

Psychedelic Effects of Ketamine in Healthy Volunteers

Relationship to Steady-state Plasma Concentrations

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Background: Ketamine has been associated with a unique spectrum of subjective "psychedelic" effects in patients emerging from anesthesia. This study quantified these effects of ketamine and related them to steady-state plasma concentrations.

Methods: Ketamine or saline was administered in a single-blinded crossover protocol to 10 psychiatrically healthy volunteers using computer-assisted continuous infusion. A stepwise series of target plasma concentrations, 0, 50, 100, 150, and 200 ng/ml were maintained for 30 min each. After 20 min at each step, the volunteers completed a visual analog (VAS) rating of 13 symptom scales. Peripheral venous plasma keta-

mine concentrations were determined after 28 min at each step. One hour after discontinuation of the infusion, a psychological inventory, the hallucinogen rating scale, was completed.

Results: The relation of mean ketamine plasma concentrations to the target concentrations was highly linear, with a correlation coefficient of $R = 0.997$ ($P = 0.0027$). Ketamine produced dose-related psychedelic effects. The relation between steady-state ketamine plasma concentration and VAS scores was highly linear for all VAS items, with linear regression coefficients ranging from $R = 0.93$ to 0.99 ($P < 0.024$ to $P < 0.0005$). Hallucinogen rating scale scores were similar to those found in a previous study with psychedelic doses of N,N-dimethyltryptamine, an illicit LSD-25-like drug.

Conclusions: Subanesthetic doses of ketamine produce psychedelic effects in healthy volunteers. The relation between steady-state venous plasma ketamine concentrations and effects is highly linear between 50 and 200 ng/ml. (Key words: Anesthesia aftereffects; complications; pharmacodynamics; pharmacokinetics; psychological responses.)

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THE first clinical trials with ketamine were reported by Corssen and Domino in 1966.¹ They subsequently introduced the term *dissociative anesthesia* to describe the anesthetic state produced by ketamine, based on the observation of dissociation of electroencephalographic activity between the thalamoneocortical and limbic areas of the cat brain.²

"Emergence reactions" refer to a constellation of subjective effects encountered on emergence from ketamine general anesthesia.^{3,4} Various referred to as "psychotomimetic," "hallucinogenic," or "psychedelic," they include intense alterations in mood, perception, thinking, body awareness, and self-control. Some patients find these terrifying, whereas others do not. "Psychotomimetic" suggests a dysphoric pathologic condition (resembling psychosis),⁵ and "hallucinogenic" is somewhat misleading, because hallucinations do not always occur. We prefer "psychedelic" because it allows for more flexibility in grouping together a disparate array of effects into a quantifiable and recognizable

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syndrome.^{6,7} Despite the potential of anesthetic drugs to profoundly alter conscious experience, there has been relatively little research directed toward understanding the psychological side effects of anesthetics. The purpose of this study was to quantify the psychedelic effects of ketamine, and to relate these effects to steady-state plasma concentrations. The hypothesis was that psychedelic effects of ketamine would be directly related to ketamine steady-state plasma concentrations.

Methods

Volunteers gave institutionally approved informed consent and received a structured clinical interview for DSM-IV, performed by a board-certified psychiatrist, demonstrating absence of all axis I disorders (psychiatrically healthy), including substance abuse. During drug infusions, participants were monitored continuously by pulse oximetry, and noninvasive blood pressure was determined intermittently. Racemic ketamine or saline was administered in a single-blinded, crossover protocol, using a computer-assisted continuous infusion with a Harvard pump 22 (Harvard Apparatus, Holliston, MA) syringe pump controlled by a DOS-based computer and the Stanpump program (Steven L. Shafer, M.D., Department of Anesthesiology, Stanford University). A step-wise series of five ketamine target plasma concentrations, 0, 50, 100, 150, and 200 ng/ml, were maintained for 30 min each. The Stanpump program uses a so-called BET infusion scheme to rapidly attain a steady-state plasma concentration, by combining a bolus (B), a constant rate infusion to compensate for drug elimination (E), and an exponentially decreasing infusion to compensate for drug distribution or transfer (T).⁸ Pharmacokinetic parameters for ketamine were taken from a previous study by Domino *et al.*⁹ Peripheral venous blood samples were drawn after 28 min at each step, and ketamine plasma concentrations were determined by gas chromatography-mass spectrometry.¹⁰

After approximately 20 min at each step, the volunteer completed a visual analog rating (VAS) of 13 scales by marking a 133-mm-long line with a range from "not at all" to "extremely." The scales were

- My body or body parts seemed to change their shape or position (BODY).
- My surroundings seemed to change in size, depth, or shape (SURROUNDINGS).
- The passing of time was altered (TIME).
- I had feelings of unreality (REALITY).

