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Pharmacology of Ketamine Isomers in Surgical Patients

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To assess the intraoperative and postoperative effects of the optical isomers of ketamine compared with the racemic mixture as sole anesthetics, equianesthetic doses of racemic ketamine (RK), 2 mg/kg, (+)ketamine (PK), 1 mg/kg, and (−)ketamine (MK), 3 mg/kg, were administered intravenously in a randomized, double-blind fashion to 60 healthy patients undergoing elective outpatient operations. Intraoperative effects, adequacy of anesthesia, and need for adjunctive agents were assessed by the same two anesthesiologists. Psychologic assessment was achieved utilizing a trait anxiety scale, a profile of mood states questionnaire, an open-ended sentence-completion form, and a postoperative check list, as well as observations made by a psychologist in the recovery room. Samples of plasma and urine were obtained for gas chromatographic analysis of ketamine and its major metabolites. The durations of anesthesia (35 ± 4 min) were the same in all three groups; however, the amounts of drug needed ranged from 2.4 mg/kg in the PK group to 8.5 mg/kg in the MK group. At the termination of anesthesia, mean plasma levels of the parent compounds were 0.9 (RK), 0.5 (PK), and 1.7 μg/ml (MK), consistent with a PK:MK potency ratio of 3.4:1. The slopes of the plasma decay curves were not significantly different among the three groups. PK was judged to produce more effective anesthesia than RK or MK (95 *vs.* 75 *vs.* 68 per cent). Verbal responses in the postanesthetic period suggested significantly more psychic emergence reactions after MK than after RK or PK (37 *vs.* 15 *vs.* 5 per cent). Furthermore, MK produced more agitated behavior than did RK or PK (26 *vs.* 10 *vs.* 0 per cent). Postoperative pain occurred more commonly in the RK (10 per cent) and MK (16 per cent) groups than in the PK group (0 per cent). The incidences of dreaming (84 per cent) were the same in all three groups. Relative to preoperatively, fear was decreased to a greater extent postoperatively in the PK group than in the RK and MK groups (43 *vs.* 13 *vs.* 30 per cent). Finally, patients found PK more acceptable than either RK or MK (85 *vs.* 65 *vs.* 63 per cent). The study disclosed differences in anesthetic potencies, intraoperative effects, analgesia, physical side effects, incidences and types of postanesthetic emergence phenomena, and anesthetic preferences among the optical isomers of ketamine. Parallelism of the plasma decay curves and similarities in the patterns of appearance and excretion of the ketamine metabolites for the three groups suggest that the differences were due to pharmacodynamic factors. (Key words: Anesthetics, intravenous: ketamine. Potency, anesthetic. Recovery: ketamine.)

KETAMINE is an easily administered parenteral anesthetic that produces profound analgesia at subanesthetic doses and lacks the cardiorespiratory depression seen with most other general anesthetic agents. Despite these important clinical advantages, disturbing emergence reactions[1] (ranging in incidence from less than 5 per cent[2,3] to more than 30 per cent[4,5]) have limited its usefulness. The ketamine molecule contains a chiral center so that it exists as two optical isomers, or enantiomers. Yet all published clinical studies to date have utilized only the racemic mixture.

Our laboratory has recently investigated the pharmacologic properties of the individual ketamine enantiomers in animals.[6–8] The (+)isomer of ketamine was shown to elicit periods of hypnosis lasting nearly twice as long as those obtained with the (−)isomer following administration of equimolar doses, with the racemate being of intermediate potency.[6,7] This difference appeared to have a pharmacodynamic basis, as differences were not found in plasma or brain ketamine levels for either the individual isomers or the racemate. Furthermore, at equihypnotic doses, (+)ketamine produced more profound analgesia and caused significantly less postanesthetic stimulation of locomotor activity. More recent studies[8] have demonstrated a differential effect of the ketamine isomers on schedule-controlled responding behavior. These differences between the enantiomers suggest both quantitative and qualitative differences in the central nervous system (CNS) effects of racemic ketamine and its individual isomers. The (+)isomer of ketamine may provide anesthesia that is safer and has fewer posthypnotic side effects than the currently used racemic mixture. To evaluate the possible clinical significance of these findings, studies with the ketamine enantiomers in man were initiated. Our study was designed to assess 1) the relative anesthetic potencies of the ketamine isomers; 2) the adequacy of anesthesia produced by each isomer compared with racemic ketamine; 3) the cardiovascular stimulation produced by the isomers; 4) possible correlations between plasma levels of ketamine and durations of anesthesia; 5) emergence behavior and side effects in the recovery room; 6) the analgesia produced following administration of equihypnotic doses of the ketamine isomers; 7) the relative incidences of posthypnotic emergence reactions at equianesthetic doses of the isomers; 8) patient acceptability of the ketamine isomers as sole anesthetics compared with the currently available racemic mixture.

