal deliveries demonstrated a number of maternal complications and depressed infants with low Apgar scores.[45,47] These problems were shown to be dose-related and when lower doses of ketamine (0.2–0.5 mg/kg, iv) were utilized, the neonate was not depressed and the complications were minimal, with high patient ac-

ceptance.[213,214] Nevertheless, when subanesthetic doses of ketamine are used to produce obstetrical analgesia, a majority of these unpremedicated patients will experience a dreamlike state. Ketamine given in combination with nitrous oxide for obstetrical anesthesia produces virtually no recall of pain during delivery and although dreaming occurred in 20 per cent of the patients, a majority of the dreams were pleasant with excellent patient acceptance.[215] The use of larger doses of ketamine (1.5 mg/kg, iv) for induction of anesthesia in unpremedicated parturients produced good surgical anesthesia; unfortunately, recovery from anesthesia was unpleasant in over 50 per cent of the cases.[216] In a large obstetrical series comparing low-dose ketamine (0.5 mg/kg, iv) with methoxyflurane (0.25–10 per cent), ketamine produced a more rapid onset of action and proved to be the superior analgesic with comparable patient acceptance.[217] However, ketamine produced a significant incidence of unpleasant dreams and the use of droperidol as an adjunctive agent prolonged the recovery period without decreasing the incidence of emergence reactions.

When compared to thiopental, ketamine provided a rapid induction, greater analgesia and amnesia with a comparable incidence of unpleasant emergence reactions when used for induction of anesthesia for cesarean section.[153] Moreover, the incidence of undesirable psychotomimetic responses is low following either ketamine or thiopental administration for cesarean section.[45,218,219] Using ketamine as the sole anesthetic for cesarean section, Bunodiere *et al.*[220] reported that fetal mortality was less than half that seen with other general anesthetic techniques. Furthermore, ketamine might be a useful analgesic for managing the preeclampic patient because of its anticonvulsant properties.[221]

There have been no reports at the clinical level on fetal acid/base changes following ketamine anesthesia; however, animal studies indicate that ketamine increases uterine blood flow and does not produce deleterious effects on fetal cardiovascular or acid/base status.[222] Evaluation of arterial blood gases in mothers and infants during ketamine analgesia for vaginal delivery, showed no significant differences between the ketamine group and a comparable group receiving regional anesthesia.[129] A comparison of ketamine and thiopental for rapid iv induction prior to cesarean section showed a greater maternal umbilical artery and vein pH and a larger base excess value following ketamine.[219] Neonatal arterial blood pressure has been reported to be less depressed after maternal ketamine anesthesia compared to a similar group receiving thiopental.[223] Neonatal neurobehavioral tests following vaginal delivery under ketamine, 0.7 mg/kg, iv, with 50 per cent nitrous oxide, thiopental, 4 mg/kg, iv, with 50 per cent nitrous oxide or chloroprocaine epidural anesthesia, revealed the greatest percentage of high scores in the epidural group, the lowest scores after thiopental–N_2O and intermediate values following ketamine–nitrous oxide.[224]

Outpatient Anesthesia

Children. Low-dose ketamine has been used successfully for brief pediatric oral surgery procedures lasting from 5 to 30 minutes, utilizing doses of 1–3 mg/kg, im, and 0.5–1.0 mg/kg, iv.[225,226] However, others have reported significant cardiovascular stimulation, partial airway obstruction and minor post-anesthetic complications, including unpleasant dreams.[227]

Intramuscular ketamine, 5–10 mg/kg, has proved useful for diagnostic and minor surgical procedures which may not require intravenous cannulae or endotracheal intubation.[182] There is a high degree of acceptance of ketamine in children undergoing repeated anesthesias, including its use in radiotherapy.[185,186] In children undergoing minor otolaryngological procedures, ketamine (2 mg/kg, iv) compared favorably with thiopental (4 mg/kg, iv) and althesin (0.55 mg/kg).[228] Operating conditions were similar in all groups; however, thiopental and althesin produced more cardiorespiratory depression and a greater need for postoperative analgesics, while ketamine was associated with a higher incidence of restlessness and a somewhat more prolonged recovery. Ketamine, 10 mg/kg, im, has reportedly been used for bronchoscopy in children without significant complications.[234] However, ketamine stimulates production of copious amounts of upper airway secretions, necessitating concomitant use of an antisialogogue. Furthermore, anecdotal reports indicate that ketamine may produce "hyperreactive" airway reflexes, especially in the presence of inflammation of the upper respiratory tract. The use of ketamine for ocular examinations under anesthesia has been widely accepted in spite of occasional problems during the recovery phase.[229] Although early clinical reports suggested that there was an increase in intraocular pressure with ketamine,[230,231] more recent studies have found this not to be the case.[232,233] Finally, rectal ketamine, 8–10 mg/kg, has been used successfully as an induction agent in pediatric anesthesia.[235]