- It was difficult to control my thoughts (THOUGHTS).
- The intensity of colors changed (COLORS).
- The intensity of sound changed (SOUND).
- I heard voices or sounds that were not real (VOICES).
- I had the idea that events, objects, or other people had particular meaning that was specific for me (MEANING).
- I had suspicious ideas or the belief that others were against me (SUSPICIOUS).
- I felt high (HIGH).
- I felt drowsy (DROWSY).
- I felt anxious (ANXIOUS).

Approximately 1 h after discontinuation of the ketamine or saline infusion, the participants completed a psychological inventory, the hallucinogen rating scale (HRS), designed by one of the authors (R.J.S.) to assess the effects of psychedelic drugs.¹¹ The HRS is based on interviews with experienced users of psychedelic drugs, especially N,N-dimethyltryptamine (also called DMT), an illicit drug with effects similar to LSD-25, mescaline, and psilocybin.¹¹ Participants were asked to respond to the questions by recalling their experiences in the immediately preceding session. Questions were scored 0 to 4: 0, "not at all"; 1, "slightly"; 2, "moderately"; 3, "quite a bit"; and 4, "extremely." The HRS items were grouped into six clinically derived clusters: (1) SOMASTHESIA—interoceptive, visceral, and cutaneous/tactile effects; (2) AFFECT—emotional/affective responses; (3) PERCEPTION—visual, auditory, gustatory, and olfactory experiences; (4) COGNITION—alterations in thought processes or content; (5) VOLITION—a change in capacity to willfully interact with themselves, the environment, or certain aspects of the experience; and (6) INTENSITY—global measure of strength of the various aspects of the experience. The results of the HRS for ketamine were compared with a previous dose-response study of intravenous N,N-dimethyltryptamine performed by one of the authors (R.J.S.).¹¹

Statistical Analysis

The relations between ketamine plasma concentration and VAS effects were analyzed by linear regression. Differences between saline control and ketamine VAS effects were analyzed by repeated-measures analysis of variance with Fischer PLSD. The accuracy of ketamine administration was assessed by comparing the predicted and measured plasma ketamine concentrations,

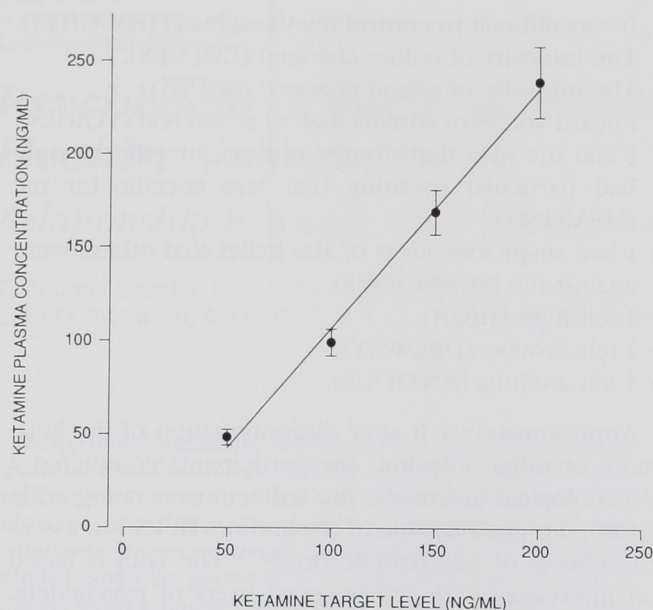


Fig. 1. Mean plasma ketamine concentration (\pm SEM) is plotted versus ketamine target concentration (50, 100, 150, and 200 ng/ml). The correlation coefficient was $R = 0.997$ ($P = 0.0027$). The slope of the regression line (1.28) was greater than unity, resulting in plasma concentrations that were close to the 50 and 100 ng/ml target, but 15–20% higher than predicted at the 150 and 200 ng/ml targets.

