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Pharmacodynamic Modeling of the EEG Effects of Ketamine and Its Enantiomers in Man

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The pharmacodynamics of a racemic mixture of ketamine R,S(±)-ketamine and of each enantiomer, S(+)-ketamine and R(−)-ketamine, were studied in five volunteers. The median frequency of the electroencephalogram (EEG) power spectrum, a continuous noninvasive measure of the degree of central nervous system (CNS) depression (pharmacodynamics), was related to measured serum concentrations of drug (pharmacokinetics). The concentration-effect relationship was described by an inhibitory sigmoid E_{max} pharmacodynamic model, yielding estimates of both maximal effect (E_{max}) and sensitivity (IC_{50}) to the racemic and enantiomeric forms of ketamine. R(−)-ketamine was not as effective as R,S(±)-ketamine or S(+)-ketamine in causing EEG slowing. The maximal decrease (mean ± SD) of the median frequency (E_{max}) for R(−)-ketamine was 4.4 ± 0.5 Hz and was significantly different from R,S(±)-ketamine (7.6 ± 1.7 Hz) and S(+)-ketamine (8.3 ± 1.9 Hz). The ketamine serum concentration that caused one-half of the maximal median frequency decrease (IC_{50}) was 1.8 ± 0.5 μg/mL for R(−)-ketamine; 2.0 ± 0.5 μg/mL for R,S(±)-ketamine; and 0.8 ± 0.4 μg/mL for S(+)-ketamine. Because the maximal effect (E_{max}) of the R(−)-ketamine was different from that of S(+)-ketamine and R,S(±)-ketamine, it was not possible to directly compare the potency (i.e., IC_{50}) of these compounds. Accordingly, a classical agonist/partial-agonist interaction model was examined, using the separate enantiomer results to

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predict racemate results. Although the model did not predict racemate results well, its failure was not so great as to provide clear evidence of synergism (or excess antagonism) of the enantiomers.

KEY WORDS: ketamine; enantiomers; EEG power-spectral analysis; pharmacodynamic modeling; median frequency.

INTRODUCTION

Previous studies involving optical isomers of centrally active drugs have demonstrated stereospecificity with respect to their effects on the central nervous system (CNS) (1-5). Prior studies with the optical isomers of ketamine have suggested both quantitative and qualitative differences between the ketamine enantiomers with respect to their effects on the CNS (6,7).

The purpose of this research was to devise a continuous, noninvasive measure of ketamine's effect on the brain in man. This was achieved using power-spectral analysis to calculate the median frequency, a measure that quantitates the decrease in the electroencephalogram (EEG) frequency induced by ketamine. By relating the median frequency to the measured serum concentrations using pharmacodynamic models, it is possible to quantitate and to compare the effectiveness of racemic ketamine and its enantiomers in causing EEG slowing. Further, pharmacodynamic models of enantiomer interaction allow one to examine the contribution of the individual enantiomers to the pharmacologic effect of the racemic mixture.

METHODS

Study Design

Five healthy male volunteers, ages 36 ± 3 years and weight 75 ± 3 kg (mean $\pm$ SD), were studied on three different occasions. The interval between each experiment was at least 7 days and, at the longest, 14 days. After an overnight fast, an intravenous catheter was placed for the drug administration in a large forearm vein, and an indwelling intravenous line was placed in the contralateral arm for blood sampling. A precordial stethoscope, ECG, and EEG leads were applied, and blood pressure was measured noninvasively with an automatic device (Dinamap^{R}). The baseline EEG was recorded for approximately 10 min in addition to blood pressure, heart rate, and respiratory rate measurements. Glycopyrolate 0.2 mg, a noncentrally active antisialagogue, was given intravenously after 5 min of baseline recording. Glycopyrolate, due to its quaternary amine structure, does not cross the brain-blood barrier and, thereby, has no effects on the CNS. Thereafter, a

constant infusion of either *R,S*(±)-ketamine, *S*(+)-ketamine, or *R*(−)-ketamine was started. The protocol was approved by the Stanford University Institutional Review Board, and informed consent was obtained from each volunteer.