Adults. In a large series comparing low-dose ketamine (0.5 mg/kg, iv) with methohexital (1 mg/kg, iv) in combination with nitrous oxide for minor gynecologic procedures,[58] ketamine was associated with fewer intraoperative problems. However, in patients premedicated with droperidol the ketamine-induced dreams were more vivid and unpleasant than those associated with methohexital. Although pentobarbital (1.5 mg/kg, im or iv) reduced the incidence of psychic emergence reactions

after ketamine, the recovery period was prolonged with concomitant barbiturate administration.[236] In a double-blind study comparing ketamine with Innovar® in combination with N_2O/O_2 for gynecologic procedures, the effects of ketamine could not be differentiated clinically from those of Innovar®.[237] However, fewer intraoperative and postoperative complications were reported after ketamine, while the degree of respiratory depression and the need for postoperative analgesics was higher in the Innovar® group. In our series evaluating the effectiveness of racemic ketamine alone (average total dose equalled 5.4 mg/kg, iv) for midtrimester abortions,[36] ketamine was found to be inadequate in 25 per cent of the cases. Commonly reported side-effects included visual distortions (45 per cent), dizziness/lightheadedness (35 per cent), and agitation/disorientation (30 per cent). Overall, 85 per cent of the patients experienced dreams (70 per cent of which were pleasant experiences), and 35 per cent stated that they would prefer a different anesthetic in the future. Although recovery was occasionally prolonged, most patients were discharged within 2 hours of awakening from the anesthetic. Others have utilized low doses of ketamine for brief gynecological procedures with highly satisfactory operating conditions, few postanesthetic side-effects and a rapid recovery from anesthesia.[66,75,238] In summary, it appears that ketamine can be used successfully for outpatient anesthesia if minimal effective doses are administered (ketamine 0.5–1.5 mg/kg iv for induction followed by continuous infusion of 10–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in combination with diazepam, 0.2–0.3 mg/kg, iv (or flunitrazepam 0.01–0.02 mg/kg, iv), and nitrous oxide in oxygen. However, the concomitant use of benzodiazepines with long elimination half-life values will prolong recovery from ketamine anesthesia. In order to provide for a more rapid recovery following brief outpatient procedures, we are utilizing a combination of 3–4 mg/kg thiopental, iv (or 1–2 mg/kg methohexital, iv) for induction followed by a continuous infusion of ketamine with nitrous oxide in oxygen.

Adjunct to Local and Regional Anesthesia

During the performance of a painful nerve block, the ideal premedicant drug would provide analgesia, sedation and amnesia without cardiorespiratory embarrassment. Thompson and Moore[239] compared the clinical effectiveness and acceptability of ketamine (2 mg/kg, iv) with diazepam (20 mg, im, and 20 mg, iv) and Innovar® (2 ml im and 3 ml iv) for sedation and analgesia prior to intercostal nerve blocks. Diazepam produced amnesia in 85 per cent of the patients (15 per cent recalled painful, unpleasant experiences); however, the sedation was judged by the anesthesiologist to be inadequate in over half of the cases. In the Innovar® group, 60 per cent of the patients were inadequately sedated (with frequent signs of respiratory depression), while 40 per cent recalled the block as a painful and unpleasant experience. Ketamine produced excellent sedation and patient acceptance; however, a 10 per cent incidence of unpleasant dreams was reported in these unpremedicated patients. Kortilla and Levanen[65] examined the untoward effects of ketamine combined with diazepam for supplementation of regional anesthesia. The use of ketamine 0.5 mg/kg, iv, combined with diazepam 0.15 mg/kg, iv, was not associated with any more side effects or a greater need for postoperative care than an unpremedicated control group undergoing similar nerve block procedures, and patient acceptance was significantly higher in the diazepam-ketamine group. Use of low-dose ketamine in combination with diazepam or flunitrazepam prior to injection of local anesthetics has become increasing popular for outpatient cosmetic surgical procedures.[75,240] Patients are reported to be comfortable, cooperative and highly satisfied with this combination. Our own experience would indicate a significant number of such patients experience dreamlike, floating sensations and even occasional unpleasant emergence reactions.