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Methods

Sixty consenting adult patients, ASA physical status I or II, who were scheduled for minor operations (*e.g.*, dilatation and extraction or curettage) were assigned in a random, double-blind fashion to one of three treatment groups. One group (n = 20) received racemic ketamine,¶ a second group (n = 21) received (+)ketamine, and the third group (n = 19) received (−)ketamine. No patient who had received ketamine previously or who was aware of the psychologic effects of the drug or its chemically-related congeners was included in the study.

Based on our studies in animals,[6-8] the (+)isomer of ketamine was assumed to be approximately three times more potent as an anesthetic than (−)ketamine. In order to assess the pharmacologic properties of the isomers at equihypnotic doses and yet allow the study to be performed in a double-blind fashion, it was necessary to administer equal volumes of different concentrations of the three agents. Hence, solutions of the ketamine isomers were prepared by dissolving the hydrochloride crystals in solutions containing sodium chloride, 3 mg/ml, benzethonium chloride, 0.1 mg/ml, and sterile water, to final free base concentrations of 25 mg/ml for the (+)isomer and 75 mg/ml for the (−)isomer. The chemical compositions of the isomer solutions were identical to that of the commercially available product except for the ketamine constituent. The purity of the crystalline hydrochloride salts of the (+) and (−)ketamine isomers was determined using optical rotation, with $[\alpha]_D25 = +92.48°$ (c2.00, water) and $[\alpha]_D25 = -91.88°$ (c2.00, water), respectively. The isomer solutions, as well as a racemic solution (50 mg/ml), were filtered and bottled aseptically, with numbers 1 through 60 assigned randomly.

Prior to a scheduled surgical procedure, the attending anesthesiologist would provide the patient with a standardized description of possible side effects and emergence phenomena that might occur following any general anesthetic agent. We were required by the UCSF Committee on Human Research to tell the patients that ketamine differed from other general anesthetics in that it produced "a higher incidence of dreaming" and that "these dreams may be vivid or disturbing." The IPAT trait anxiety scale,[9] a simple self-analysis form consisting of 40 statements (patients respond with "yes," "in between," or "no") was administered at the time of the preoperative visit. Patients received no premedicant except glycopyrrolate, 0.005 mg/kg, which was administered intravenously as an antisialagogue approximately 5–10 min prior to induction of anesthesia.

Since the anesthesiologist administering the ketamine was unaware of which of the three solutions was being employed, equivolumic induction and maintenance doses of 0.04 ml/kg and 0.02 ml/kg, respectively, were used. Therefore, patients receiving racemic ketamine received 2 mg/kg for induction with periodic maintenance bolus injections of 1 mg/kg as needed to complete the operation. Patients receiving either the (+) or the (−) isomer solution received a 1 mg/kg or a 3 mg/kg bolus injection, respectively, for induction of anesthesia, and 0.5 mg/kg and 1.5 mg/kg bolus injections, respectively, for maintenance when the operations necessitated deeper or more prolonged anesthesia. All doses were given intravenously. The anesthetics were administered by titrating the dose of ketamine against clinical signs of anesthesia, which consisted primarily of the presence or absence of purposeful responses to noxious stimuli. In cases where adequate surgical anesthesia could not be achieved with ketamine alone, adjunctive agents (*e.g.*, thiopental and nitrous oxide) were employed. The dosing intervals, total volume of drug injected, and duration of anesthesia (*i.e.*, time from induction to initiation of a purposeful response to a command) were recorded, as well as the maximum changes in systolic blood pressure, heart rate, and respiratory rate. The attending anesthesiologist recorded the degrees of spontaneous movement, hypertonus, and vocalizations on an arbitrary scale ranging from 0 to 4+ (maximum). In addition, the presence of either upper-airway obstruction or nystagmus was recorded. At the completion of the operation, the adequacy of anesthesia was assessed by the anesthesiologist and surgeon based on the above criteria and whether or not adjunctive agents were needed to complete the operation. Venous blood samples were obtained at 1-, 5-, 10-, 15-, 20- and 30-min intervals initially and subsequently at hourly intervals until the time of discharge (range two to four hours). Additionally, urine specimens were obtained two to four hours after induction of anesthesia. The plasma and urine specimens were assayed for ketamine and its principal metabolites, N-demethylated or norketamine (metabolite I) and its cyclohexenone oxidation product (metabolite II), using a modified version of the gas chromatographic procedure of Chang and Glazko[10] as described previously.[11]

Following completion of the operation, the patients were taken to the recovery room, where they were observed by a psychologist, who recorded their verbal and motor responses during emergence from ketamine anesthesia, side effects from the anesthesia,

¶ Ketalar®, Parke-Davis Products, Division of Warner-Lambert Company, Morris Plains, New Jersey 07950.