expressed as the percentage performance error: $\%PE = (\text{measured} - \text{predicted}) / \text{predicted} \times 100$. The absolute value of the percentage performance error was also determined.^{12,13}

Results

All the volunteers were men, with a mean age of 22.3 yr (range, 21–25 yr). There were no perturbations of heart rate, blood pressure, or oxygen saturation that required treatment during the study. All participants had lateral gaze nystagmus at the 200 ng/ml target concentration.

The relation between mean ketamine plasma concentrations and target concentrations was highly linear, with a correlation coefficient of 0.997 ($P = 0.0027$; fig. 1). Mean ketamine concentrations were nearly identical to 50 and 100 ng/ml targets but about 15–20% higher than the 150 and 200 ng/ml targets, resulting in a linear regression slope greater than unity of 1.28. The mean performance error was -7.3% , -1.1% , 12.6% , and 19.2% for the 50, 100, 150, and 200 ng/ml target concentrations, respectively. The mean absolute perfor-

mance error was 23.1%, 19.3%, 22%, and 25.5% for the 50, 100, 150, and 200 ng/ml target concentrations, respectively.

The plasma ketamine concentration versus effect relation was highly linear for all VAS items, with linear regression correlation coefficients of at least $R = 0.93$ ($P < 0.024$). Complete data for a representative VAS item, HIGH, is shown in figure 2, and summary data for all VAS items are included in table 1. For the saline control data, linear regression was performed for the target concentration versus effect relation, because there were no actual drug concentrations. The correlation coefficients for saline controls were not significant ($P > 0.05$; table 1), except for BODY and TIME. The interaction between step (target concentration) and drug (ketamine versus saline) was significant (by repeated-measures analysis of variance; $P \leq 0.05$) for all items except SUSPICIOUS (table 1).

Figure 3 shows the HRS cluster scores for ketamine and saline. The difference between ketamine and saline was significant (by repeated-measures analysis of variance; $P < 0.05$) for all clusters except VOLITION. The score for VOLITION was elevated for ketamine and saline. Volunteers also had the opportunity to make writ-

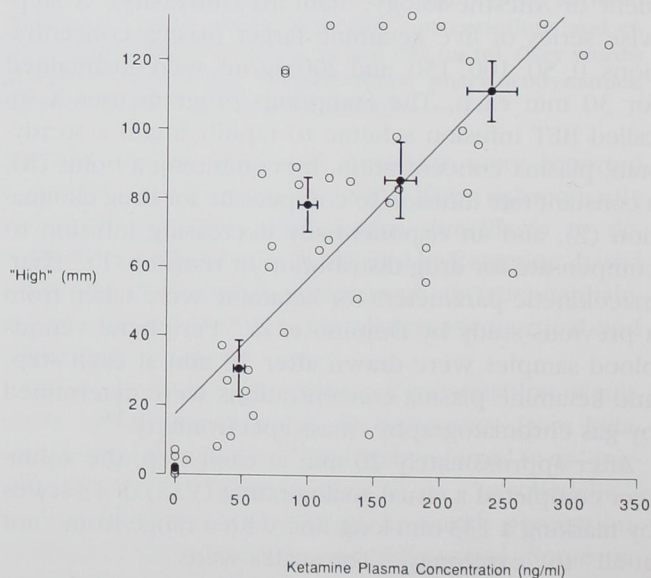


Fig. 2. Visual analog scores for scale item HIGH ("I felt high") are plotted versus ketamine plasma concentrations. Each open circle represents one pair of data points. Mean values (\pm SEM) are shown for each target concentration step (closed circles). Targets were 0, 50, 150, and 200 ng/ml. The fit of the data by linear regression is indicated by the line. Table 1 lists correlation coefficients and probability values for all VAS items.