Cardiothoracic Anesthesia

Extensive experience with ketamine for pediatric cardiac catherizations has shown it to be highly effective with fewer catheter-associated arrhythmias than other general anesthetics.[204,241,242] Interestingly, when ketamine was used for adult cardiac catherization it produced a significant decrease in blood pressure in 22 per cent of the patients.[243] When ketamine was administered utilizing a continuous infusion technique in combination with high-dose diazepam and N_2O/O_2, Hatano *et al.*[244] reported that anesthesia was smooth and simple with minimal effect on the cardiorespiratory system, excellent antegrade amnesia, satisfactory analgesia and no postoperative emergence reactions. Diazepam, 0.3–0.5 mg/kg, iv, was effective in preventing a rise in the rate-pressure product following administration of ketamine to patients with coronary artery disease.[116] In a study comparing a morphine–diazepam–nitrous oxide combination with ketamine-nitrous oxide anesthesia for coronary bypass surgery, Reves *et al.*[245] found that although the incidence of hemodynamic changes in the rate-pressure product were similar, the mean maximal increases in systolic blood pressure and the rate-pressure product were significantly higher in the ketamine group. These investigators found no significant difference in the two anesthetic techniques in terms of perioperative morbidity and mortality. In a controlled study of the circulatory responses during induction and maintenance of anesthesia in patients undergoing heart-valve replacement, Dhadphale *et al.*[246] found no significant differences between the ketamine–diazepam/N_2O and morphine/N_2O tech-

TABLE 2. Chronological Summary of Clinical Studies Using Continuous Infusion Techniques for Administering Ketamine

Investigator and Reference	Surgical Procedure	Premedication	Induction Agents		Maintenance Agents		Cardiovascular Stimulation*	Emergence Reactions*
			Adjuncts (mg/kg)	Ketamine (mg/kg)	Ketamine $\mu g \cdot kg^{-1} \cdot min^{-1}$	Adjuncts (Per Cent)		
Oduntan and Gool (1970)[44]	general	0	0	1.0–1.2	25–33	O_2 (100)	++	+
Little *et al.* (1972)[47]	obstetrical	0	0	1.5–2.2	80–110	O_2 (100)	+++	++
Jastak and Gorretta (1973)[227]	oral	diazepam 5–10 mg	0	0.5–1.0	65–70	N_2O/O_2 (50/50)	++	+
Vaughan and Stephens (1974)[206]	thoraco-abdominal†	0	0	2.0	18–20	N_2O/O_2 (50/50)	++	+
Ito and Ichiyanagi (1974)[249]	postoperative pain	secobarbitone 100 mg hydroxyzine 50 mg	0	0	25	O_2 (100)	0	0
Hatano *et al.* (1976)[244]	cardiac	diazepam 10–15 mg	diazepam 0.3–0.5	1.0	12	N_2O/O_2 (50/50)	0	0
El-Naggar *et al.* (1977)[237]	gynecological	diazepam 10 mg	0	0.3	17–34	N_2O/O_2 (66/34)	+	0
Hatano *et al.* (1978)[251]	abdominal	hydroxyzine 50–100 mg or diazepam 7.5–15 mg	diazepam 0.2–0.3	1.3–2.0	10–15	N_2O/O_2 (66/34)	+	0
Houlton and Downing (1978)[73]	abdominal	omnopon 10–15 mg	flunitrazepam 0.03	0	33	O_2 (100)	0	0
Jackson *et al.* (1978)[116]	cardiac	morphine sulfate 5–15 mg	diazepam 0.4	2.0	90	O_2(100)	0	0
Kamm and Bewes (1978)[252]	general	haloperidol 0.1 mg/kg	0	0.5–1.0	14–28	O_2(100)	++	++
Lilburn *et al.* (1978)[253]	plastics-gynecological	lorazepam 4 mg	0	1.0	66–83	O_2 (100)	++	0
Dhadphale *et al.* (1979)[245]	cardiac	morphine sulfate 5–10 mg	diazepam 0.4	2.0	17	N_2O/O_2 (50/50)	+	0
Idvall *et al.* (1979)[77]	abdominal†	atropine 0.5 mg	0	2.0	41	N_2O/O_2 (50/50)	++	+
Wilson *et al.* (1979)[254]	general	diazepam 0.1 mg/kg	diazepam 0.2–0.3	1.0	64	N_2O/O_2 (66/34)	0	0
Barclay *et al.* (1980)[74]	gynecological	papaveretum 10–15 mg atropine 0.6 mg	flunitrazepam 0.03	0	16–31	N_2O/O_2 (40/60)	+	+
Pandit *et al.* (1980)[255]	none	atropine 0.3 mg diazepam 0.2 mg/kg	0	1.0	8–17	0	+	+

* Relative scale: 0 = none or minimal, + = mild, ++ = moderate, +++ = severe.

