Ketamine kinetics in unmedicated and diazepam-premedicated subjects

Plasma ketamine concentrations after diazepam and placebo pretreatment were examined in a double-blind, randomized, cross-over study. Eight healthy male subjects received either diazepam or a 0.9% NaCl placebo before ketamine and received the alternate combination 5 to 24 days later. Ten minutes before ketamine dosing, diazepam, 0.3 mg/kg, or placebo in equal volume was injected intravenously at a rate not exceeding 5 mg/min. Ketamine, 2.2 mg/kg iv, was injected over 1 min. For the clinically relevant period for anesthesia (1 to 30 min), diazepam-ketamine treatment resulted in higher plasma levels at most time points, but diazepam pretreatment did not alter plasma levels of metabolite KI and pseudometabolite KII nor the 24-hr urinary excretion of ketamine, KI, and KII. Ketamine kinetics followed a three-term exponential decline under both treatment conditions. After placebo-ketamine dosing, plasma t½s were as follows: distribution ($\pi t½$) = 24.1 sec, redistribution ($\alpha t½$) = 4.68 min, and elimination ($\beta t½$) = 2.17 hr. After diazepam-ketamine dosing, t½s were: $\pi t½ = 25.0$ sec, $\alpha t½ = 6.37$ min, and $\beta t½ = 2.32$ hr.

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It has been shown that, when injected intravenously just before ketamine dosing, benzodiazepines such as diazepam markedly improve the course of anesthesia.[8–10] The diazepam-ketamine combination has been reported to increase patient acceptance[4, 16, 17] and to induce less cardiovascular stimulation than ketamine anesthesia without diazepam pretreatment. We compared ketamine kinetics after placebo and diazepam premedication. A report of a two-compartment open model analysis of ketamine kinetics from 5 min to 24 hr after dosing revealed that ketamine plasma clearance was reduced by diazepam premedication,[6, 7] and plasma ketamine kinetics are triexponential in hospitalized surgical patients.[5] These findings prompted a more detailed kinetic analysis of ketamine.

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Table I. *Analysis of variance for ketamine plasma levels (ng/ml)*

Time after ketamine dosing	*Placebo (N = 8)*	*Diazepam (N = 7)*	*P*
1 min	27600 ± 9420	28500 ± 6930	NS
2 min	6370 ± 1070	7150 ± 734	NS
3 min	3600 ± 209	4470 ± 482	<0.05
4 min	2280 ± 125	3510 ± 413	<0.05
5 min	1910 ± 91.0	2880 ± 392	<0.05
10 min	1270 ± 84.3	1750 ± 168	<0.05
20 min	826 ± 84.9	1050 ± 128	NS
30 min	610 ± 73.3	721 ± 64.6	NS
1 hr	372 ± 37.5	438 ± 54.0	<0.05
2 hr	288 ± 31.2	301 ± 47.8	NS
4 hr	158 ± 22.9	198 ± 40.1	NS
5 hr	116 ± 13.8	135 ± 19.9	NS
6 hr	86.2 ± 13.0	106 ± 22.1	NS
8 hr	45.9 ± 7.29	59.2 ± 13.1	<0.05
12 hr	30.4 ± 7.60	23.6 ± 5.65	NS
24 hr	8.14 ± 4.59	2.71 ± 2.04	NS

Data are $\bar{X}$ ± SE.

Table II. *Analysis of variance for metabolite KI plasma levels (ng/ml)*

Time after ketamine dosing	*Placebo (N = 8)*	*Diazepam (N = 7)*	*P*
5 min	59.4 ± 32.1	28.9 ± 31.1	NS
10 min	218 ± 15.0	297 ± 55.0	NS
20 min	387 ± 69.5	367 ± 276	NS
30 min	301 ± 47.3	387 ± 38.0	NS
1 hr	267 ± 36.4	315 ± 36.1	NS
2 hr	542 ± 244	417 ± 95.6	NS
4 hr	857 ± 173	951 ± 251	NS
5 hr	781 ± 184	627 ± 131	NS
6 hr	480 ± 99.5	396 ± 55.3	NS
8 hr	546 ± 139	456 ± 105	NS
12 hr	243 ± 39.2	308 ± 54.6	NS
24 hr	163 ± 61.7	48.3 ± 18.4	<0.05

Data are $\bar{X}$ ± SE.

