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Stereoselective Pharmacokinetics of 3,4-Methylenedioxymethamphetamine in the Rat

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ABSTRACT Studies to characterize the pharmacokinetics of the enantiomers of MDMA were conducted in rats using the iliac arterial cannulation. Two routes of administration, intravenous and subcutaneous, were evaluated at two dose levels for each route [20 and 40 mg/kg (±)-MDMA for subcutaneous, 10 and 20 mg/kg (±)-MDMA for intravenous administrations]. The average half-life (±SD) for all dosing groups was 2.5 ± 0.8 h for (−)-(R)-MDMA and 2.2 ± 0.8 h for (+)-(S)-MDMA. The more rapid clearance of (+)-(S)-MDMA compared with (−)-(R)-MDMA is consistent with the area under the curve (AUC) data of the parent drug and its primary metabolite MDA. The mean (±SD) AUC S/R ratios of MDMA and MDA were 0.70 ± 0.05 and 3.1 ± 0.8, respectively. Following a 20 mg/kg dose of racemic MDMA iv the mean (±SD) of the percent dose excreted as (−)-(R)-MDMA, (+)-(S)-MDMA, (−)-(R)-MDA, and (+)-(S)-MDA were 20 ± 10, 12 ± 6, 3 ± 1, and 6 ± 2, respectively.

KEY WORDS: MDMA, MDA, kinetics, enantiomers, behavioral effects, neurotoxicity

INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA) has been shown to be a selective serotonin (5-HT) neurotoxin in rats and monkeys.[1–3] Biochemical changes such as a decrease in 5-HT, 5-hydroxyindoleacetic acid, and 5-HT reuptake sites characterize the long-term neurotoxicity of MDMA, suggesting that this drug causes a retrograde destruction of 5-HT neurons.[4–6] MDMA contains one asymmetric carbon which is an important determinant of its toxicity. In rats, the (+)-(S)-isomer of MDMA causes the long-term 5-HT neurotoxicity which is not evident with the (−)-(R)-isomer.[7]

MDA, the demethylated analog of MDMA, stereoselectively accumulates in blood of animals following a racemic dose of MDMA.[8] Although the exact mechanism of this stereoselective metabolism remains unclear, the difference in the amount of MDA isomers formed may be important pharmacologically, since the (+)-(S)-isomer of MDA is thought to be amphetamine-like whereas the (−)-(R)-isomer is hallucinogenic-like.[9] Unlike MDMA, both isomers of MDA cause long-term serotonin neurotoxicity.[10,11]

Prior to this investigation there were no studies concerning the pharmacokinetics of MDMA. In the present study we administered racemic MDMA and investigated the pharmacokinetic behavior of the enantiomers of MDMA and its demethylated metabolite MDA.

MATERIALS AND METHODS

Reagents

N-Trifluoroacetyl-L-prolyl chloride (LTPC), 0.1 *M* in $CHCl_3$ (lot #P82-223-3, stated by manufacturer to contain 1.2% of its enantiomer, *N*-trifluoroacetyl-D-prolyl chloride; DTPC), was obtained from Regis Chemical Co., Chicago, IL. *N*-Hexane, 1-butanol, ethyl acetate, 1% ethanol stabilized chloroform, dichloromethane, 2-propanol, and acetonitrile were all HPLC grade. All other chemicals were reagent grade. Racemic methoxyphenamine · HCl, the internal standard, was purchased from Sigma Chemical. Racemic MDMA was synthesized as described previously.[12] Normal saline was obtained from Travenol (IL). Heparin (1000 units/ml) derived from porcine intestine was obtained from Elkins-Sinn, Inc. (Cherry Hill, NJ). Lactated Ringers was obtained from Abbott Laboratories (N. Chicago, IL). Metofane was obtained from Pittman-Moore Inc. (Washington Crossing, NJ). Combiotic was obtained from Barber Veterinary Supply (Richmond, VA).

