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Metabolism of Ketamine Stereoisomers by Human Liver Microsomes

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Ketamine is used clinically as a racemic mixture of optical isomers that differ in their analgesic properties and psychomimetic effects. Administered individually, or together as the racemate, ketamine enantiomers differ in their hepatic clearance and duration of anesthetic effect. S(+) ketamine exhibits a greater clearance and faster anesthetic recovery compared to the racemate and a greater clearance compared to R(−) ketamine. Ketamine undergoes extensive hepatic metabolism, primarily *via* N-demethylation to norketamine, yet little is known about the human metabolism of ketamine enantiomers. The purpose of this investigation therefore was to characterize ketamine racemate and enantiomer metabolism by human liver and to test the hypothesis that differences in hepatic ketamine enantiomer metabolism can account for observed differences in ketamine enantiomer pharmacokinetics. Ketamine N-demethylation by microsomes from three human livers was measured by gas chromatography-mass spectrometry. At ketamine concentrations typically achieved during anesthesia (5 μM), the rate of S(+) ketamine demethylation was 20% greater than that of R(−) ketamine and 10% greater than that of the racemate ($P < .05$). At all ketamine concentrations, the rate of racemate demethylation was less than the sum of the rates for the individual enantiomers, reflecting a metabolic enantiomeric interaction whereby one ketamine enantiomer inhibits the metabolism of the other enantiomer. N-demethylation of racemic ketamine and each enantiomer was catalyzed by two apparent enzymes, a high affinity-low capacity enzyme (K_{m_1} 30–50 μM, V_{max_1} 2–6 nmoles · min^{-1} · nmole^{-1}) and a low affinity-high capacity enzyme (K_{m_2} 600–800 μM, V_{max_2} 9–15 nmoles · min^{-1} · nmole^{-1}). At therapeutic concentrations, ketamine metabolism is catalyzed predominantly by one enzyme (the low K_m enzyme), permitting calculation of the *in vitro* clearance parameter V_{max_1}/K_{m_1}. *In vitro* clearances of ketamine enantiomers and the racemate were excellent predictors of the relative *in vivo* clearances. These results demonstrate relative enantiomeric selectivity in human liver ketamine metabolism, which accounts for observed differences in the clinical pharmacokinetics of racemic ketamine and ketamine enantiomers. (Key words: Anesthetics, intravenous: ketamine. Metabolism: ketamine. Stereochemistry.)

THE IMPORTANCE OF stereochemistry in clinical pharmacology and therapeutics has achieved considerable recognition in the last decade,[1–3] particularly in the arena of new drug development.[4] Most drugs are optically active and are used clinically as a racemate (the equal mixture of optical isomers, also referred to as enantiomers).§ Individual enantiomers may differ in their receptor effects, disposition and toxicity. The potential advantages of using pure enantiomers rather than a racemate include a less complex and more selective pharmacologic profile, a greater therapeutic index, less complex pharmacokinetics, less complex drug interactions, and less complex concentration-response relationships.[6] This newfound awareness has recently been applied to the evaluation of anesthetic agents.[7]

Ketamine represents a unique drug in anesthesia, both because it occupies a distinct place in clinical practice, and because considerable information is available about the pharmacodynamics and pharmacokinetics of individual ketamine stereoisomers.[8,9] Ketamine is used clinically as a racemate, yet the S(+) and R(−) enantiomers differ in their pharmacokinetics and pharmacodynamic effects. The analgesic and hypnotic potency of S(+) ketamine is approximately four times greater than that of the R(−) isomer, which is only a partial agonist.[10–12] In contrast, psychic emergence reactions and agitated behavior are far less common with S(+) ketamine than with its R(−) antipode or with the racemate.[10,13] Stereoselective differences in ketamine affinity for NMDA receptors, and ketamine effects on NMDA receptor currents, catecholamine reuptake, and acetylcholinesterase activity have also been observed.[12,14–16]