TABLE 1. Age, Weight, State and Trait Anxiety Levels and Preoperative Assessment of Personality Profiles for the Three Study Groups (Means ± SEM)

	Range	Racemate	(+)Ketamine	(−)Ketamine
Number of patients	19–21	20	21	19
Age (years)	18–68	26 ± 2	26 ± 2	31 ± 4
Weight (kg)	42–95	64 ± 3	60 ± 2	66 ± 3
Trait anxiety (IPAT score)	7–53	29 ± 3	35 ± 2*	28 ± 2
Sten score	1–10	5.3 ± 0.5	6.6 ± 0.4*	5.2 ± 0.4
Personality trait components†				
Q_3 (low self-control)	0–11	5.0 ± 0.5	5.9 ± 0.4	4.9 ± 0.4
C (emotional instability)	1–8	4.1 ± 0.4	5.1 ± 0.4*	3.5 ± 0.4
L (suspicion)	0–8	2.9 ± 0.4	3.8 ± 0.2*	2.5 ± 0.3
O (apprehension)	3–16	9.2 ± 0.6	11.1 ± 0.5*	9.3 ± 0.5
Q_4 (tension)	0–18	7.1 ± 0.8	8.8 ± 0.7	7.6 ± 0.9
State anxiety (degree of fear‡)	1–4	2.3 ± 0.2	2.8 ± 0.2	2.7 ± 0.3

* Isomer group that differed significantly ($P \leq 0.05$) from either the racemic group or its enantiomer.

† Intensity of the personality component is directly related to the magnitude of the score recorded.

‡ Scaled score: 1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much.

and any specific therapy needed, as well as the duration of time in the recovery room. All patients were told where they were, that "everything was all right," and that someone would remain with them in the recovery room. The patients were given a profile of mood states (POMS)[12] questionnaire one to two hours after awakening from anesthesia. The following day, each patient completed a repeat POMS, an open-ended sentence-completion form, and a check list of possible emergence phenomena developed by Garfield *et al.*[13] (the check list was administered after the sentence-completion form to avoid biasing the responses). Patients were contacted three to four months after operation to reassess their opinions of ketamine anesthesia and to inquire whether any untoward sequelae (*e.g.*, "flash-back" reactions) had occurred during this period. Follow-up evaluations were obtained from 48 (80 per cent) of the patients.

Responses to the IPAT were scored with respect to overall trait anxiety, and a Sten score obtained by comparing a given patient's score with published norms for an equivalent population matched for sex, age, and educational background. In addition, subscores for primary overt and covert anxiety components (*e.g.*, self-control, emotional stability, tension, apprehension, and suspicion/jealousness) were obtained. The IPAT scores, as well as all other continuous variables, for the three groups were statistically analyzed using SPSS version 7.0 one-way analysis of variance. The POMS questionnaire assessed tension/anxiety, depression/dejection, anger/hostility, vigor, fatigability and confusion/bewilderment. The POMS scores recorded in the recovery room immediately after emerging from anesthesia were compared with the follow-up scores using a Student *t* test for paired data. The motor and verbal responses recorded in the recovery room, as well as the responses to the sentence completion form, were condensed to quantifiable data by a coding system that assigned the responses to mutually-exclusive categories. Categorical variables were analyzed using SPSS version 7.0 chi-square analysis. Finally, the patients' preferences for future anesthesia and factors that might predispose to adverse reactions to ketamine anesthesia were evaluated using three-dimensional crosstabulation analyses.

Results

The three ketamine treatment groups (table 1) were comparable with respect to age, weight, and preoperative state anxiety (*i.e.*, expressed fear). However, the (+)ketamine group had the most preoperative anxiety on the IPAT scale. In further analyzing the differences in overall anxiety scores with respect to the primary trait components, it became apparent that the (+)isomer group was more emotionally unstable and easily upset, as well as more suspicious, jealous and "hard-to-fool." Evaluating how the patients stated they felt before the surgical procedures showed that 80 per cent of the (+)ketamine group reportedly felt scared or apprehensive, in contrast to 70 per cent and 60 per cent for the racemic and (−)ketamine groups, respectively. With respect to the object of their fear, 21 per cent of the patients overall were concerned about the anesthesia; however, there was no significant difference among the three groups.