† Elderly, high-risk patient populations.

TABLE 3. General Recommendations for the Use of Ketamine as a Sedative, Analgesic and Anesthetic Agent

1) Premedication: A benzodiazepine administered either orally (*e.g.*, diazepam, 15–30 mg, lorazepam, 2–5 mg) 60–90 min before surgery or smaller doses iv immediately prior to induction as an adjunct to ketamine. If preoperative sedation is contraindicated, a benzodiazepine can be administered iv prior to the termination of surgery. A noncentrally active antisialogogue (*e.g.*, glycopyrrolate, 0.005 mg/kg, iv) administered 5–10 min prior to induction.

2) Induction of anesthesia: Ketamine, 0.5–1.5 mg/kg, iv, or 4–6 mg/kg, im. Lower doses of ketamine are used if thiopental (1–2 mg/kg, iv) is used as an adjunct in place of the benzodiazepine or if the patient is critically ill.

3) Maintenance of anesthesia: Ketamine, 10–30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (1–2 mg/min) via continuous iv infusion. If high concentrations of inspired oxygen are not required to maintain adequate tissue oxygenation, supplemental N_2O 50–70 per cent in oxygen will reduce the ketamine requirement.

4) Sedation and analgesia: Ketamine, 0.2–0.75 mg/kg, iv (over 2–3 min) or 2–4 mg/kg, im, followed by continuous ketamine infusion 5–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with or without supplemental oxygen.

niques. It would appear that high-dose diazepam (0.5 mg/kg, iv) in combination with ketamine (1–2 mg/kg for induction and 15–30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for maintenance) is a satisfactory alternative to morphine–N_2O anesthesia for patients with coronary artery disease as well as for those undergoing heart valve replacement. A potential advantage of the diazepam/ketamine technique is that the nitrous oxide concentration is not critical and therefore 100 per cent oxygen can be utilized.

When used for induction of anesthesia in patients with valvular heart disease ketamine produced increases in pulmonary vascular resistance and increased the minute work of the heart.[247] Thus, ketamine might be deleterious to patients with limited right ventricular functional reserve (*e.g.*, pulmonary emboli). However, many cardiac anesthetists consider ketamine the drug of choice for induction and maintenance of anesthesia in patients with cardiac tamponade or constrictive pericarditis because of its ability to maintain sympathetic nervous system activity, even though the pulmonary vascular resistance may be further increased by ketamine. Finally, when one-lung anesthesia is utilized during thoracic surgery, patients with impaired pulmonary function are reportedly improved with regard to Pa_{O_2} and calculated pulmonary shunt fraction when a diazepam–ketamine–relaxant oxygen anesthetic technique is compared to a conventional inhalational technique.[248]

Conclusions

Ketamine is a safe, rapid-acting parenteral anesthetic and analgesic agent which has been in clinical use for more than 10 years. In early investigations, it was noted that ketamine produced marked elevations in blood pressure and heart rate, profuse salivation, lacrimation, dia-

TABLE 4. Clinical Uses of Ketamine and Contraindications to Its Use

I. Indications for ketamine anesthesia or analgesia
- A. Aged and poor-risk patients:
  1. shock or cardiovascular instability
  2. severe dehydration
  3. respiratory failure or bronchospasm
  4. severe anemia
  5. major thoracoabdominal procedures
  6. cardiac tamponade and constrictive pericarditis
- B. Obstetrical patients:
  1. rapid induction of general anesthesia
     a. severe hypovolemia
     b. acute hemorrhage
     c. acute bronchospasm
  2. low-dose for analgesia
     a. supplement regional technique
     b. transient analgesia at the time of delivery or during postpartum period
- C. Adjunct to local and regional anesthetic techniques:
  1. low-dose for sedation and analgesia during performance of nerve block procedure
  2. supplemental analgesia for inadequate block
- D. Outpatient surgery:
  1. Pediatric anesthesia
     a. brief diagnostic and therapeutic procedures (*e.g.*, cardiac cath; endoscopy; oral surgery; head and neck surgery; orthopedic surgery; opthalmalogy; radiotherapy)
     b. induction of anesthesia (*e.g.*, intramuscular or rectal route)
  2. Adult anesthesia
     a. brief surgical procedures (*e.g.*, gynecological, head and neck, orthopedic, urologic)
     b. supplement local and regional techniques
     c. diagnostic and therapeutic procedures (*e.g.*, endoscopy)
- E. Patients with reactive airway disease:
  1. asthmatics with acute bronchospasm
  2. chronic obstructive pulmonary disease with bronchospasm
- F. Patients with thermal injuries:
  1. debridement and skin grafting
  2. dressing changes
- G. Postoperative analgesia:
  1. recovery room
  2. intensive care units