Differences also exist in the pharmacokinetics of ketamine enantiomers. Geisslinger *et al.* recently showed using a stereoselective assay that the clearance of S(+) ketamine was significantly greater (15%) than that of R(−) ketamine when the two were administered together as the racemate.[17] Administered individually, the plasma clearance of S(+) ketamine was 22% greater than that of the R(−) enantiomer.[10] Similarly, anesthetic recovery from racemic ketamine was significantly slower than recovery from either of the individual enantiomers.[10] Based on these clinical observations, White *et al.* suggested that the presence of R(−) ketamine in the racemate could exert an inhibitory influence on the recovery from the more potent S(+) enantiomer, theorizing that inhibition of S(+) ketamine metabolism by the R(−) enantiomer could account for the prolonged recovery from the racemate.[10] However, since

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§For an excellent review of stereochemistry terminology and concepts relevant to stereoselective drug metabolism, see Testa and Mayer.[5]

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concentrations of individual ketamine and norketamine enantiomers were not measured following administration of the racemate, differences in the rates of enantiomer metabolism could not be assessed.

Racemic ketamine is rapidly and extensively metabolized, predominantly *via* N-demethylation, to the primary metabolite norketamine.[18,19] Norketamine metabolite concentrations exceed those of the parent soon after ketamine administration.[13,20] Little is known however, regarding differences in the hepatic metabolism of individual ketamine enantiomers. The purpose of this investigation therefore was to characterize the human liver demethylation of racemic ketamine and ketamine enantiomers. Two hypotheses were tested: 1) differences in hepatic ketamine enantiomer demethylation account for observed differences in ketamine enantiomer pharmacokinetics; 2) demethylation rates of S(+) and R(−) ketamine present together in the racemate differ from demethylation rates of the isolated enantiomers due to a kinetic interaction between enantiomers.

Materials and Methods

Chemicals

Racemic ketamine hydrochloride was supplied by Warner-Lambert/Parke-Davis Pharmaceutical Research Division (Ann Arbor, MI). S(+) and R(−) ketamine hydrochloride, resolved by recrystallization of the (+) or (−) tartaric acid salts, were the gift of Dr. Paul White (Washington University, St. Louis, MO). The S(+) ketamine hydrochloride salt had a melting point of 258–261° C and $[\alpha]_D^{25} = +93.6°$ ($c = 2.0$, water), the R(−) ketamine hydrochloride salt had a melting point of 256–258° C and $[\alpha]_D^{25} = -93.5°$ ($c = 2.0$, water), and optical purity exceeded 90% for each enantiomer.[10] All identification of sign of optical rotation refers to the hydrochloride salts, and solution compositions refer to the concentration of free base. High purity solvents were purchased from J.T. Baker (Phillipsburg, NJ). Pentafluoropropionic anhydride was obtained from Pierce Chemical (Rockford, IL). All other reagents were from Sigma (St. Louis, MO).

Norketamine was synthesized according to the method of Parcell and Sanchez.[21] The internal standard, deuterated norketamine, was similarly prepared from d_9-bromocyclopentane (MSD Isotopes, St. Louis, MO) followed by back-exchange of labile deuterium on the cyclohexanone ring using triethylamine and NaOH[22] and conversion to the hydrochloride salt. The isotopic composition of the final product (excluding natural isotopic abundances) was 0.03% d_0, 0.03% d_1, 0.03% d_2, 0.08% d_3, 1.1% d_4, 9.3% d_5, 88.5% d_6, 0.6% d_7, and 0.03% d_8, and was considered to be d_6-norketamine.