Analytical Method

Whole blood concentrations of MDA and MDMA enantiomers were determined by gas chromatography/mass spectroscopy according to an indirect enantiomeric separation technique.[12]

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Animals and Dosing

All rats were Sprague–Dawley (245–355 g) from Dominion Laboratories (Dublin, VA). During the time the experiments were conducted the animals were given food and water ad libitum.

Two routes of administration (intravenous [iv] and subcutaneous [sc]) and two dose levels (10 and 20 mg/kg for iv, 20 and 40 mg/kg for sc), which had been used in previous studies, were chosen to characterize the pharmacokinetics of MDMA enantiomers. Doses are expressed as the amount of the free base administered.

Surgical Procedure

Animals were denied food for 30 min prior to induction of anesthesia. Animals were anesthetized by placing them into a large desiccator containing a Metofane soaked pad. Within 2 min the animals were rendered unconscious and were checked for the level anesthesia by integumental stimulation, respiration rate, and corneal reflex. Anesthesia was supplemented as needed by placing a 50 ml beaker containing a Metofane soaked gauze pad temporarily over the animal's nose.

The iliac artery was cannulated.[13] Following surgery animals are given an intramuscular (hind leg) injection of 0.3 ml Combiotic and observed until recovery from anesthesia. Cannula flow was maintained by a constant infusion of heparinized saline at a rate of 2 units/h. Animals were allowed 48 to 96 h postoperative recovery time before experiments were conducted.

Blood Sampling Protocol

The cannula was cleared by withdrawing blood to the tip of the heparin lock. The heparin lock was purged with whole blood by withdrawing 0.2 ml of blood through it into a 1 ml syringe. This sample was saved and replaced after the test sample was obtained. After the heparin lock was purged, 0.2 ml of blood was withdrawn for the test sample. The time this sample was withdrawn was recorded and the sample was transferred to a heparinized tube containing the internal standard (400 ng methoxyphenamine). After the blood sample had been obtained the purged blood was replaced followed by 500 μl of heparinized (5 units/ml) lactated Ringers solution. Of the 500 μl, 250 μl served to refill the cannula and 250 μl acted as replacement fluid for blood withdrawn.

For intravenous and subcutaneous studies in which 20 blood samples were taken the times of these draws (in minutes) were 2, 4, 7, 10, 15, 20, 25, 30, 40, 50, 60, 80, 100, 130, 160, 190, 240, 480, and 720. For the intravenous study in which only 9 blood samples were taken the times of these draws (in minutes) were 20, 60, 100, 200, 300, 400, 500, 700, and 900.

Calculation of Pharmacokinetic Parameters

The pharmacokinetic parameters calculated were terminal half-life ($t_{1/2}$, hours), systemic clearance (Cl_s, ml/min), volume of distribution (V_d, liters), area under the whole blood curve (AUC, mg · h/liter) of parent drug, and area under the curve (AUC, mg · h/liter) of MDA. Pharmacokinetic parameters were calculated for each animal individually and averages were then calculated for each dosing group.

Terminal elimination rate constants (K) were calculated from the slope of the linear portion of the semilog plots of concentration vs time data.

$$\text{slope terminal phase} = -K/2.303$$

Half-lives were calculated from the rate constant (K) by the formula

$$t_{1/2} = 0.693/K$$

Systemic clearance was calculated as

$$Cl_s = \text{dose}/AUC_{0 \text{ to } \infty}$$

AUC from time of dosing until the end of the time course (t^*) was calculated using the trapezoid rule. To this partial AUC the area from the end of the time course until infinity was added. The AUC from t^* to infinity was calculated as

$$AUC_{t^* \text{ to } \infty} = C^*/K$$

where C^* is the blood concentration at t^*.