The infusion rates were chosen in accordance with previously reported potency ratios in surgical patients (6). By adjusting for the potency differences of the enantiomers with the infusion rates, one could attempt to achieve the same degree of drug effect in a similar duration of infusion. The *S*(+)-ketamine was infused at a rate of 25 mg/min, the rate *R,S*(±)-ketamine was 50 mg/min, and that for *R*(−)-ketamine was 75 mg/min. The sequence in which the compounds were administered was *R,S*(±)-ketamine, *S*(+)-ketamine, and *R*(−)-ketamine for the last three volunteers studied. The constant infusion was maintained for 5 to 7 min until a profound anesthetic state was observed (both absent response to verbal stimuli and absent eyelash reflex) and maximal slowing of EEG was apparent in all of the four EEG leads. The total doses administered were *R,S*(±)-ketamine, 275 ± 25 mg; *S*(+)-ketamine, 140 ± 22 mg; and *R*(−)-ketamine, 420 ± 41 mg (mean ± SD).

The EEG was continuously recorded for 60 to 120 min until the baseline pattern returned. Clinical end points during the recovery phase included responsiveness to verbal commands (positive handgrip), early orientation (to person), and full orientation (to person, place, and time).

Venous blood samples were drawn for the analyses of *R,S*(±)-ketamine, *S*(+)-ketamine, and *R*(−)-ketamine serum concentrations at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12.5, 15, 20, 30, 45, and 60 min after the infusion was started. By 60 min, all the volunteers had recovered to their baseline levels.

Analytical Techniques

Total (free and protein-bound) serum ketamine concentrations were measured after using a modified version of the gas-chromatographic procedure of Chang and Glatzko (8), described previously (9). This assay is not enantiospecific. Racemic ketamine hydrochloride was obtained from Parke, Davis and Company, Detroit, MI. Resolution of the two enantiomers followed a procedure involving recrystallization of the (+)- or (−)-tartaric acid salts (7). The free base *R*(−)-ketamine had a melting point of 110 to 117°C and $[\alpha]_D^{25} = -58.25°$ (c = 2.0, ethanol). On treatment with HCl, the *S*(+)-ketamine hydrochloride salt was formed with a melting point of 258 to 261°C and $[\alpha]_D^{25} = +93.6°$ (c = 2.0, water). The free base *S*(+)-ketamine had a melting point of 119 to 120°C and $[\alpha]_D^{25} = +55.90°$ (c = 2.0, ethanol). On treatment with acid *R*(−)-ketamine hydrochloride was formed with a melting point of 256 to 258°C and $[\alpha]_D^{25} = -93.5°$ (c = 2.0, water). The two

enantiomers were always used as HCl salts, and all designations of sign of optical rotation refer to such salts. All chemicals used in the resolution were of reagent grade. The (+)- and (−)-tartaric acids from Aldrich Chemical Company, Milwaukee, WI. Repeat analysis revealed no significant changes in the optical rotation of the isomers with time (3 to 6 months). The enantiomers were reconstituted in isotonic saline at the appropriate concentration. The racemic mixture *R,S*(±)-ketamine contained the enantiomers in a ratio of 1:1. Amounts and concentrations given are referring to the free base.

EEG Analysis

A four-lead EEG (F_1-O_1, F_2-O_2, C_z-O_1, C_z-O_2; according to the international 10-20 system) was monitored. In addition, two leads for an electro-occulogram (EOG) were applied. The signals were amplified by a Beckman Accutrace^R EEG machine and were recorded by a paper chart recorder and on magnetic tape, using an 8-channel FM recorder (Vetter Model^R). A PDP 11/23 computer (Digital Equipment Corporation) was used for off-line signal analysis. Serial epochs of 8 sec were digitalized at a rate of 200 Hz with a 10-bit resolution. Gross artifacts (eye and head movements) detected with the EOG were rejected and substituted by the last epoch free of artifacts. Fast Fourier analysis was performed to resolve the EEG signal into frequency and amplitude components to achieve a power (function of amplitude) *vs.* frequency histogram or power spectrum (10). The median frequency (MF), defined as the frequency that divides the area under the power spectrum curve into two equal parts (11), was used to quantitate the change of the EEG frequency induced by ketamine. A moving arithmetic mean of the median frequency of 5 epoch before and after a given epoch was used as the smoothed signal; thus, each median frequency represents the average of 80 sec of EEG signal.