Ketamine Metabolism

All experiments were approved by the Institutional Human Subjects Review Committee. Human livers were obtained from organ transplant donors, cut into 1 cm^3 pieces, frozen in liquid nitrogen, and stored at −80° C until used. Microsomes were prepared by thawing liver pieces in 3 volumes 0.25 M sucrose-0.05 M potassium phosphate buffer (pH 7.4) containing 1 mM EDTA and homogenizing 20 s in a Waring blender followed by five passes in a glass-Teflon homogenizer (Thomas Scientific, Swedesboro, NJ). The homogenate was centrifuged at 11,000*g* for 25 min and the supernatant centrifuged at 105,000*g* for 60 min. The microsomal pellet was resuspended in 0.1 M sodium pyrophosphate buffer (pH 7.4) containing 1 mM EDTA and centrifuged as above. The final microsomal pellet was resuspended in 50 mM potassium phosphate buffer (pH 7.4) containing 1 mM EDTA and 25% glycerol and stored at −80° C. Microsomal protein concentrations were determined by the method of Lowry *et al.*[23] using bovine serum albumin as the standard and cytochrome P-450 content was determined from the reduced minus oxidized carbon monoxide difference spectra.[24]

Ketamine N-demethylation was determined in a reaction mixture containing 0.005–5 mM ketamine, 0.5 mg microsomal protein, 1 mM NADPH, and 0.1 M potassium phosphate buffer (pH 7.4) in a total volume of 0.5 ml. Reactions (37° C) were initiated by adding NADPH following a 3-min preincubation and terminated after 10 min by adding an aliquot of the incubation mixture to 1 ml 0.1 M NaOH.

Analytical Procedure

Each sample was spiked with 110 ng d_6-norketamine internal standard and extracted twice by vortexing with 4 ml diethyl ether for 1 min. After centrifugation for 10 min at 2,500 rpm, the combined organic layers were dried over sodium sulfate and evaporated to dryness at 40° C under a stream of nitrogen. The pentafluoropropionyl derivative of norketamine was prepared by dissolving the residue in 90 μl ethyl acetate, adding 25 μl pentafluoropropionic anhydride, and reacting at 60° C for 30 min. Unreacted derivatizing reagent was evaporated at 40° C under a stream of nitrogen, the residue diluted with ethyl acetate, and transferred to an autosampler vial for gas chromatography-mass spectrometry (GC-MS) analysis.

Analyses were performed on a Hewlett-Packard 5890 Series II GC/5971 mass selective detector using a J&W DB-5 fused silica capillary column (15 m × 0.32 mm × 0.25 μm film thickness). The injector (250° C), containing a quartz liner, was operated in the splitless mode. Other instrument parameters were: helium flow rate 60

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ml/min, 5 psi column head pressure, and transfer line temperature 270° C. The oven was held at 50° C for 0.5 min, increased at 30° C/min to 150° C, then increased at 15° C/min to 250° C. The retention time of pentafluoropropionyl-norketamine was 9.0 min under these conditions. Quantitation was performed by selected ion monitoring of derivatized norketamine (*m/z* 334)[25] and the internal standard d_6-norketamine (*m/z* 340). Standard curves of peak area ratios (d_0/d_6 norketamine) *versus* ng d_0 norketamine added (50–20,000 ng/ml) were prepared using blank microsomes and used to quantify norketamine concentrations in unknowns. Results of duplicate samples of known concentration agreed to within 5%. Norketamine formation was expressed as nmoles norketamine · min^{-1} · nmole cytochrome P-450^{-1}.

ANALYSIS

Enzyme kinetic data were analyzed by iteratively reweighted (inverse square of the predicted velocity) nonlinear least squares regression (SPSS/PC+) of norketamine formation *versus* ketamine concentration.[26] Results of parameter estimates are tabulated along with the standard error of the estimate provided by the regression program. The regression model chosen (one or two enzymes) was based on prior graphic Eadie-Hofstee analysis of the data, which also provided initial parameter estimates. Differences in the measured rates of norketamine formation, expressed as the mean ± SD, were tested for significance by analysis of variance.