Methods

A double-blind, randomized, crossover design was used. Our subjects were eight healthy men aged 26 to 41 yr ($\bar{X}$ =32.3 yr) weighing 59.9 to 81.8 kg ($\bar{X}$ =72.8 kg) who were selected from 24 inmates at the Jackson State Prison of Southern Michigan. Subjects fasted the night before medication. Each received either diazepam or a 0.9% NaCl placebo before ketamine and received the alternate combination 5 to 24 days later. By chance, the one subject tested at a 5-day interval received placebo-ketamine first. Ten minutes before ketamine dosing, diazepam, 0.3 mg/kg, or placebo in equal volume was injected intravenously at a rate not exceeding 5 mg/min. Ketamine, 2.2 mg/kg iv, was injected over 1 min. One of the subjects (No. 4) refused to complete the second portion of the study; thus symmetric data are available on only seven subjects, and data from subject No. 4 were not used in any paired comparisons. Venous injections were made in a convenient vein in one arm

Table III. *Analysis of variance for pseudometabolite KII plasma levels (ng/ml)*

Time after ketamine dosing	*Placebo (N = 8)*	*Diazepam (N = 7)*	*P*
10 min	9.10 ± 9.71	38.5 ± 32.7	NS
20 min	50.9 ± 43.8	88.5 ± 60.2	NS
30 min	37.9 ± 17.0	45.2 ± 36.1	NS
1 hr	91.9 ± 45.0	99.1 ± 55.3	NS
2 hr	95.7 ± 18.4	151 ± 114.3	NS
4 hr	103 ± 14.9	70.8 ± 29.8	NS
5 hr	118 ± 18.3	67.9 ± 14.4	*
6 hr	48.2 ± 9.11	33.7 ± 9.43	*
8 hr	61.0 ± 23.2	58.0 ± 10.7	*
12 hr	47.4 ± 13.4	9.30 ± 3.80	*
24 hr	26.1 ± 14.5	0.00 ± 0.00	*

Data are $\bar{X}$ ± SE.

*Insufficient data after 5 hr with which to do meaningful analysis of variance.

Table IV. *Ketamine kinetics for a three-compartment open model*

	Placebo-ketamine (N = 7)	*Diazepam-ketamine (n = 7)*
$\pi t_{1/2}$ sec	31.1 ± 16.8 (24.1)	27.2 ± 7.7 (25.0)
$\alpha t_{1/2}$ min	7.79 ± 6.21 (4.68)	6.70 ± 1.72 (6.37)
$\beta t_{1/2}$ hr	2.25 ± .45 (2.17)	2.41 ± .49 (2.32)
k_{12}*(hr^{-1})	35.5 ± 20.4	36.4 ± 8.0
k_{21}*(hr^{-1})	14.8 ± 9.00	12.0 ± 2.4
k_{13}*(hr^{-1})	35.4 ± 27.3	29.6 ± 13.9
k_{31}*(hr^{-1})	0.874 ± 0.296	0.707 ± 0.164
k_{10}*(hr^{-1})	26.3 ± 23.7	28.2 ± 24.1
Vd_1† (*l*/kg)	0.063 ± 0.049	0.043 ± 0.034
Vd_2† (*l*/kg)	0.207 ± 0.202	0.132 ± 0.101
Vd_3† (*l*/kg)	1.51 ± 0.619	1.34 ± 0.689
Vd_{SS}† (*l*/kg)	1.78 ± 0.738	1.517 ± 0.815
Plasma clearance (*l*/kg/hr)	0.848 ± 0.316	0.719 ± 0.293‡

Data are $\bar{X}$ ± SD. Values in parentheses are harmonic means. All kinetic parameters were calculated from the coefficients and exponents of the least-squares regression analysis of the data in Table I.

*First-order rate parameters.

†Volume of distribution parameters.

‡$P < 0.08$ (two-tailed paired comparison Student t test); $P < 0.05$ (one-tailed test).

and venous samples were drawn from the other arm. The radial artery was used for arterial blood pressure recordings and blood sample collections. Times of sampling are listed in Tables I, II, and III. All samples were assayed in duplicate. The deviation from scheduled sample time was less than 5 to 10 sec.