Pharmacodynamic Data Analysis

The ketamine serum concentration and median frequency data were examined for the presence of temporal delays as previously described (12). Since no significant degree of hysteresis was present, the median frequency was directly related to the ketamine serum concentrations with the following pharmacodynamic model (13):

$$\text{Median frequency} = E_0 - \frac{E_{max} \cdot C_p^{\gamma}}{IC_{50}^{\gamma} + C_p^{\gamma}} \quad (1)$$

In this model, E_0 (Hz) represents the median frequency of the EEG power spectrum when the volunteer is awake (baseline); E_{max} is the maximal

decrease (Hz) of the median frequency caused by the CNS depressant effect of the drug either (±)-ketamine, $S(+)$-ketamine, or $R(-)$-ketamine; C_p is the concentration ($\mu g/ml^{-1}$) of the drug; γ is a power parameter describing the steepness of the sigmoid curve; and IC_{50} is the drug concentration necessary to achieve 50% of the maximal effect ($\frac{1}{2} \cdot E_{max}$). Values of the pharmacodynamic parameters were determined by ordinary least squares nonlinear regression analysis (ELSFIT), using measured drug concentrations. γ was constrained to be the same value for both enantiomers. One-way analysis of variance ($p < 0.05$) was used to compare the pharmacodynamic parameter estimates between the two enantiomers and the racemic compound. An unpaired t-test with the Bonferroni correction was used as a contrast procedure.

A standard model (competitive interaction) for nonsynergistic combined action of the enantiomers was used (14). This model predicts for the racemate that

$$\text{Median frequency} = E_0 - \frac{(E_{max_+}) \cdot (x/IC_{50+})^\gamma + (E_{max_-}) \cdot (x/IC_{50-})^\gamma}{1 + (x/IC_{50+})^\gamma + (x/IC_{50-})^\gamma} \quad (2)$$

where x is one-half the racemate concentration (i.e., the actual concentration of each enantiomer). The additional subscript + or − on E_{max} and IC_{50} denotes the values of these parameters for $S(+)$-ketamine or $R(-)$-ketamine when given alone.

Alternatively, model 1 can, of course, be used for the racemate, ignoring the data from administration of the enantiomers alone, and serves as an empirical, possibly synergistic alternative to the nonsynergistic model 2.

RESULTS

EEG Analysis

The morphological changes of the EEG caused by ketamine could be described by three sequential phases (Fig. 1): *Phase I*: Loss of alpha rhythm (6–14 Hz) in combination with a decreased amplitude and frequency; *Phase II*: Persistent rhythmic theta activity (4–6 Hz) with increasing amplitude; and *Phase III*: Intermittent polymorphic delta activity (0.5–2 Hz) of large amplitude.

Phases II and III, in addition, were superimposed by a fast beta activity (14–20 Hz) of low amplitude. Phases I to III could be observed in each volunteer when $R,S(\pm)$-ketamine and $S(+)$-ketamine were administered. When $R(-)$-ketamine was administered, however, it was not possible to

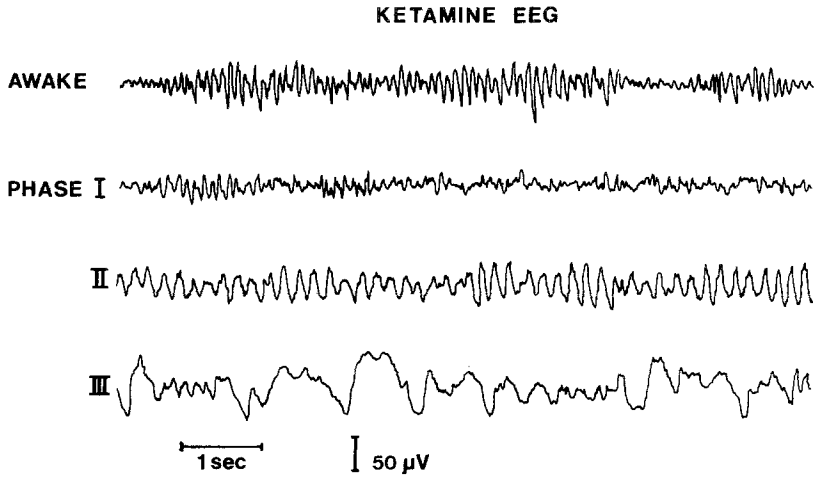

Fig. 1. EEG phases produced by ketamine. Phases I to III were seen with *R,S*(±)-ketamine and *S*(+)-ketamine. With *R*(−)-ketamine, the maximal EEG effect was Phase II.