Results

Human liver microsomes efficiently catalyzed the N-demethylation of racemic ketamine and ketamine enantiomers. Norketamine formation was linear throughout the 10-min incubation period (data not shown). The relationship between norketamine formation and S(+), R(−) and RS ketamine concentration for a single, representative human liver is displayed in figure 1. Rates of demethylation were 15–30% greater for S(+) ketamine compared to R(−) ketamine, while rates for the racemic mixture were intermediate to those of the individual enantiomers. Ketamine plasma concentrations during anesthesia are typically 1.0–2.5 μg/ml.[13,17,20,27] Human plasma protein binding of ketamine (12–27%) has insignificant effects on free drug concentration and is not different for racemic ketamine and ketamine enantiomers.[28] Therefore plasma ketamine concentrations were assumed to reflect liver ketamine concentrations at the site of metabolism (4–10 μM). Rates of racemic ketamine and ketamine enantiomer demethylation were thus compared at therapeutic concentrations (5 μM) for a series of three livers (table 1). At therapeutic concentrations, the rate of S(+) ketamine demethylation averaged 20% greater than that of R(−) ketamine ($P < .05$) and 10% greater than that of the racemate ($P < .05$). The rate for the racemic mixture was between that of the individual enantiomers. Results were comparable in all three livers studied.

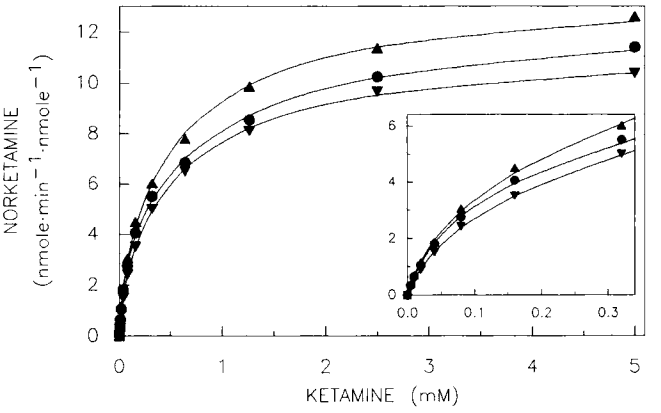

FIG. 1. Metabolism of racemic ketamine and ketamine enantiomers by human liver microsomes. S(+) ketamine (filled triangles), R(−) ketamine (filled inverted triangles), and racemic ketamine (filled circles) were incubated separately with 0.5 mg microsomal protein, and norketamine formed was quantitated by GC-MS. The insert depicts norketamine formation at low substrate concentrations. Symbols denote the mean of duplicate determinations. Lines are predicted values, based on nonlinear regression analysis. The data were best fit using a 2-enzyme model. Michaelis-Menten kinetic parameters are provided in table 2. Results are shown for one of the three livers studied (HL115).

Racemic ketamine demethylation exhibited biphasic kinetics, evidenced by nonlinear Eadie-Hofstee plots, indicating the catalytic participation of more than one enzyme (fig. 2A). The data were best fit by a two-enzyme model, suggesting the apparent catalytic participation of at least two enzymes in racemic ketamine demethylation. This apparent activity of more than one enzyme could arise from the stereoselective metabolism of each ketamine enantiomer by different enzymes with dissimilar values for K_m and V_{max}. Such a condition would generate linear Eadie-Hofstee plots for the demethylation of each individual enantiomer. Alternatively, two enzymes could catalyze the demethylation of each ketamine enantiomer, either nonselectively (two enzymes total) or stereoselectively (four enzymes total). This process would be characterized by nonlinear Eadie-Hofstee plots for each ketamine enantiomer. Experimental results revealed that demethylation of both S(+) and R(−) ketamine enantiomers exhibited biphasic kinetics, indicating that two enzymes catalyzed the demethylation of each enantiomer (fig. 2B). The two enzymes catalyzing S(+) ketamine demethylation may be identical to or different from those metabolizing R(−) ketamine. The Michaelis-Menten kinetic parameters for N-demethylation of racemic ketamine and individual

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TABLE 1. Ketamine Stereoisomer and Racemate Metabolism at Therapeutic Concentrations