Volume of distribution was calculated as

$$V_d = \text{dose}/(K \cdot AUC_{0 \text{ to } \infty})$$

The terminal half-life of MDA could not be calculated since MDA was being formed throughout the study period. Since the terminal half life of MDA is not known the $AUC_{t^* \text{ to } \infty}$ could not be calculated. AUC of MDA represents time from initial dosing until t^*. Time to maximum concentration and maximum concentration of MDA were determined directly from plots of concentration vs time.

For the subcutaneous route of administration, half-life, AUC parent, AUC metabolite, and volume of distribution were determined as for the iv route. Time to maximum concentration (t_{max}) and maximum concentration (C_{max}) were determined directly from plots of concentration vs time. Absorption constants were determined by the method of residuals.[14]

Statistics

A one-tailed paired t test was used to determine if significant differences existed in the pharmacokinetic parameters (volume of distribution, clearance, area under the curve, elimination half-life, time to maximum concentration, and maximum concentration) of the (+)-(S) and (−)-(R)-isomers within each group. A two-tailed unpaired t test was used to determine if significant differences in pharmacokinetic parameters existed between dose groups. The level of significance for all pharmacokinetic studies was $P = 0.05$.

RESULTS

Tables 1 and 2 show a summary of pharmacokinetic parameters of MDMA for the various dosing groups. Figures 1 and 2 show the time course of the enanti-

TABLE 1. Summary of the pharmacokinetic parameters of MDMA after intravenous and subcutaneous routes of administration. Dose represents concentration of racemic MDMA free base[a]

Dose (mg/kg)	N	Half-life (h)		Clearance (ml/min)		Volume of dist. (liters)	
		(−)-(R)	(+)-(S)	(−)-(R)	(+)-(S)	(−)-(R)	(+)-(S)
10 iv	3	1.7 ± 0.5	1.7 ± 0.7	13 ± 2*	18 ± 0.4*	2.0 ± 0.7	2.4 ± 0.7
20 iv	4	3.5 ± 2.1	3.6 ± 2.4	14 ± 6*	19 ± 5.0*	3.8 ± 1.6	5.8 ± 3.4
20 iv (9 pts)	4	1.8 ± 0.4	1.5 ± 0.2	15 ± 5*	23 ± 9.0*	2.4 ± 0.7	3.0 ± 1.0
20 sc	4	2.2 ± 0.5*	1.8 ± 0.3*	nc	nc	1.1 ± 0.2*	1.2 ± 0.3*
40 sc	4	3.2 ± 1.5	2.3 ± 0.6	nc	nc	1.5 ± 0.3*	1.8 ± 0.3*

[a]Asterisk indicates a significant difference ($P = 0.05$ by a paired t test) between the stereoisomers for a given pharmacokinetic parameter. Data are represented as mean ± standard deviation. Parameters which were not calculated are denoted by nc.

TABLE 2. Areas under the curve following racemic doses of MDMA

Dose (mg/kg)	N	AUC (mg · h/liter)					
		(−)-(R)-MDMA	(+)-(S)-MDMA	S/R ratio	(−)-(R)-MDA	(+)-(S)-MDA	S/R ratio
10 iv	3	2.0 ± 0.4	1.5 ± 0.2	0.76 ± 0.09	0.23 ± 0.28	0.55 ± 0.34	4.6 ± 3.1
20 iv	4	3.9 ± 1.5	2.7 ± 0.8	0.72 ± 0.10	0.61 ± 0.38	1.6 ± 0.8	2.7 ± 0.3
20 iv (9 pts)	4	3.3 ± 1.3	2.2 ± 0.9	0.66 ± 0.03	0.45 ± 0.31	1.0 ± 0.5	2.7 ± 0.9
20 sc	4	7.6 ± 2.1	5.5 ± 1.6	0.72 ± 0.02	0.75 ± 0.23	1.9 ± 0.3	2.6 ± 0.5
40 sc	4	19 ± 10	12 ± 5.0	0.65 ± 0.09	1.5 ± 0.5	4.5 ± 1.4	3.1 ± 0.1

omers of MDMA and MDA following a 20 mg/kg iv and a 20 mg/kg sc dose of racemic MDMA, respectively.