Table I. Median Frequency (Hz) of the EEG Related to Clinical Observations Following the Administration of *R,S*(±)-Ketamine, *S*(+)-Ketamine, and *R*(−)-Ketamine

Subject no.	Dose (mg)	Isomeric form	Baseline (awake)	Maximal effect	Responsiveness	Early orientation	Full orientation
1	275	(±)	9.2	0.9	5.7	6.5	7.0
2	250	(±)	8.5	1.4	6.1	6.5	7.4
3	300	(±)	9.9	1.8	7.3	7.7	8.5
4	300	(±)	9.9	0.8	6.8	8.7	9.3
5	250	(±)	10.9	3.0	5.7	6.0	6.8
Mean	275		9.5	1.6[a]	6.3	7.1	7.8
±SD	25		0.6	0.9	0.7	1.1	1.1
1	125	(+)	9.9	2.0	5.4	6.0	7.0
2	150	(+)	9.9	1.8	5.9	6.2	7.7
3	175	(+)	10.0	2.0	5.9	6.3	6.5
4	125	(+)	10.0	1.3	6.5	7.4	8.7
5	125	(+)	9.9	3.7	5.0	5.8	6.2
Mean	140		9.9	2.2[a]	5.7	6.3	7.2
±SD	22		0.1	0.9	0.6	0.6	1.0
1	375	(−)	9.2	5.6	6.1	6.4	7.2
2	450	(−)	10.0	5.2	6.2	6.4	7.0
3	450	(−)	10.0	5.2	5.8	5.8	6.3
4	450	(−)	9.8	4.1	6.4	7.0	8.5
5	450	(−)	10.0	5.0	6.0	6.4	6.7
Mean	420		9.8	5.0[a]	6.1	6.4	7.1
±SD	41		0.3	0.6	0.2	0.4	0.8

[a] Significantly different from the baseline and responsiveness clinical end points.

suppress the EEG activity more than Phase II even though much higher doses were administered.

Table I indicates the median frequencies seen in the study at the various clinical end points of ketamine anesthesia. Although the degree of EEG slowing was less with the *R*(−)-ketamine than with the racemic compound or the *S*(+)-ketamine, it was not possible to clinically distinguish a difference in the degree of CNS depression using the simple quantal measures of responsiveness and orientation. The median frequency was significantly lower at the maximal drug effect when compared to the baseline or the responsiveness clinical end point. It was not possible to statistically demonstrate a difference in the median frequency between the responsiveness, early, and full orientation clinical end points. Nonparametric statistical tests for paired data were applied as well and revealed borderline statistical significant differences for every comparison between two EEG stages.

The EEG suppression as indicated by the median frequency from increasing concentrations of *S*(+)-ketamine is displayed in Fig. 2. The median frequency and serum concentrations *vs.* time curves for the *R*(−)-ketamine and *R,S*(±)-ketamine were similar to that shown in Fig. 2. There was no significant time delay (hysteresis) between the median frequency values and the venous serum concentrations of *R,S*(±)-ketamine, *S*(+)-ketamine, or *R*(−)-ketamine during and after the infusion.

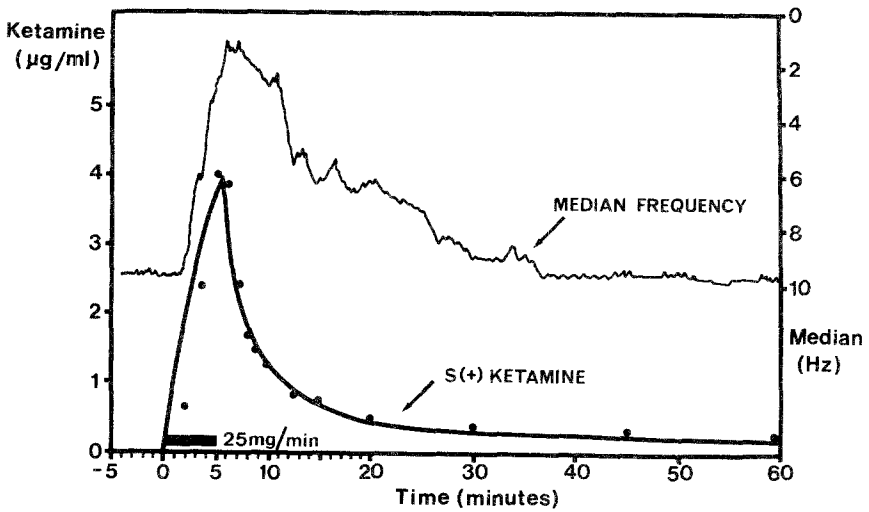

Fig. 2. A representative median frequency and ketamine serum concentrations *vs.* time curve. The solid bar is the duration of the *S*(+)-ketamine infusion. Note that the median frequency axis has been inverted to have the drug concentration and EEG effect move in the same direction.