The patients were given equianesthetic induction doses and additional maintenance injections, equal to half the induction doses, as needed to complete the operations. The mean total doses of ketamine administered per patient ranged from 143 mg for the (+)isomer to 557 mg for the (−)isomer (table 2); how-

TABLE 2. Intraoperative Assessment of Ketamine Anesthesia, Including Total Dosage Administered, Duration of Anesthesia, Cardiorespiratory Changes, Verbal and Motor Activity, and Adequacy of Anesthesia (Means ± SEM)

	Range	Racemate	(+)Ketamine	(−)Ketamine
Induction dose (mg/kg)	1–3	2	1	3
Total dosage				
(mg)	73–2,183	348 ± 48	143 ± 10*	557 ± 101*
(mg/kg)		5.4	2.4	8.5
Duration of anesthesia (min)†	15–175	41 ± 8	32 ± 4	33 ± 7
Peak increase in systolic blood pressure (torr)	10–80	32 ± 3	25 ± 3	32 ± 4
Peak increase in heart rate (beats/min)	5–70	35 ± 4	25 ± 3*	30 ± 3
Peak increase in respiratory rate (breaths/min)	0–10	0.5 ± 0.3	1.2 ± 0.7	0
Presence of any upper airway obstruction (per cent)		20	10	16
Spontaneous movements‡	0–4	1.9 ± 0.4	1.1 ± 0.2*	1.9 ± 0.3
Hypertonus‡	0–4	0.8 ± 0.3	0.6 ± 0.2	0.9 ± 0.3
Vocalizations‡	0–4	0.7 ± 0.2	1.1 ± 0.2	1.5 ± 0.4
Eyes open (per cent)		93	87	92
Nystagmus (per cent)		67	78	100
Adequate anesthesia (per cent)†		75	95*	68
Adjunctive agents necessary (per cent)		20	5*	26

* Isomer group that differed significantly ($P \leq 0.05$) from either the racemic group or its enantiomer.

† Refer to Methods section for definitions of duration and adequacy of anesthesia.

‡ Scaled score: 0 = none, 1 = minimal, 2 = moderate, 3 = severe, and 4 = extreme.

ever, the durations of anesthesia produced were not significantly different. A calculated ratio based on total dose, body weight, and duration of anesthesia revealed that the (+)isomer of ketamine was approximately 3.4 times more potent as an anesthetic agent than the (−)isomer. The time from onset of anesthesia to discharge from the outpatient surgery department was two to three hours, and the ratios of time prior to discharge relative to the duration of anesthesia were identical for all three groups.

Evaluation of the intraoperative effects of ketamine and its isomers (table 2) showed that heart rate and systolic blood pressure were increased in all three groups; however, the (+)isomer produced less stimulation of heart rate and less increase in the rate–pressure product following administration of equihypnotic doses. While neither isomer caused upper-airway obstruction or a significant change in respiratory rate, (+)ketamine produced less spontaneous motor activity than either racemic ketamine or the (−)isomer. In terms of the overall adequacy of anesthesia, (+)-ketamine was judged to produce more effective anesthesia than either racemic or (−)ketamine. Of the patients receiving the (−)isomer, 26 per cent needed adjunctive agents to complete the operation, while an inadequate anesthetic state was judged to occur in only one case when (+)ketamine was used alone.

Evaluation of emergence phenomena and the side effects of ketamine and its isomers in the immediate postanesthetic period by analysis of the verbal responses suggests that significantly more psychic emergence reactions (*e.g.*, vivid illusions, "weird trips," sensations of drunkeness or delirium) occurred after (−)ketamine (table 3). Also, a lower incidence of amnesia for the operation was recorded following (−)ketamine anesthesia. With respect to observed motor activity in the recovery room, emergence from (−)ketamine was associated with significantly more restlessness, thrashing or combative behavior. Disorientation, agitation and pain also occurred more commonly in the racemic and (−)ketamine groups. A further assessment of the analgesic properties of the ketamine enantiomorphs revealed that four times as many patients in the (−)isomer group reported experiencing pain as compared with the (+)ketamine group (table 4). Although medication was rarely needed to control pain or any of the other side effects following ketamine anesthesia, narcotics were more commonly administered to patients in the (−)ketamine group.

The POMS questionnaire administered in the recovery room revealed significantly higher levels of confusion–bewilderment and fatigue, with a corresponding lower level of vigor, than was recorded in

the follow-up study after the patients had fully recovered from the effects of ketamine. However, there was no statistically significant difference among the groups.