The analysis of ketamine and some of its metabolites (ketamine metabolite I [KI] and ketamine pseudometabolite II [KII]) in arterial and venous plasma and urine was by gas chromatography-mass fragmentography.[11] Heptafluorobutyric anhydride derivatives of ketamine, its two metabolites, and the internal standard (the *o*-BR analog of ketamine) were prepared after extraction. It should be noted that KII does not exist in vivo and is an in vitro chemical decomposition product of hydroxylated ketamine metabolites.[14] Although KII is an in vitro decomposition product, it does repre-

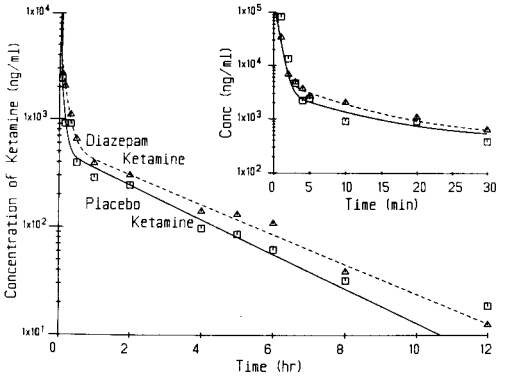

Fig. 1. Plasma ketamine concentrations in nonsurgical subject No. 1 after diazepam or placebo pretreatment. Table I lists $\bar{X} \pm SE$ values for all subjects. Two separate three-term exponential equations were fit by weighted nonlinear least-squares analysis (weighed $1/C^2$) to diazepam-ketamine *(dashed line)* and placebo-ketamine *(solid line)* data.

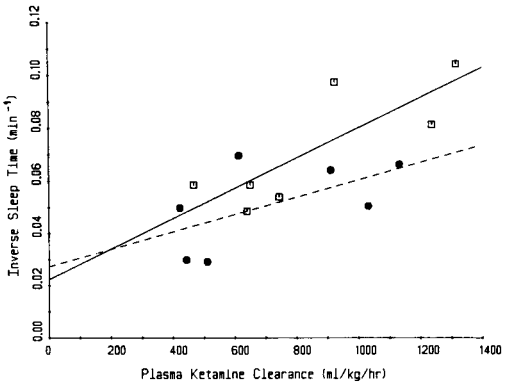

Fig. 2. Relation of plasma ketamine clearance to sleep time under diazepam-ketamine and placebo-ketamine anesthesia. Analysis of covariance of the two treatments revealed an overall correlation of inverse sleep time and plasma clearance ($P < 0.01$). When broken into groups, placebo-ketamine treatment (□) revealed a correlation ($P < 0.05$), while diazepam-ketamine treatment (●) did not. Mean sleep time was elevated in the diazepam-pretreated group ($P < 0.05$). There was no alteration in slopes of the regression lines, but there was a trend toward an additive effect of diazepam on duration of anesthesia independent of alterations in clearance ($P = 0.092$). An analysis of covariance is summarized in Table V.

sent at least two in vivo hydroxylated metabolites. Therefore, data on this decomposition product are included in this report as an index of these compounds.

Quantitative analyses were by a Finnigan

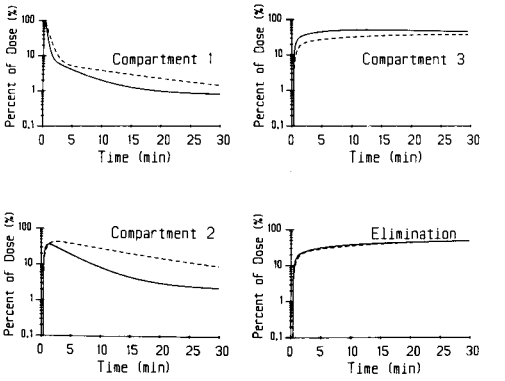

Fig. 3. Comparison of compartmental amounts of ketamine after diazepam or placebo pretreatment in subject No. 7. The time course of the amounts in each compartment of a three-compartment model were calculated from the model obtained from plasma levels after diazepam-ketamine *(dashed lines)* and placebo-ketamine *(solid lines)* in Subject No. 7. In compartments one and two, ketamine amounts were slightly elevated, while in compartment three, amounts were slightly diminished under the diazepam-ketamine treatment. Elimination was unchanged between each condition. Note the parallel decline of levels in compartments one and two from 5 to 10 min onward. A similar model applies for mean data of all subjects.