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Table 1. Visual Analog Scale Results

Item	Mean Plasma Ketamine Concentration vs. Mean VAS Response		Saline Control "Target Concentration" vs. Mean VAS Response		VAS Score at Highest Saline Dose [mean \pm (SD)]	VAS Score at Highest Ketamine Dose [mean \pm (SD)]	ANOVA <i>P</i> Value*
	R Value	<i>P</i> Value for R	R Value	<i>P</i> Value for R			
Anxious	0.98	0.0029	0.69	0.20	2.8 (4.1)	28.5 (32.2)	0.022
Body	0.98	0.0039	0.96	0.0093	2.7 (3.8)	60.4 (51.8)	0.0002
Colors	0.98	0.0034	0.70	0.19	1.8 (3.0)	64.5 (51.6)	<0.0001
Drowsy	0.93	0.024	0.75	0.15	26.0 (21.1)	62.6 (49.5)	0.029
High	0.96	0.010	0.76	0.14	3.6 (5.5)	111.4 (27.4)	<0.0001
Meaning	0.99	0.0014	0.49	0.39	1.7 (2.6)	24.4 (33.8)	0.0078
Sound	0.98	0.0040	0.62	0.26	3.6 (6.2)	63.6 (38.3)	<0.0001
Surroundings	0.99	0.0005	0.42	0.49	1.35 (2.3)	87.3 (40.1)	<0.0001
Suspicious	0.95	0.013	0.46	0.44	1.7 (2.7)	16.0 (30.3)	0.12
Thoughts	0.99	0.0010	0.68	0.20	5.2 (7.0)	72.7 (42.8)	<0.0001
Time	0.99	0.0018	0.98	0.0021	4.6 (7.0)	84.0 (33.0)	<0.0001
Unreality	0.94	0.016	0.37	0.54	1.8 (3.0)	79.2 (51.4)	<0.0001
Voices	0.95	0.0133	0.68	0.20	1.7 (2.8)	48.5 (44.6)	<0.0001

VAS = Visual Analog Scale.

* ANOVA interaction of step (target level) and drug (ketamine vs. saline).

ten comments on the HRS form. Several of them described altered physical sensations or body image: "tingling sensation in the limbs, followed by numbness"; "floating, very carefree feelings throughout entire

body"; "felt so different. Wasn't able to describe the way I was feeling"; "floating in space"; "almost complete annihilation of physical self, shrunken"; "dizzy, shaky, lightheaded." One subject wrote the following summary: "The experience seems to be a mystical experience, an incomprehensible comprehension of the universe. There seemed to be no past, present or future, no time, just existence. Life and death at the same time." All but one participant spontaneously reported feelings of intoxication and perceptual distortion during the ketamine infusion; one of these persons also reported these symptoms during the placebo infusion. Three participants became moderately dysphoric during the ketamine infusion, but none of them experienced dysphoria during the placebo infusion. One participant developed a mildly paranoid state characterized by multiple questions about the procedure and an intense affect. Another volunteer, who had experienced emotional stress in the recent past, experienced tearfulness, a sad mood, and moderately intense ruminations about recent stressful events.

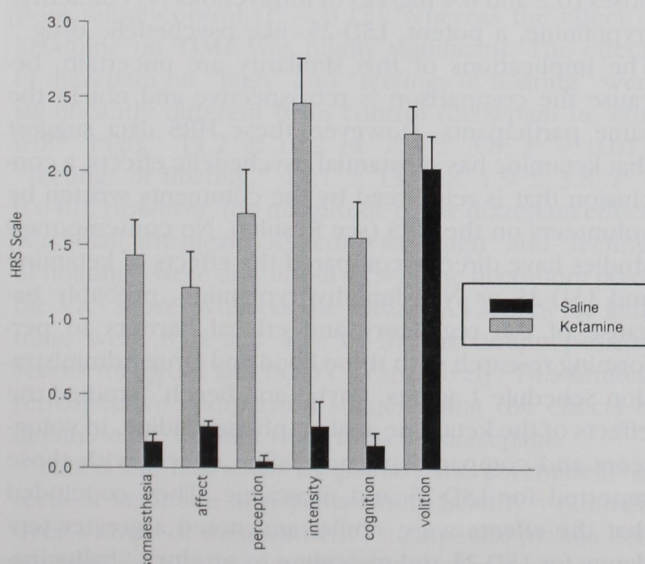


Fig. 3. Mean cluster hallucinogen rating scores (HRS; \pm SEM) are shown for ketamine and saline (see Methods section for description of HRS scores). The difference between ketamine and saline was statistically significant (analysis of variance; $P < 0.05$) for all clusters except VOLITION.