Liver	Norketamine Formation		
	RS Ketamine	S (+) Ketamine	R (−) Ketamine
HL114	0.42 ± 0.01	0.45 ± 0.02	0.37 ± 0.01
HL115	0.33 ± 0.01	0.36 ± 0.01	0.28 ± 0.01
HL124	0.48 ± 0.01	0.54 ± 0.01	0.46 ± 0.01

Ketamine concentrations were 5 μM in all incubations. Rates of norketamine formation are the mean ± SD of five determinations (nmol · min^{-1} · nmol^{-1}). For all livers, the rate of S(+) ketamine demethylation was significantly greater than that of R(−) ketamine ($P < .05$). For all livers the rate of racemate demethylation was significantly different from the rate for each enantiomer ($P < .05$).

ketamine enantiomers by the three human livers studied are provided in table 2. N-demethylation of racemic ketamine and each enantiomer was catalyzed by a high affinity-low capacity enzyme (K_{m_1} 30–50 μM, V_{max_1} 2–6 nmoles · min^{-1} · nmole^{-1}) and a low affinity-high capacity enzyme (K_{m_2} 600–800 μM, V_{max_2} 9–15 nmoles · min^{-1} · nmole^{-1}). One liver (HL124) showed a higher K_{m_1} for the metabolism of S(+) ketamine, consistent with the participation of a third enzyme with a substantially lower affinity which could not be resolved mathematically to yield a separate K_m.

Rates of racemic ketamine metabolism were significantly less than the sum of the rates for the individual enantiomers when each enantiomer was incubated separately (fig. 3). For example, norketamine formation from 10 μM racemic ketamine (5 μM of each enantiomer) was 0.76 ± 0.01 nmole · min^{-1} · nmole^{-1}, significantly less than the sum of the rates for 5 μM S(+) and R(−) ketamine when incubated individually (0.82 ± 0.01; $P < .05$). This difference became more pronounced with increasing substrate concentrations.

The *in vitro* intrinsic clearance (K_{m_1}/V_{max_1}) for norketamine formation by the three livers was calculated using kinetic parameters for the high-affinity enzyme. Table 3 presents the *in vitro* intrinsic clearance values for racemic ketamine and ketamine enantiomers.

Discussion

N-demethylation is the major route of ketamine biotransformation,[18] resulting in metabolites with significantly attenuated pharmacologic effect.[8,29] Norketamine can undergo subsequent ring hydroxylation at several positions to form hydroxynorketamine metabolites, a minor pathway of metabolism. Hydroxynorketamine metabolites are reported frequently as dehydronorketamine, in actuality an artifact of metabolite decomposition which occurs during sample workup and analysis.[25] Ring hydroxylation of ketamine without prior demethylation, and hydroxynorketamine formation *via* demethylation of hydroxyketamine, are quantitatively inconsequential routes of metabolism. In humans, N-demethylation to norketamine is the major route of racemic ketamine biotransformation following systemic administration,[13,20] and human liver microsomes convert racemic ketamine and