3200 GCMS system operated in the electron impact mode. A 5 ft × 2 mm glass U-tube column packed with 3% OV-17 on 100/120 mesh Gas-Chrom Q was conditioned by heating overnight at 250°. Chromatographic conditions were a column temperature of 180° isothermal and an injector temperature of 210°. Carrier gas (He) flow was 20 ml/min, glass jet separator temperature was 210°, and electron energy was 70 eV.

A polyexponential weighted least-squares regression analysis was performed by the computer program NONLIN[12] with initial estimates from CSTRIP.[13] The regression analysis was weighted by the inverse of the squared concentration of ketamine ($1/C^2$). Kinetics were calculated from the coefficients and exponents of the least-squares regression according to the method of Wagner.[15] The optimal number of exponential terms for a polyexponential fit was obtained by the F test.[3] Compartmental amounts were calculated by the method of Benet.[1] Statistical calculations, including two-way analysis of variance and one-way analysis of covariance, were by the Michigan Interactive

Table V. *One-way analysis of covariance*

A. Analysis of variance of 1/sleep time (N = 14); covariate plasma clearance,* treatments = Diazepam-ketamine and placebo-ketamine

Source	*Degrees of freedom*	*Sum of squares*	*Mean square*	*F*	*P*
Between means	1	0.00149			
Covariates	1	0.00248	0.00248	11.9	0.006
Error	11	0.00230	0.000209		
Regression	1	0.00326			
Equal adjusted means	1	0.000712	0.000712	3.41	0.092
Error	11	0.00230	0.000209		
Overall regression	1	0.00326			
Equal regressions	2	0.000887	0.000443	2.09	0.174
Equal adjusted means	1	0.000712			
Equal slopes	1	0.000175	0.000175	0.826	0.385
Error (each regression)	10	0.00212	0.000212		
TOTAL	13	0.00626			

B. Means and regression results

	Placebo-ketamine	*Diazepam-ketamine*
Mean	0.0723	0.0516
Adjusted mean	0.0693	0.0546
SE	0.00553	0.00553
Intercept	0.323	0.0177
N	7	7
Constant	0.0225	0.0274
Plasma clearance slope	0.0000588	0.0000336
Regression SE	0.0143	0.0149
R^2	0.671	0.346
Significance	0.024	0.165

Note Plasma clearance = dose/AUC ~ 1/sleep time; hence, sleep time ~ AUC.
*Coefficient = 0.0000471; SE = 0.0000137; t test value = 3.44; P = 0.006.

Data Analysis System. All calculations were performed on an Amdahl 470/V8 computer of the Michigan Terminal System.

Results

Ketamine exhibited triexponential decay under both test conditions (as confirmed by the F test). Fig. 1 shows ketamine concentrations for each condition in a representative subject and the corresponding fit to a three-term exponential equation. Table I lists the means and corresponding differences between plasma concentrations of ketamine under each treatment condition. Diazepam pretreatment was associated with elevated ketamine levels 3, 4, 5, 10, 20 min and 1 and 8 hr after dosing ($P < 0.05$; two-way analysis of variance). When calculated according to the trapezoidal rule, the AUC from 2 min to 8 hr exhibited corresponding differences between the two treatments. AUC was elevated by diazepam pretreatment ($P < 0.05$). These differences correlated positively with differences in body weight ($P < 0.05$), but the time points were not associated with differences in levels of KI and KII (Tables II and III). There were no significant differences in AUC of KI and KII from 2 to 30 min as well as from 2 to 8 hr.

Kinetics were calculated for each condition and are summarized in Table IV. Although there were no apparent differences in the first-order rate parameters, plasma clearance was

Table VI. *Correlation of ketamine plasma levels with duration of anesthesia*

Subject No.	Weight (kg)	Placebo-ketamine			
		Duration No. 1* (min)	Plasma level (ng/ml)	Duration No. 2† (min)	Plasma level (ng/ml)
1	73.2	17.0	907	17.0	907
2	81.8	18.4	1200	18.4	1200
3	70.0	20.5	1080	23.8	961
5	68.0	12.2	1040	18.9	589
6	69.2	17.0	1070	18.5	973
7	59.9	9.5	1050	12.1	891
8	71.6	10.2	1240	10.2	1240
$\bar{X}$ ± SE		15.0 ± 1.6	1080 ± 40	17.0 ± 1.8	966 ± 82

*Time to follow a simple command (P = 0.021).
†Time to answer with simple sentences (P = 0.037).