The hematocrit of a group of animals ($N = 4$) over the sampling period was monitored using the identical sampling protocol (12 h, 20 samples) as for iv pharmacokinetic studies. Hematocrits of the animals had decreased significantly at the end of the time course (see Fig. 3).

The effect this decrease in hematocrit was having on the pharmacokinetic parameters was examined by dosing another group of animals with 20 mg/kg of racemic MDMA iv with the exception that 9 blood samples were drawn instead of 20. No statistically significant differences (unpaired t test) were detected ($P = 0.05$) between the terminal half-lives calculated using 20 and 9 blood samples. In addition to blood, urine from this group of animals [20 mg/kg (±)-MDMA iv 9 data points] was also collected and the enantiomeric content of MDMA and MDA was determined. The percent of the dose of each compound excreted in urine over a 48 h period is shown in Table 3. To express MDA as percent of dose excreted it was necessary to multiply the weight of MDA excreted in ug by a correction factor of 193/179, which is the ratio of the molecular weight of MDMA/MDA.

The overall average terminal half-life of MDMA for intravenous studies was about 2.3 h for both isomers. After combining all three groups studied by the intravenous route there was no significant difference between terminal half-life of (−)-(R)-MDMA and (+)-(S)-MDMA using a paired t test ($P = 0.05$).

The mean terminal half-life of (+)-(S)-MDMA for both subcutaneous dose levels was 2.05 h while that of the (−)-(R)-isomer was 2.66 h. This mean difference (0.61 h) was significant at $P = 0.05$ (paired t test). There were no significant differences in the absorption rate constants of the parent drug.

It appears that the terminal half-life increased with higher doses (see Table 1) but this difference was not significant (unpaired t test $P = 0.05$). There was no evidence of nonlinear kinetics.

DISCUSSION

Results of intravenous dosing demonstrated significant differences in the pharmacokinetics of the stereoisomers of MDMA and MDA following a racemic dose of MDMA. For all dose groups the AUC of the (−)-(R)-MDMA was greater than that of the (+)-(S)-MDMA. Stereoselective formation of the (+)-(S)-isomer of MDA contributed to the more rapid systemic clearance of the (+)-(S)-MDMA. The AUC of the (+)-(S)-MDA was about 2.5 times greater than that for the (−)-(R)-isomer. In addition, the peak concentration of (+)-(S)-MDA was about 3 times greater than that of (−)-(R)-MDA. No differences in the time required to reach a peak concentration of the two stereoisomers of MDA were noted. Further evidence that stereoselective metabolism is important for the observed differences was that almost twice as much (+)-(S)-MDA is excreted in urine as (−)-(R)-MDA (see Table 3).

The subcutaneous administration studies also demonstrated significant differences in the pharmacokinetics of the enantiomers of MDMA and MDA. The same stereoselective trends seen in the intravenous studies such as increased AUC of (−)-(R)-MDMA relative to (+)-(S)-MDMA, larger AUC of (+)-(S)-MDA relative to