Discussion

Plasma ketamine concentrations were reasonably close to target concentrations. The infusion algorithm is based on average ketamine pharmacokinetic param-

ters from a study of a relatively small number of persons. Any randomly selected participant is likely to deviate from the average. Therefore the targets will not be achieved precisely in each participant. A mean variation of the measured concentrations of 20–30% from the target concentrations is expected with a computer-assisted continuous infusion system.^{12–14} The mean performance error and the mean absolute performance error in this study were less than 30%. The relation between the target concentration and the measured concentration was highly linear, but the slope was greater than unity, resulting in a trend for plasma ketamine concentrations in the last two steps, 150 and 200 ng/kg, to exceed the target. The cause for this overshooting of the target concentrations is unknown; presumably there was a discrepancy between the pharmacokinetic parameters used in the computer-assisted continuous infusion system and the actual pharmacokinetic behavior of the participants.

There was a highly linear relation between ketamine steady-state concentration and effect for all of the VAS items. The intensity of effects varied considerably for different items. The intensity was greatest for HIGH, REALITY, TIME, SURROUNDINGS, THOUGHT, and SOUND, items that might be regarded as indicating psychedelic effects. The intensity was lowest for ANXIETY, SUSPICIOUS, and MEANING, items that might be regarded as indicating psychotomimetic effects. Furthermore, the difference between ketamine and saline for SUSPICIOUS was not significant (by analysis of variance; $P \leq 0.05$); the difference for all other items was significant.

There was a significant linear relation between saline target concentration and effect for BODY and TIME, although the magnitude of the effect was much smaller than with ketamine. Probably these small but significant effects of saline on BODY and TIME were due to immobility and confinement in the laboratory for several hours.

The linearity of the concentration *versus* effect relation suggests that the mind-altering effects of ketamine are continuous and graded, and that even very small doses of ketamine produce these effects to some degree. Anesthesiologists tend to associate the psychedelic effects of ketamine with emergence from anesthesia, after use of ketamine as an induction agent, which is often referred to as "emergence reactions." The published descriptions of this syndrome do not give any sense of a dose *versus* effect relation. However, these data clearly demonstrate a relation between ketamine

plasma concentration and psychedelic effects. Awareness of these effects may help clinicians using subanesthetic doses of ketamine improve their management of patients, particularly with regard to effective communication with patients.

The cumulative dose-response design of this study has strengths and weaknesses. The major strength lies in the ability to attain a series of steady-state plasma concentrations during a single experimental session. The major weakness is that participants might anticipate an increase in drug effects at each step up and bias their responses accordingly. An alternative design that avoids the bias problem is dose randomization. Because ketamine has a relatively long half-life, stepping plasma concentrations up and down randomly requires substantially more time than a series of steps up, with attendant problems of participant fatigue and possibly development of tolerance. We cannot preclude the possibility that some responses were inflated by the expectation that effects would increase. However, there were large differences in the maximum responses between the VAS scales (table 1), suggesting that participants were responding to "real" pharmacologic effects, rather than simply marking the VAS based on an expectation of increasing effects.

The effect of ketamine on HRS subscales was very similar to results reported previously for psychedelic doses (0.2 and 0.4 mg/kg) of intravenous N,N-dimethyltryptamine, a potent, LSD-25-like psychedelic drug.¹¹ The implications of this similarity are uncertain, because the comparison is retrospective and not in the same participants. However, these HRS data suggest that ketamine has substantial psychedelic effects, a conclusion that is reinforced by the comments written by volunteers on the HRS (see Results). No contemporary studies have directly compared the effects of ketamine and LSD-25 or N,N-dimethyltryptamine, probably because of the regulatory and ethical barriers to performing research with these Food and Drug Administration Schedule 1 agents. Davies and Beech¹⁵ studied the effects of the ketamine analog, phencyclidine, in volunteers and compared phencyclidine effects with those reported for LSD-25 and mescaline. They concluded that the effects were similar and noted a greater tendency for LSD-25 and mescaline to produce "hallucinations." Cohen *et al.*¹⁶ compared phencyclidine with LSD-25 and amobarbital and found that phencyclidine impaired interpretation of proverbs and performance on a standard serial sevens task (that is, participants

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count backwards from 100 by sevens) but LSD-25 did not.