Table VII. *Twenty-four–hour urinary excretion data (mg/24 hr)*

Subject No.	Placebo-ketamine	Diazepam-ketamine
Ketamine (t = 0.102; P > 0.30)		
1	9.71	10.00
2	6.84	6.81
3	2.37	1.77
4	1.74	4.19*
5	2.50	0.15
6	1.48	1.79
7	5.86	4.82
8	3.45	4.01
$\bar{X}$	4.24	4.19
KI (t = 0.460; P > 0.30)		
1	2.92	2.70
2	7.76	6.22
3	2.39	1.91
4	3.81	4.68*
5	3.38	0.57
6	3.10	3.44
7	4.03	8.84
8	7.07	9.11
$\bar{X}$	4.31	4.68
KII (t = 0.526; P > 0.30)		
1	10.8	14.3
2	38.9	36.1
3	10.2	8.2
4	28.0	22.3*
5	24.4	18.3
6	11.0	10.7
7	12.0	31.9
8	30.8	36.8
$\bar{X}$	20.7	22.3

*Estimated from mean of remaining seven values.

decreased by diazepam from 848 to 719 ml/kg/hr ($P < 0.05$; one-tailed t test). Comparison of these kinetic parameters with duration of anesthesia revealed several interesting results. AUC, as calculated from the integrated triexponential fit for each subject, correlated positively with duration of anesthesia, as measured by time until first ability to follow a simple command as well as time to answer verbal commands with simple sentences ($P < 0.05$). Since plasma clearance is equal to dose/AUC, the inverse of sleep time correlated with plasma clearance. One-way analysis of covariance indicated a positive linear relationship between inverse sleep time and plasma clearance for the overall condition as well as for placebo pretreatment ($P < 0.05$; Table V). There was an additional trend that suggested another additive effect of diazepam on sleep time that was unrelated to alterations in plasma clearance of ketamine itself ($P = 0.046$; one-tailed t test). These effects corresponded to a relative increase in duration of anesthesia (as measured by ability to follow simple commands) from 15.0 ± 1.6 min in the placebo condition to 21.7 ± 3.2 min with diazepam pretreatment. Fig. 2 illustrates this analysis and shows the relationship between plasma clearance and the inverse of sleep time for each subject under both treatment conditions. It should be noted that sleep time is proportional to AUC. Since AUC = dose/plasma clearance, sleep time is

Diazepam-ketamine			
Duration No. 1 (min)*	*Plasma level (ng/ml)*	*Duration No. 2† (min)*	*Plasma level (ng/ml)*
14.3	1640	17.3	1360
20.0	892	24.3	809
33.2	964	36.7	925
15.0	909	15.0	909
34.0	835	43.0	721
19.7	866	19.7	866
15.5	1350	15.5	1350
21.7 ± 3.2	1070 ± 120	24.5 ± 4.2	991 ± 97

proportional to 1/plasma clearance and 1/sleep time is proportional to clearance. We chose the latter plot for Fig. 2 because we believe that plasma clearance is a more physiologic measure than AUC. Fig. 2 can also be viewed as a plot of AUC against sleep time in which the greater the AUC, the longer the sleep time, which obviously makes good sense. After all, it is the drug in the body (as reflected by the AUC) that induces the "sleep" or anesthesia.

Although there was no correlation between plasma concentrations and duration of anesthesia, the thresholds at which anesthesia occurred were remarkably close. Plasma concentrations ($\bar{X} \pm SE$) at which subjects were first able to follow commands were 1080 ± 40 ng/ml after placebo and 1070 ± 120 ng/ml after diazepam (Table VI). The time course of anesthesia, however, correlated more closely in most subjects with the time course of ketamine within the second compartment of the model. This is illustrated for subject No. 7 in Fig. 3. Peak levels of ketamine are attained approximately 2 to 3 min after injection and fall exponentially in the ensuing period. After approximately 5 to 10 min, the second compartment exhibits a parallel decline. Commonly described as at pseudo-equilibrium between these compartments, plasma levels would reflect those of the second compartment at the later time points. As can be seen in Fig. 3, compartment two shows slightly elevated levels under the diazepam-ketamine condition. This is consistent with the increases in mean plasma ketamine levels at some time points after diazepam. Additional information obtained from the time course of ketamine in the three-compartment model predicts that there would be no differences in elimination (percent dose) under the two conditions. This prediction was confirmed by actual urinary ketamine, KI, and KII data (Table VII).