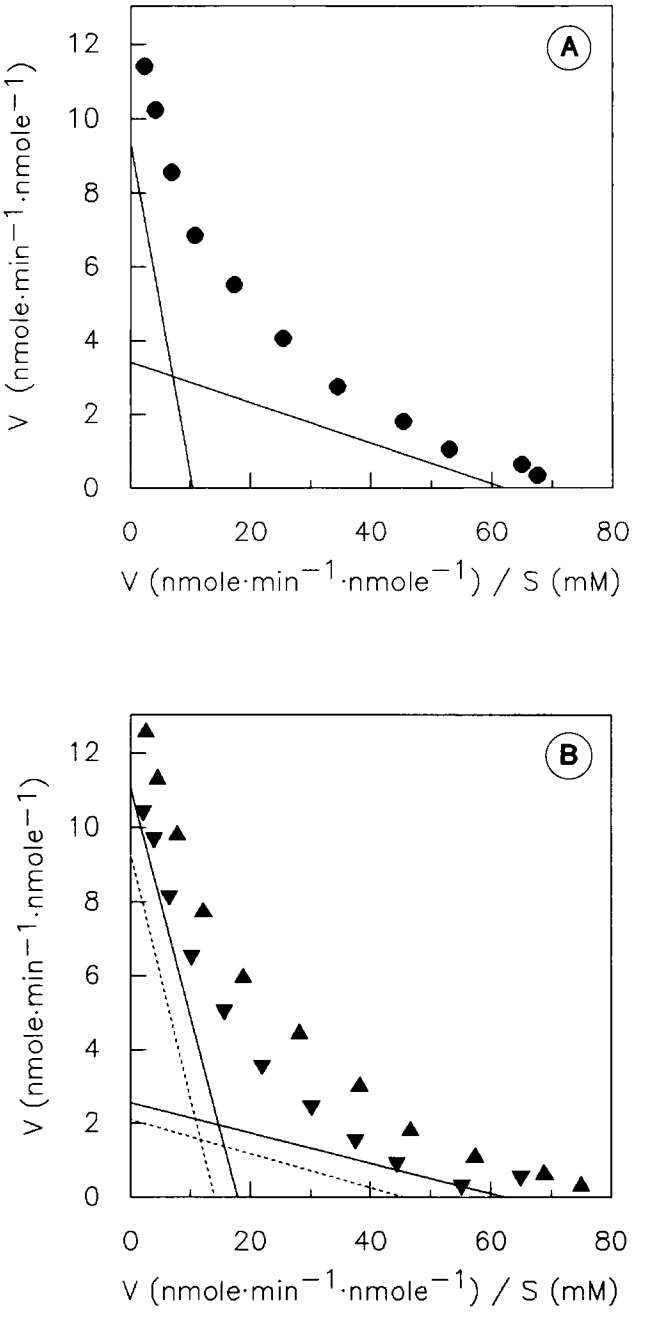

FIG. 2. Eadie-Hofstee analysis of ketamine metabolism. Data were replotted from figure 1. *A:* Norketamine formation from racemic ketamine. *B:* Norketamine formation from S(+) ketamine (filled triangles, —) and R(−) ketamine (filled inverted triangles, · · · ·). Straight lines represent resolution of norketamine formation into the sum of rates from two enzymes with linear kinetics.

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TABLE 2. Apparent Kinetic Parameters for Ketamine Demethylation by Human Liver Microsomes

Liver	Ketamine	V_{max_1} (nmol · min^{-1} · nmol^{-1})	K_{m_1} (μM)	V_{max_2} (nmol · min^{-1} · nmol^{-1})	K_{m_2} (μM)
HL114	RS	3.6 ± 0.5	48 ± 7	12.0 ± 0.5	810 ± 160
	S(+)	3.0 ± 0.4	40 ± 5	15.0 ± 0.4	610 ± 60
	R(−)	2.1 ± 0.2	32 ± 3	12.0 ± 0.2	680 ± 70
HL115	RS	3.4 ± 0.3	55 ± 5	9.3 ± 0.3	900 ± 120
	S(+)	2.6 ± 0.4	41 ± 5	11.1 ± 0.3	620 ± 80
	R(−)	2.1 ± 0.3	48 ± 5	9.3 ± 0.2	660 ± 70
HL124	RS	4.1 ± 0.5	44 ± 5	8.8 ± 0.4	690 ± 120
	S(+)	5.7 ± 0.4	54 ± 3	10.9 ± 0.4	1020 ± 140
	R(−)	3.1 ± 0.3	36 ± 3	10.6 ± 0.2	640 ± 60

Parameters (±SE of the estimate) were determined by nonlinear regression analysis.

ketamine enantiomers predominantly to norketamine.[19,30] In rat liver microsomes, norketamine accounted for 80% of ketamine metabolites while hydroxynorketamine and hydroxyketamine accounted for 15% and 5%, respectively.[25] In rabbits, 68% of a ketamine dose was converted *in vivo* to norketamine.[31] Therefore N-demethylation represents the initial and predominant pathway of ketamine metabolism and inactivation, and was the focus of this analysis of human ketamine metabolism.