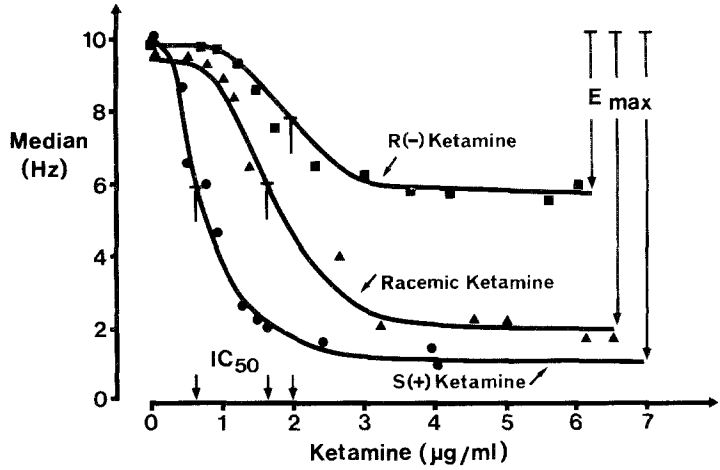

Fig. 3. Pharmacodynamic characterization of the ketamine serum concentrations *vs.* median frequency relationship. The solid line is the data characterization using equation 1 (see Methods) for one subject (≠4) who received the *R,S*(±)-ketamine and its two enantiomers. The IC_{50} and E_{max} values for the data are indicated.

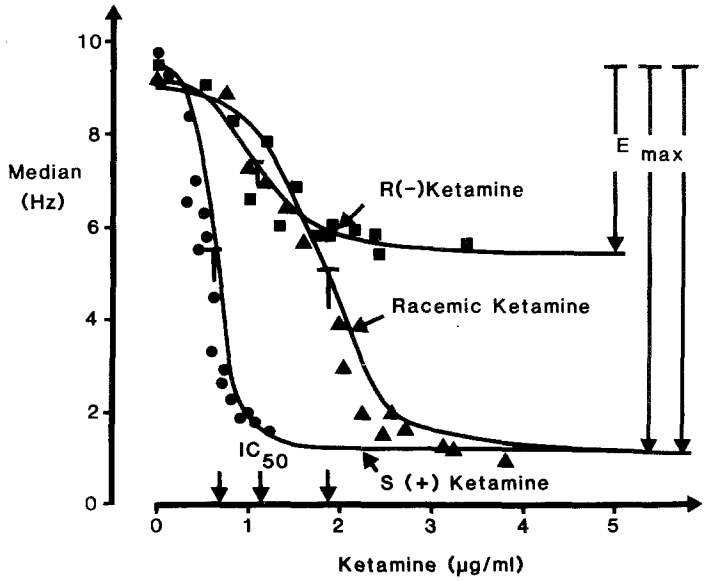

Fig. 4. Pharmacodynamic characterization of the ketamine serum concentration *vs.* median frequency relationship. The solid line is the data characterization using equation 1 (see Methods) for one subject (≠1) who received the *R,S*(±)-ketamine and its two enantiomers.

Pharmacodynamic EEG Modeling

The sigmoid concentration response relationships between the median frequency and the serum levels of *R*, *S*(±)-ketamine, *S*(+)-ketamine, and *R*(−)-ketamine for two of the volunteers are displayed in Figs. 3 and 4. The pharmacodynamic model parameters for all volunteers when each compound was individually modeled are summarized in Table II. The E_{max} value for *R*(−)-ketamine was significantly different from that of *S*(+)-ketamine and *R*, *S*(±)-ketamine, as was the IC_{50} of *S*(+)-ketamine from that of *R*(−)-ketamine and *R*,*S*(±)-ketamine.