Although a higher percentage of patients in the (+)ketamine group reported being conscious during the surgical procedure (table 4), none of the patients was actually aware of the events taking place in the operating room. Of the patients who reported being conscious during ketamine anesthesia, none was inadequately anesthetized clinically, nor did they express negative feelings about the anesthetic. The overall incidence of dreaming was 84 per cent, and incidences did not differ significantly among the three groups. Of the patients reporting dreams during ketamine anesthesia, 70–80 per cent stated that the dreams were unlike any they had experienced previously. Many of our patients described the dreams as a sensation of traveling through space and time while consciousness was dissociated from the physical body. Although the overall frequency of unpleasant dreams was low, the (−)ketamine group reported the highest incidence.

Postoperative fear (table 4) was decreased to a greater extent, relative to preoperative fear (table 1), in the (+)ketamine group (43 per cent) than in either the racemic (13 per cent) or (−)ketamine (30 per cent) groups. When compared with the racemate (table 4), the incidence of a postoperative feeling of loss of control was found to be decreased in the (+)ketamine group, while nausea and dizziness were reported less frequently in the (−)ketamine group. Happiness and a general sense of well-being were reported more frequently in the (+)ketamine group. A floating sensation was reported by 40–50 per cent of the patients studied.

When questioned regarding the type of anesthesia they would prefer in the event that further surgical treatment was necessary, patients reported that they

TABLE 3. Incidences of Commonly Recorded Verbal and Motor Responses, Side Effects, and Therapeutic Interventions during Emergence from Ketamine Anesthesia: Values Represent Percentages of Patients in a Given Group

	Racemate	(+)Ketamine	(−)Ketamine
Verbal responses (per cent)			
1) Complained of physical side effects secondary to operation or anesthesia	25	29	11
2) Amnesia regarding the surgical procedure	15	24	5*
3) Discussed dreaming and/or floating sensation	10	29	11
4) Complained of vivid illusions, "weird trip" or sensation of drunkenness	5	5	37*
5) Delirious with spontaneous vocalization	10	0*	16
6) Miscellaneous responses (*e.g.*, groggy, pain, concern about anesthetic)	35	10	21
Motor responses (per cent)			
1) Calm, quiet, relaxed and cooperative	50	71*	47
2) Slurred speech, otherwise calm	0	10	0
3) Spontaneous movements of extremities only	35	10	11
4) Restless, thrashing and/or combative	10	0*	26
5) Miscellaneous responses (*e.g.*, tremulous, shivering, grimacing, vomiting)	5	10	16
Side effects (per cent)			
1) Dizziness and/or lightheadedness	35	48	37
2) Visual distortions	45	24	32
3) Agitation and/or disorientation	30	0*	32
4) Pain	10	0*	16
5) Nausea and/or vomiting	45	33	21
Therapy required (per cent)			
1) Sedative–hypnotic	10	0	5
2) Narcotic analgesic	5	0*	16
3) Phenothiazine antiemetic	0	10	5

* Isomer group that differed significantly ($P \leq 0.05$) from either the racemic group or its enantiomers by univariant analysis.

TABLE 4. Patients' Evaluations of the Operative and Emergence Periods and Future Anesthetic Preferences Following Complete Recovery from Ketamine Anesthesia: Values Represent Percentages of Patients in a Given Group

	Racemate	(+)Ketamine	(−)Ketamine
Operative period (per cent)			
Conscious during operation	5	21	6
Dreaming,† overall	85	84	83
Pleasant experiences	70	63	56
Unpleasant experiences	5	11	22
Unable to recall	10	11	6
Emergence period (per cent)			
Pain	10	5	22
Loss of control	40	16*	44
Nausea	45	42	17*
Dizziness	75	84	50*
Happy and felt like laughing	40	74*	33
Postoperative anxiety (scaled score)			
State anxiety, degree of fear	2.0 ± 0.2	1.6 ± 0.1*	1.9 ± 0.2
Anesthetic preference (per cent)			
Ketamine desirable or acceptacle	65	85*	63

Note: Data are based on information obtained 24 hours or more after the patients awakened from ketamine anesthesia.

* Isomer group that differed significantly ($P \leq 0.05$) from either the racemic group or its enantiomer.

† Refer to Discussion section for definition of dreaming.

‡ Scaled score: 1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much.