II. Contraindications to the use of ketamine
- A. Cardiovascular disease:
  1. poorly controlled hypertension
  2. intracranial, thoracic or abdominal aneurysms
  3. unstable angina or recent myocardial infarction
  4. right or left heart failure
- B. Central nervous system disorders:
  1. cerebral trauma
  2. intracerebral mass or hemorrhage
- C. Open-globe injury to eye or increased intraocular pressure*
- D. Thyrotoxic states*
- E. Otolaryngologic procedures involving pharynx, larynx or trachea*
- F. Psychiatric disorders (*e.g.*, schizophrenia) or history of adverse reaction to ketamine or one of its congeners*

* Indicates a *relative* contraindication to the use of ketamine.

phoresis, skeletal muscle hypertonus, involuntary purposeless movements, and agitation or even frank delirium during emergence. Subsequent studies have shown that benzodiazepines, are highly effective in preventing the marked cardiovascular responses and unpleasant emergence reactions associated with ketamine anesthesia. Furthermore, by utilizing a continuous infusion technique the anesthetist can titrate the drug more closely and thereby reduce the amount of drug administered. In table 2 we have summarized the clinical studies which have appeared in the literature during the last ten years using a variety of adjunctive ketamine infusion techniques. The information contained in table 2 indicate the efficacy of various adjunctive agents in attenuating the adverse cardiovascular and psychic emergence reactions associated with ketamine anesthesia. Utilizing this information and our own clinical experience with ketamine, we have developed table 3 which summarizes our general recommendations regarding the use of ketamine.

It is obvious that many of the goals desirable in an ideal intravenous anesthetic (table 1) have not been reached with currently available agents. In fact, ketamine is the only available iv agent which can function as a sole anesthetic (without requiring adjunctive agents) because of its unique sedative, amnestic, analgesic, and anesthetic properties. How well then do racemic ketamine and its (+) isomer compare to the ideal iv anesthetic agent? In terms of physical properties, both of these drugs possess all the desired properties. They are water-soluble, stable in solution, and painless and nonirritating following parenteral injection. Racemic ketamine produces a rapid onset of action, frequent excitatory activity and hypertonus, minimal (if any) cardiorespiratory depression, analgesia, amnesia, rare (if any) hypersensitivity reactions, and a relatively rapid recovery with frequent emergence reactions. S(+)-ketamine has similar anesthetic properties, however, it is associated with a lower incidence of excitatory motor activity, less marked tachycardia, and a smoother recovery without emergence excitement or delirium. Although (+)-ketamine comes very close to the ideal, it seems unlikely that a single drug will be developed which will possess all the properties desired in the ideal iv agent. The use of iv anesthetic techniques utilizing combinations of short-acting compounds with mutually complementary pharmacologic properties allows for more control in terms of the depth and duration of anesthesia, while reducing the potential for adverse drug interactions in the postoperative period. We would speculate that combining S(+)-ketamine with midazolam, a water-soluble benzodiazepine possessing a pharmacokinetic profile similar to that of ketamine, would produce an ideal iv anesthetic combination.

We see potential clinical applications for adjunctive ketamine techniques in anesthesia for major surgery and outpatient anesthesia (as an anesthetic, analgesic, and sedative adjunct during general, regional and local anesthesia), as well as increased use in the recovery area for postoperative pain relief.[249,250] The current clinical uses of ketamine as well as the contraindications to its use are summarized in table 4. It should be noted that in several areas the indications and contraindications are not supported by well-controlled clinical studies.

It has been our intent in this review to bring the pharmacologic information available on ketamine into focus and to then use this information as a background upon which to discuss ketamine's potential clinical uses. It is apparent that this drug is not the ideal intravenous anesthetic; however, its many useful pharmacologic properties hopefully will spur the search for agents which will be closer to the ideal.

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