Equation 2 was simulated using the parameter values obtained by the fits to the separate enantiomer data. Figure 5 superimposes the racemate data on this simulation for the same volunteer Fig. 4 and also shows the

Table II. Individual Pharmacodynamic Characterization of Racemic Ketamine and Its Enantiomers

Subject	Dose (mg)	Isomeric form	E_0[f] (Hz)	E_{max}[g] (Hz)	IC_{50}[h] (μg/ml)	γ[i]
1	275	(±)	8.8	8.2	1.8	4.3
2	250	(±)	7.6	4.9	2.0	45.3
3	300	(±)	8.5	8.5	2.9	3.7
4	300	(±)	8.6	6.9	1.9	5.4
5	250	(±)	10.2	9.4	1.6	1.8
Mean	275		8.7	7.6	2.0[a]	3.8[d]
±SD	25		0.9	1.7	0.5	1.5[d]
1	125	(+)	9.7	9.7	0.6	3.2
2	150	(+)	9.6	9.6	0.8	5.8
3	175	(+)	8.5	8.5	1.5	2.5
4	125	(+)	10.4	8.9	0.7	2.5
5	125	(+)	9.2	5.0	0.3	4.9
Mean	140		9.5	8.3	0.8	3.8
±SD	22		0.7	1.9	0.4	1.5
1	375	(−)	9.4	4.0	1.0	3.2[e]
2	450	(−)	9.6	4.2	2.3	5.8[e]
3	450	(−)	10.2	4.9	1.7	2.5[e]
4	450	(−)	9.8	5.0	2.0	2.5[e]
5	450	(−)	9.8	4.1	2.0	4.9[e]
Mean	420		9.8	4.4[c]	1.8[b]	
±SD	41		0.3	0.5	0.5	

[a] $p < 0.05$ for *R*,*S*(±)-ketamine *vs.* *S*(+)-ketamine.
[b] $p < 0.05$ for *R*(−)-ketamine *vs.* *S*(+)-ketamine.
[c] $p < 0.05$ for *R*(−)-ketamine *vs.* *S*(+)-ketamine and *R*(−)-ketamine *vs.* *R*,*S*(±)-ketamine.
[d] Outlying value for Subject 2 omitted.
[e] Fixed equal to corresponding values for (+) enantiomer.
[f] E_0 baseline EEG median frequency when volunteers are awake.
[g] Maximal decrease of EEG median frequency induced by ketamine.
[h] Concentration of ketamine necessary to cause ½ of maximal EEG median frequency decrease.
[i] Dimensionless term describing the slope of the sigmoid concentration *vs.* effect curve.

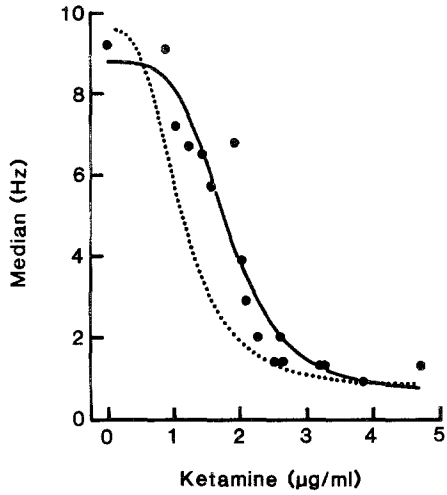

Fig. 5. The solid circles are the same data as Fig. 4 (racemate only) with the solid line being the fit for model 1, the dotted line for model 2.

fit of this data to equation 1. Model 2 does not fit the data as well as (the empirical) model 1. The discrepancy, which suggests more antagonism between the two enantiomers than expected from simple competitive inhibition, is not so great, however, that a major degree of such excess antagonism is clearly suggested.

DISCUSSION

The EEG patterns we report from *R*, *S*(±)-ketamine are not different from those data published by Domino *et al.* (15). We have previously reported the effects of ketamine enantiomers on the EEG in a descriptive, nonquantitative manner (16). Although qualitative differences are seen in the EEG patterns of the ketamine enantiomers, power-spectral analysis is required to quantify these changes. Power-spectral analysis of the EEG has been used previously to detect different degrees and types of drug effect on the brain (17). Only recently, however, has it been used in conjunction with drug concentrations in serum for pharmacodynamic modeling purposes. The spectral edge frequency has been used to characterize the EEG slowing induced by thiopental (18,19) and fentanyl (20). A similar measure, the median frequency has been reported to describe accurately the hypnotic effect of etomidate (11,21) and midazolam (22). The spectral edge proved to be a less reliable and useful predictor of the ketamine clinical effect in this study. This is due to the low-amplitude high-frequency activity that

superimposes on the predominant high-amplitude delta wave activity (Fig. 1). This produces a shift of the spectral edge value to a relatively high frequency and, therefore, less change in value with progressively more drug effect. The median frequency is by definition the 50th percentile of the frequency distribution, and, therefore, it is the less affected by the high-frequency activity that contains a relatively small amount of the area of the epoch.