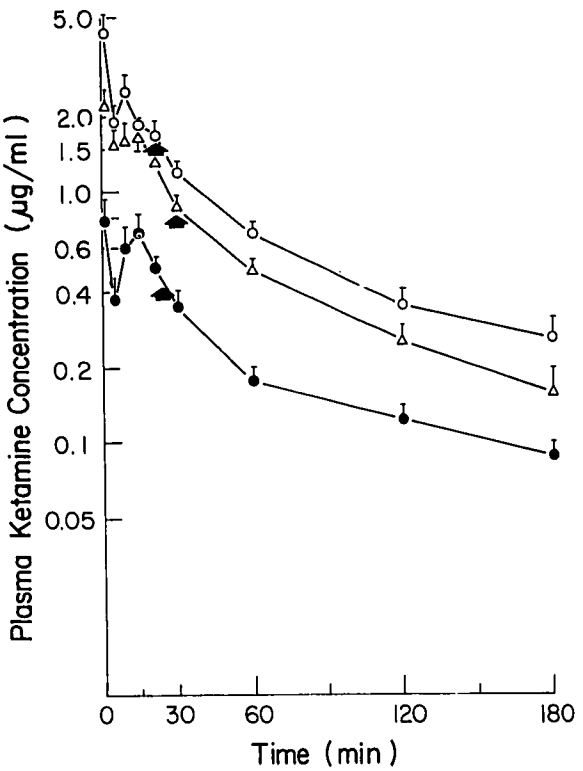

FIG. 1. Plasma levels of ketamine on a logarithmic scale as a function of time in those patients who received at most two additional bolus injections after induction with racemic ketamine, 2 mg/kg, iv (n = 7, △——△), (+)ketamine, 1 mg/kg, iv (n = 8, ●——●), or (−)ketamine, 3 mg/kg, iv (n = 7, ○——○). Arrowheads indicate time of emergence from anesthesia (*i.e.*, time of purposeful response to a command). Values are means ± SEM.

found (+)ketamine more acceptable than either the racemate or (−)ketamine (table 4). In general, patients that were interviewed at a later date in order to re-evaluate their opinions of ketamine indicated either no change or more positive feelings about ketamine anesthesia. Only one patient reported a subsequent psychological experience that might be classified as a late sequela (*i.e.*, a subsequent dream reminiscent of the ketamine anesthesia dream), after receiving racemic ketamine.

At the time of emergence from anesthesia (*i.e.*, the time a purposeful response was made to a verbal command), the mean plasma levels of the racemate, (+)ketamine, and (+)ketamine were 0.9, 0.5, and 1.7 μg/ml, respectively (fig 1). The increase in plasma ketamine concentrations that occurred 10–15 min following induction represents maintenance doses given. The plasma decay curves for the parent compound and norketamine (metabolite I) are not different in slope among the three groups (figs. 1 and 2). Similarly, the rates of appearance of the cyclohexenone metabolite (metabolite II) appeared to be similar following administration of the racemate and either of the ketamine isomers (fig. 3). Finally, the urinary excretion patterns for ketamine and its major metabolites were similar in all three groups. Of the compounds recovered from the urine during the first two to four hours following induction of anesthesia, metabolite II accounted for approximately three fourths, and the remaining fourth was almost evenly divided between metabolite I and ketamine itself.

Discussion

Our study has disclosed several pharmacologic differences among the individual optical isomers of ketamine. These include differences in anesthetic potencies, as well as clinically important differences in intraoperative effects, analgesia, physical side effects, incidences and types of postanesthetic emergence phenomena, and future anesthetic preferences.

An objection to ketamine anesthesia has been the unacceptably high incidences of spontaneous move-