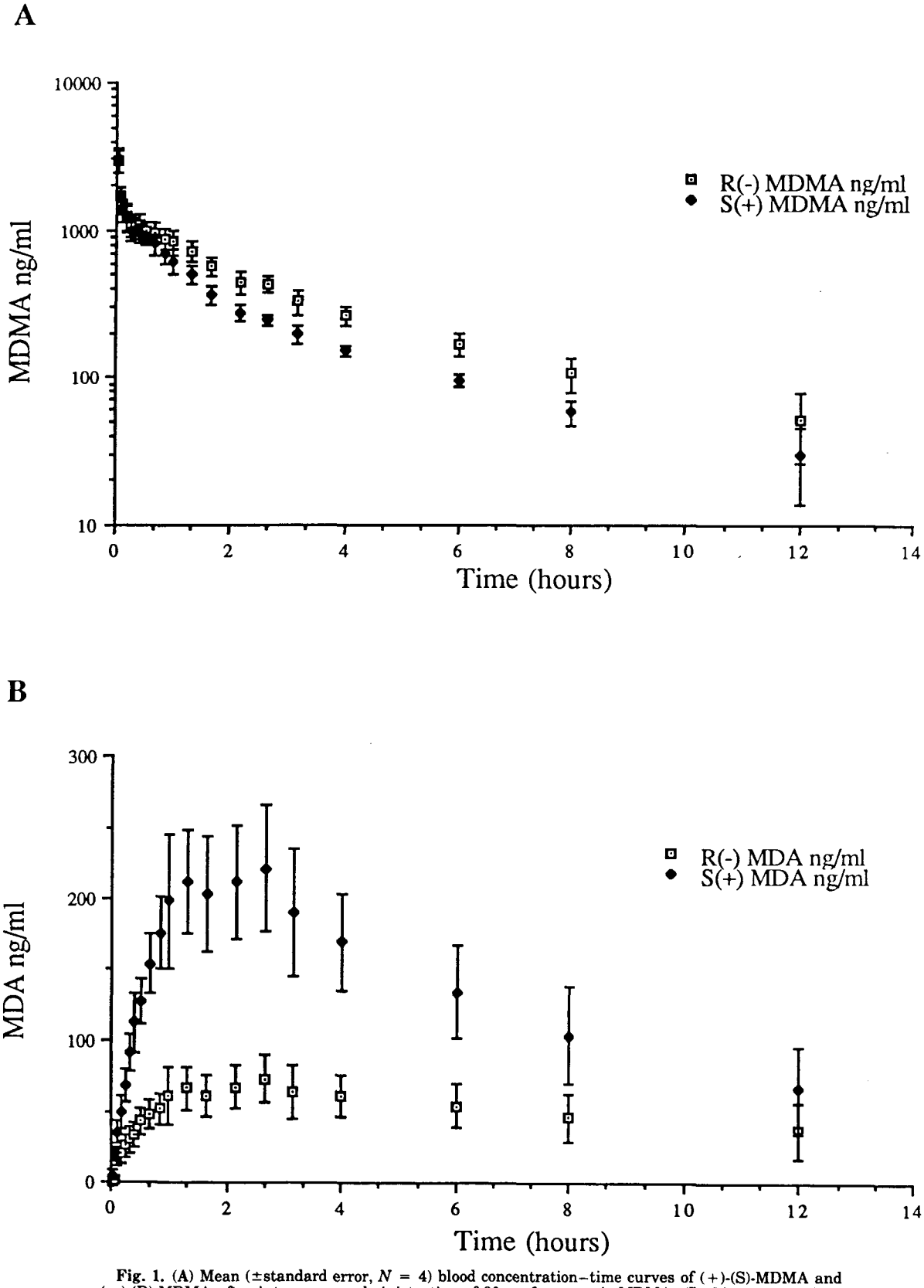

Fig. 1. (A) Mean (±standard error, $N = 4$) blood concentration–time curves of (+)-(S)-MDMA and (−)-(R)-MDMA after intravenous administration of 20 mg/kg racemic MDMA. (B) Mean (±standard error, $N = 4$) blood concentration–time curves of (+)-(S)-MDA and (−)-(R)-MDA after intravenous administration of 20 mg/kg racemic MDMA.