There was a peculiarity of the HRS results that requires comment. The VOLITION score for saline was elevated and similar to the score for ketamine. Probably this was due to the enforced immobility of the participants in the laboratory, which they may have interpreted as impaired volition on HRS volition items such as "Able to move around if asked to do so" and "In control."

A comparison of the mind-altering effects of ketamine with a sedative-hypnotic drug would also be of interest. Although we did not compare ketamine directly with a sedative-hypnotic drug, eight of the ten volunteers in this study participated in a previous cumulative dose-response study of diazepam.¹⁷ A total diazepam dose of 200 mg/kg given intravenously resulted in a mean peak plasma concentration of approximately 600 ng/ml. Participants completed a VAS that was similar but not identical to the VAS used in the present study of ketamine. Three scales on the diazepam VAS, "high," "distorted sense of time," and "feelings of floating," were comparable to ketamine VAS scales, HIGH, TIME, and BODY. We reanalyzed the data from the diazepam study for the eight persons who participated in the diazepam and the ketamine studies to compare the effects of ketamine with diazepam. The maximum effect of diazepam on "distorted sense of time" was not significantly different from saline control ($P = 0.12$), whereas the effect of ketamine on TIME was highly significant. The effects of diazepam on "high" and "feelings of floating" were significantly different from control (diazepam *vs.* control: "high," 14.2 ± 10.2 *vs.* 2.4 ± 3.8 ; $P = 0.014$; "feelings of floating," 14.1 ± 13.8 *vs.* 1.9 ± 3.8 ; $P = 0.040$). However, the magnitude of the diazepam effects was small: the mean VAS scores for "high" and "feelings of floating" were only about 12% of the maximum possible VAS score, whereas the mean VAS scores for ketamine were 83% and 45% of the maximum possible scores for HIGH and BODY, respectively. This limited, retrospective comparison suggests that the effects of ketamine are distinct from those of diazepam.

This is the first study to quantify the psychedelic effects of ketamine in psychiatrically healthy volunteers over a range of subanesthetic, steady-state plasma concentrations. However, previous studies of subanesthetic doses of ketamine also found evidence of psychedelic effects.¹⁸⁻²¹ Krystal *et al.*²⁰ administered 0.1 mg/kg or 0.5 mg/kg ketamine as a 40-min infusion; plasma concentrations were not measured. Participants completed

various psychological tests during and after ketamine administration. The investigators concluded that ketamine produced an altered state of consciousness that was distinct from schizophrenia. Hartvig *et al.*²¹ administered 0.1 mg/kg or 0.2 mg/kg S-ketamine over 1 min. Positron emission tomography scanning was then performed for 45–55 min to quantify ketamine binding in the brain. After positron emission tomography scanning, participants answered a psychological questionnaire. Plasma ketamine concentrations were measured during positron emission tomography scanning but not afterward. Dose-related psychedelic effects were accompanied by evidence of increased regional binding of S-ketamine in the brain. There is also anecdotal evidence of psychedelic effects of ketamine. Phencyclidine and ketamine have been used as drugs of abuse, and users have clearly described the effects as psychedelic in nature.²² Extensive descriptions of the psychedelic effects of ketamine in recreational users have been published.²²

The results of this randomized, blinded, placebo-controlled study of psychiatrically healthy volunteers demonstrate a linear relation between psychedelic effects of ketamine and steady-state plasma concentrations between 50 and 200 ng/ml, a range of plasma concentrations that is clinically relevant for patients receiving ketamine for analgesia or sedation, or awakening from general anesthesia with ketamine. Plasma concentrations of ketamine on awakening from general anesthesia have been reported in the range of 600–1100 ng/ml.²³ Analgesic concentrations are approximately 100–200 ng/ml.²³ This should be considered when weighing the advantages and disadvantages of ketamine as an anesthetic, analgesic, or sedative drug.

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