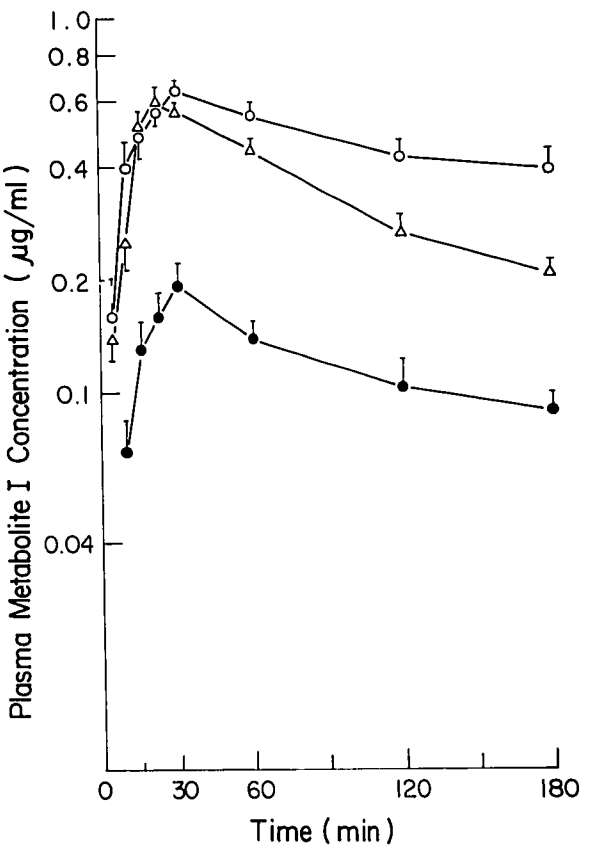

FIG. 2. Plasma levels of norketamine (metabolite I) on a logarithmic scale as a function of time in patients receiving at most two additional bolus injections after induction with racemic ketamine, 2 mg/kg, iv (n = 7, △——△), (+)ketamine, 1 mg/kg, iv (n = 8, ●——●), or (−)ketamine, 3 mg/kg, iv (n = 7, ○——○). Values are means ± SEM.

ments, hypertonus, and vocalizations occurring during the intraoperative and postoperative periods. The (+)isomer of ketamine provided significantly better operating conditions with less spontaneous motor activity than either (−)ketamine or the racemate. In the recovery period, patients who had received the (−)isomer of ketamine were found to be significantly more restless, agitated, disoriented, and combative. In general, patients recovering from (+)-ketamine anesthesia were calm, quiet and cooperative in the recovery room. In those rare situations (5 per cent overall) where sedative–hypnotic medication was needed to calm an agitated, disoriented, delirious or combative patient, diazepam, 5–10 mg, intravenously, was found to be highly effective.

Although the preoperative assessment of trait anxiety revealed that the patients in the (+)ketamine group were more anxious than those in the other two groups in our study, there were no significant differences in the levels of preoperative state anxiety. The overall levels of state anxiety were decreased in all three groups postoperatively; however, the decrease in the (+)ketamine group was significantly greater. Thus, even though the group receiving the (+)isomer was more apprehensive and scared about the anesthetic preoperatively, they were less fearful postoperatively and expressed a greater preference for ketamine anesthesia in the future. While it is possible that the higher level of preoperative trait anxiety in the (+)ketamine group contributed to their stated preference for future anesthesia, we found no correlation between age, trait anxiety, adequacy of anesthesia or consciousness during the surgical procedure and dreaming or future preference for ketamine anesthesia.

A major clinical advantage of ketamine anesthesia is the profound analgesia it produces, which has been reported to occur at subhypnotic doses.[14,15] In mice,[7] the analgesic potency ratio between the ketamine isomers exceeded the ratio for hypnotic activity. In our study, analgesia was detected at subanesthetic levels for both isomers; however, this was most evident in the (+)ketamine group. Although the incidences of postoperative pain were low in all three groups, none of the patients in the (+)ketamine group reported experiencing pain while in the recovery room. Thus, it would appear that at equianesthetic doses, the (+)-isomer of ketamine may be an even more potent analgesic than the (−)isomer.

The major objection to the use of ketamine in adult patients has been the reportedly high incidence of psychic emergence reactions.[4,5] Based on results from a controlled study, Garfield *et al.*[13] concluded that ketamine has the property of producing visual,

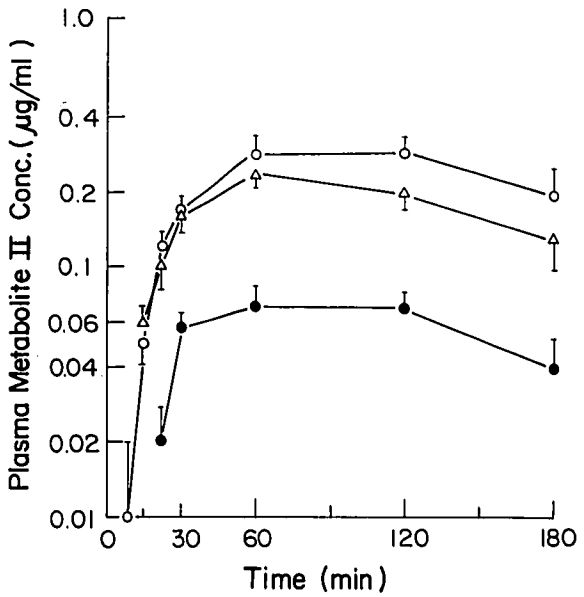

FIG. 3. Plasma levels of the cyclohexenone metabolite of norketamine (metabolite II) on a logarithmic scale as a function of time in patients receiving at most two additional bolus injections after induction with racemic ketamine, 2 mg/kg, iv (n = 7, △——△), (+)ketamine, 1 mg/kg, iv (n = 8, ●——●), or (−)ketamine, 3 mg/kg, iv (n = 7, ○——○). Values are means ± SEM.