Twenty-four hours after each subject completed both treatments (placebo-ketamine or diazepam-ketamine), he was asked to comment on the two sessions with respect to verbalization of each experience (first or second), recall of events, recall of emergence, and whether he would be willing to repeat each experience. These data were assigned to the appropriate treatment sequence when the study was completed and data were summarized. When asked to describe the experience after what turned out to be diazepam-ketamine treatment, six of seven subjects felt it was pleasant or favorable and one of seven felt it was unfavorable. After the placebo-ketamine treatment, five of eight subjects felt it was unfavorable and three of eight felt it was favorable ($P < 0.05$; chi-square analysis). Five subjects said they would repeat the diazepam-ketamine anesthesia and two said they would not; four subjects said they would repeat the placebo-ketamine regimen, while three said they would not and one was undecided. After eliminating the one who was undecided from analysis, chi-square analysis indicated a P value >0.05.

Discussion

Our results with ketamine are in close agreement with previous reports and our own experience with surgical volunteers.[5] Ketamine kinetics appear to follow at least a three-term exponential decay, corresponding to a three-compartment model of plasma and tissue distribution. The time course of anesthesia follows that of the predicted second compartment more closely than that of the plasma compartment, as plasma levels fall rapidly in the first few minutes after injection while anesthesia persists for a longer period. Duration of anesthesia was linearly related to AUC and inversely related to clearance. Thus the longer the duration of anesthesia, the larger the AUC. It should be noted that it is generally preferable to model the onset and offset of pharmacologic effects with a separate effect compartment rather than to assign the biophase to one of the compartments of the three-compartment model. It is likely that the locus of ketamine action does not correspond to any of the compartments used to model the kinetics of its duration.

Diazepam pretreatment raised plasma ketamine levels slightly and decreased its rate of clearance. It prolonged sleep time in these subjects, which was most likely a result of two independent effects: the additive sedative effect of diazepam and the fact that diazepam decreases ketamine clearance, thereby prolonging sleep time. While ketamine clearance from plasma partially determines the termination of its effects, redistribution from the brain is also important. Diazepam reduces the cardiac stimulant effect of ketamine, which provides a possible explanation of the enhanced plasma levels and decreased clearance of ketamine after pretreatment with diazepam.[4, 10, 16, 17]

There appeared to be little correlation between duration of ketamine anesthesia and appearance of KI and KII. The decline in plasma levels during anesthesia duration did not correlate with the appearance of these substances. It is interesting that the total 24-hr urinary excretion of ketamine, KI, and KII (Table VI) accounts for only about 20% of the total ketamine dose. Ketamine and its metabolites may be sequestered in body tissues such as fat, suggesting the existence of a depot compartment not detectable on the basis of the present 24-hr plasma data. It is also known that there are additional potential ketamine metabolites that were not identified by this assay. Obviously, more investigations are required to determine whether ketamine anesthesia is terminated by redistribution from the second compartment rather than by biotransformation. As a working hypothesis, however, redistribution of ketamine seems to be the more important variable.

Diazepam pretreatment has been associated with a decrease in the frequency of emergence delirium from ketamine anesthesia,[8] and we found it enhanced subject acceptance of ketamine. There are several possibilities regarding this interaction. It has been suggested that ketamine may be biotransformed to a psychotomimetic that induces this effect. Diazepam pretreatment may thus reduce the formation of these substances. There is in vitro evidence that diazepam does reduce ketamine biotransformation,[2] but we found no evidence for such an effect on ketamine metabolism. Alternative hypotheses are that diazepam may enhance γ-aminobutyric acid–mediated transmission, which may be altered by ketamine, or that diazepam may simply reduce delirium by means of nonspecific sedative and/or amnestic properties. In any case, our study provides evidence that diazepam pretreatment has significant effects on ketamine anesthesia and kinetics. After diazepam, ketamine plasma levels are slightly enhanced, plasma ketamine clearance is slightly reduced, and ketamine anesthesia is more acceptable. Our data also indicate that much more needs to be learned about this remarkable drug whose place in clinical anesthesia is still being debated.

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