The results of the present investigation demonstrate that human hepatic microsomes catalyze the demethylation of ketamine enantiomers at different rates, a property referred to as substrate stereoselectivity. The rate of S(+) ketamine N-demethylation exceeded that of the R(−) enantiomer in the three livers studied at all substrate concentrations. These findings explain the observations of Trevor *et al.*, using a single substrate concentration, that

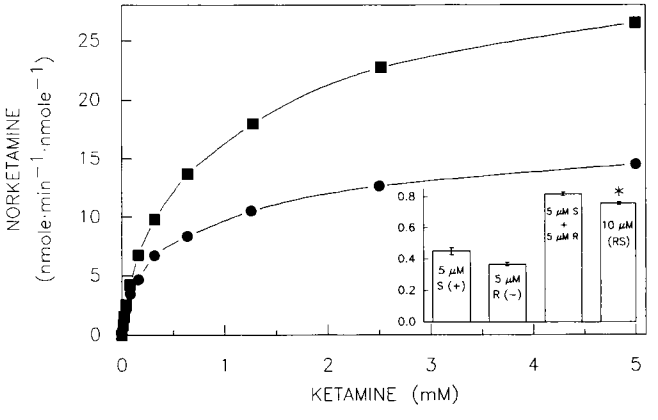

FIG. 3. Metabolic enantiomeric interaction in ketamine metabolism. Solid circles = the rate of racemic ketamine demethylation; solid squares = the sum of demethylation rates for individual S(+) and R(−) enantiomers at concentrations equivalent to those present in the racemate. The inset shows ketamine demethylation at therapeutic concentrations. Shown are the individual rates for 5 μM S(+) and R(−) ketamine, the sum of the two rates, and the rate for 10 μM racemic ketamine [containing 5 μM each S(+) and R(−) ketamine]. The rate of racemic ketamine demethylation was significantly less ($P < .05$) than the sum of the rates for the individual enantiomers at all concentrations studied. Results are shown for one of the three livers studied (HL114).

the percentage of norketamine derived from the S(+) enantiomer somewhat exceeded that from the R(−) enantiomer when human liver microsomes were incubated with racemic ketamine.[30] At plasma concentrations typically achieved during ketamine anesthesia, the *in vitro* rate of S(+) ketamine demethylation was 15–30% faster than the rate of R(−) ketamine demethylation. Human liver microsomes also exhibit selectivity with respect to the formation of hydroxylated norketamine metabolites, termed product stereoselectivity, with the S(+) and R(−) norketamine enantiomers undergoing preferential hydroxylation at different positions on the cyclohexanone ring.[30] Thus human metabolism of ketamine enantiomers exhibits moderate degrees of both substrate and product stereoselectivity.

For each ketamine substrate there was constancy of the K_m values and variability in the V_{max} values over the three livers studied. The uniformity of the K_m values reflects the concept that K_m is unique for a given enzyme-substrate pair and constant regardless of the enzyme source. The twofold variation between livers in the V_{max} values for the high-affinity and low-affinity N-demethylase enzymes is fully anticipated, presumably reflecting differences in the specific contents of these enzymes in the three livers.

Comparison of the rates of ketamine enantiomer and racemate metabolism reveals the complex nature of ketamine racemate biotransformation. Simple inspection shows that rates of racemic ketamine demethylation were

TABLE 3. *In Vitro* Ketamine Intrinsic Clearance Estimates

	V_{max_1}/K_{m_1} (ml · min^{-1} · μmol P-450^{-1})				Predicted* Cl_{int} (ml · min^{-1} · kg^{-1})
	HL114	HL115	HL124	Mean	
S (+) ketamine	77	62	106	82	8.8
R (−) ketamine	67	44	87	66	7.1
RS ketamine	75	62	93	77	8.2

* Predicted from the mean *in vitro* intrinsic formation clearances (V_{max_1}/K_{m_1}) for all three livers. Calculations are for an average liver cytochrome P-450 content of 7,500 nmol[37] and an average body weight of 70 kg.