With the use of quantal clinical measures of anesthetic depth, we were able to distinguish a significant difference in the median frequency at the maximal drug effect relative to the awake baseline and the recovery of responsiveness to verbal stimuli using parametric statistical tests. When nonparametric testing was applied, the EEG median frequency was able to distinguish between all neighboring stages of clinically observed end points. However, only borderline ($p > 0.05$ to 0.06) statistical significance could be achieved because of the small group ($n = 5$).

Subjects receiving the $R(-)$-ketamine had a median frequency of 5.0 ± 0.6 Hz at the maximal drug effect, relatively close to the median frequency 5.7 ± 0.6 Hz seen at the responsiveness end point for $S(+)$-ketamine. The similarity of EEG frequency at different clinical end points of anesthetic depth may reflect a dissociation of clinical end points of CNS depression relative to EEG frequency or the relative imprecision with which we were able to measure the depth of CNS depression with clinical measures such as responsiveness to verbal stimuli. When the changes in ketamine serum concentrations during and after the infusion were related to the median frequency changes, no temporal lag (hysteresis) was seen between the venous serum concentration and EEG effect. This lack of hysteresis is most likely due to an arterio-venous concentration difference that eliminates hysteresis. This phenomenon has been seen with thiopental where the half-time of equilibration between the blood and brain EEG effects is approximately 1–2 min. Arterial blood sampling demonstrates hysteresis, whereas venous sampling does not (19). Lack of hysteresis in the ketamine data suggests that the blood : brain equilibration is very rapid and allows drug concentrations to be related directly to the drug effect with the appropriate pharmacodynamic model.

The ketamine serum concentration *vs.* median frequency relationship is characterized adequately by an inhibitory sigmoid E_{max} pharmacodynamic model. The inability of $R(-)$-ketamine to cause as much EEG slowing as $S(+)$-ketamine or $R,S(+)$-ketamine is revealed by the significantly smaller E_{max} value obtained from the fit to the pharmacodynamic model 1. Assuming that both enantiomers share a common mechanism of action, $R(-)$-ketamine thus appears to be a partial agonist relative to $S(+)$-ketamine. This predicts that when used in combination, the $R(-)$-ketamine will act antagonistically

to *S*(+)-ketamine. The data bear out this prediction. Model 2 is a theoretical model for nonsynergistic partial antagonism, and when the effect of the racemate is predicted by this model, the correspondence between observations and prediction is good, although not perfect (see Fig. 5). In fact, if anything, the actual data reveal greater antagonism (i.e., some negative synergism) than predicted by theory (Fig. 5: Actual points are shifted to the right relative to model 2 predictions).

Differences in the pharmacological activity of enantiomers have been demonstrated for numerous drugs that act on the CNS. The potency interaction of individual enantiomers relative to the racemic mixture varies in these studies. In some cases, the racemic mixture appears to be an additive sum of the individual isomers (1,23,24). However, in other cases this is not so. All previous studies have used some form of dose–response methodology to estimate the enantiomer and racemic mixture potency. Differences in potency could be pharmacodynamic (tissue responsiveness) or pharmacokinetic (distribution and elimination). It is difficult to assess the individual contribution of the above factors to the potency differences of isomers and racemic mixtures observed in previous studies. In addition, most previous investigators have not carefully tried to relate the potency of individual isomers to that of the racemic mixture. By measuring serum concentrations of ketamine, we eliminated possible pharmacokinetic causes of apparent differences in potency of the enantiomers and the racemic mixture. We have shown that the pharmacokinetic distribution and elimination of each isomer is not different from the racemic compound (16). By modeling the pharmacodynamic interaction of the enantiomers we examined whether the racemic action is purely additive or not. Our results suggest that the effect of the racemic mixture of ketamine is almost but not quite accounted for by classical competitive interaction (nonsyngerstic).

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