auditory, proprioceptive, and confusional illusions, in common with other general anesthetics, although the incidence was higher with ketamine. Garfield *et al.*[13] and others[16] have described dreaming as a common experience during emergence from ketamine anesthesia, with incidences variously reported at 30–60 per cent. A dream-like state occurred in a majority of the patients in our series; however, most patients recalled a pleasant experience with ketamine anesthesia. Several patients volunteered that their altered state of consciousness allowed them to explore and resolve emotional issues relating to their surgical procedures. The unpleasant dreams that were reported apparently resulted from an expressed difficulty in separating the altered state of consciousness from reality. The patients were informed preoperatively that they might experience vivid dreams after ketamine anesthesia and this factor might explain, in part, the higher incidence of dreaming in our study than was found in a similar investigation using racemic ketamine alone.[13] In our study, the occurrence of vivid illusions, unusual dreaming (occasionally described as a "weird trip"), or delirium was significantly more common following (−)ketamine than after either the racemate or (+)ketamine.

The term "dreaming" may be misleading in describing emergence from ketamine anesthesia if one defines dreaming as a more or less coherent sequence of events or feelings during a sleep state. In

this study, patients frequently used the term to describe an altered state of consciousness during an apparent awake state, which was unlike any dream in the past. They frequently described having an unusual experience which was difficult to describe accurately but which seemed to be most closely akin to a dissociative or extracorporeal experience, and which in several cases appeared to be similar to the "near-death" experiences reported by Moody.[17]

Although ketamine was used alone in this study, in general we would not advocate using ketamine without premedication or adjunctive agents because we believe that the incidences of unpleasant dreams (5–22 per cent) and unacceptable anesthetic experiences (15–37 per cent) when racemic ketamine or one of its isomers were used alone are unacceptable. Diazepam, 0.2–0.3 mg/kg, given intravenously prior to induction of ketamine anesthesia, has been shown to decrease the incidence of dreams significantly and to prevent postoperative illusions.[16,18] Furthermore, the addition of diazepam prior to the administration of ketamine can significantly decrease ketamine-induced cardiovascular stimulation.[19] Others[20] have suggested that using thiopental for induction of anesthesia diminishes the untoward psychotomimetic reactions on arousal from ketamine anesthesia. We expect the incidences of both unpleasant dreams and unacceptable anesthetic experiences to be significantly decreased when ketamine is used as part of a balanced anesthetic technique, utilizing diazepam, thiopental, or nitrous oxide as adjunctive agents. In our experience, (+)ketamine would be an acceptable anesthetic for outpatient surgery; however, patients undergoing brief operations (*e.g.*, 20–30 min in duration) may require a one to two-hour observation period after awakening from anesthesia prior to discharge.

Under the conditions of the anesthetic procedure, which involved drug administration as needed to complete the operation, a precise pharmacokinetic analysis of the biodisposition data was not possible. Although it is not possible to make direct potency comparisons, if the assumption is made that at termination of anesthesia the brain levels of the individual isomers are proportional to the plasma levels, then the apparent anesthetic potency ratio of (+)ketamine to (−)ketamine is 3.4:1. The parallelism of the plasma decay curves for the parent compounds (fig. 1) suggests similar elimination rates for racemic ketamine and the individual optical isomers. Although the absolute levels of the parent drugs and their metabolites differ among groups because different doses were administered, the overall patterns of appearance and excretion of the ketamine metabolites were not significantly different for racemic ketamine and the individual isomers. Thus, the differences in anesthetic potency appear to be due to pharmacodynamic rather than pharmacokinetic factors. However, the absolute plasma levels of the metabolites of the individual isomers were different, especially in the postanesthetic period. Thus, it remains possible that differences in other CNS effects, the duration and intensity of which cannot be estimated as accurately as the anesthetic state, may be due to biodispositional factors.

These data suggest both quantitative and qualitative differences between the ketamine enantiomorphs in their effects on the CNS. It appears that stereospecificity is an important factor in determining the pharmacodynamic effects of this general anesthetic. Furthermore, this study illustrates the importance of considering racemates as unique chemical species with pharmacodynamic or pharmacokinetic profiles that may differ from those of their individual enantiomorphs. Our clinical observations, however, constitute but one point on the dose–response curve, and the interpretations are therefore limited. A number of clinical investigations using the separated ketamine isomers are planned, including studies to extend the present findings to other clinical situations and to assess the potential advantages of combining (+)-ketamine with diazepam, thiopental, or nitrous oxide. Although (+)ketamine is not a uniquely different anesthetic, it may offer distinctive clinical advantages over the currently used racemic mixture.

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