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between those of S(+) and R(−) ketamine, entirely consistent with racemate composition as an equimolar mixture of enantiomers. Careful scrutiny however shows that the rate for the racemate was significantly less than that expected simply by summing the rates for the individual enantiomers. Thus ketamine metabolism reflects an intricate drug interaction whereby one ketamine enantiomer inhibits the metabolism of the other enantiomer, termed a metabolic enantiomeric interaction. Preliminary evidence suggests a mechanism of dual interaction, whereby R(−) ketamine inhibits the metabolism of S(+) ketamine, and S(+) ketamine inhibits the metabolism of the R(−) enantiomer as well.[32] The most likely explanation for this phenomenon is that S(+) and R(−) ketamine are metabolized by the same low K_m enzyme and by the same high K_m enzyme. This hypothesis is currently under investigation. The ketamine metabolic enantiomeric interaction may provide an explanation for the observation that R(−) ketamine in the racemate prolongs anesthetic recovery relative to S(+) ketamine, confirming the hypothesis of White *et al.* that R(−) ketamine inhibits the metabolism of S(+) ketamine.[10]

Differences in the rate of human hepatic ketamine enantiomer N-demethylation account for and predict differences in the pharmacokinetics of ketamine enantiomers. When ketamine was administered as a racemic mixture, plasma clearance of the S(+) enantiomer was 15% greater than that of the R(−) enantiomer.[17] When the enantiomers were administered individually, S(+) ketamine plasma clearance exceeded that of R(−) ketamine by 22%, although this difference did not reach statistical significance.[10] These differences can be explained by the greater rate of S(+) ketamine metabolism. *In vitro* intrinsic formation clearances can be calculated from the kinetic parameters V_{max} and K_m.[33] Although ketamine is metabolized by more than one enzyme, 80–90% of the demethylation is catalyzed by the low K_m enzyme at therapeutic concentrations. Thus the *in vitro* intrinsic formation clearance for norketamine is calculated as K_{m_1}/V_{max_1}. The *in vitro* intrinsic formation clearances for racemic ketamine and enantiomers are listed in table 3. These *in vitro* clearances clearly predict both the rank order and relative magnitude of the differences for the systemic clearances of S(+), R(−) and racemic ketamine.

Differences in enantiomer pharmacodynamics (receptor binding, efficacy, potency, and toxicity) and pharmacokinetics (protein binding, metabolism and clearance) are generally the rule rather than the exception.[2,34] Mechanistic aspects and clinical significance of substrate and product stereoselectivity in drug metabolism, metabolic interactions between enantiomers, and metabolic interactions between enantiomers and inhibitors have also been described.[5,35,36] Although widely recognized for other classes of drugs, only recently has the importance of chirality been appreciated in anesthesiology. Pharmacokinetic and pharmacodynamic differences between ketamine enantiomers have been identified. S(+) ketamine possesses superior efficacy with fewer side effects, and faster elimination and anesthetic recovery compared to the racemate.[10,11,13] These differences strongly suggest S(+) ketamine to be preferable compared to the racemic form of the drug, and argue for replacement of the currently used racemate with the S(+) enantiomer.

In summary, we have shown that human liver microsomes catalyze the N-demethylation of ketamine with enantiomeric selectivity, that metabolism exhibits biphasic kinetics with one enzyme predominating at therapeutic concentrations, and that a metabolic enantiomeric interaction alters metabolism of ketamine enantiomers present together in the racemate. Stereoselectivity in ketamine metabolism may explain previous clinical observations regarding differences in ketamine enantiomer and racemate pharmacokinetics.

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