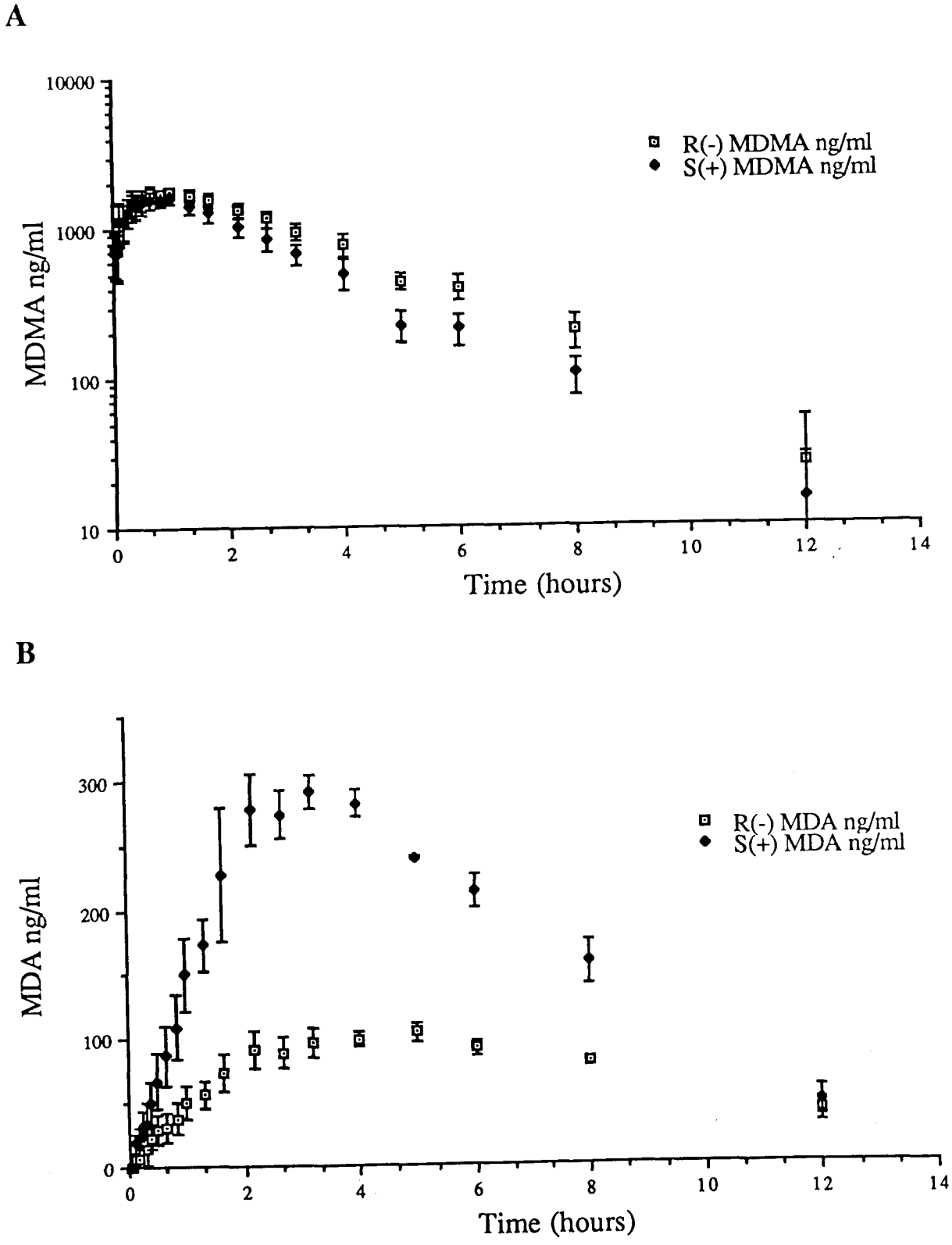

Fig. 2. (A) Mean (±standard error, $N = 4$) blood concentration–time curves of (+)-(S)-MDMA and (−)-(R)-MDMA after subcutaneous administration of 20 mg/kg racemic MDMA. (B) Mean (±standard error, $N = 4$) blood concentration–time curves of (+)-(S)-MDA and (+)-(R)-MDA after subcutaneous administration of 20 mg/kg racemic MDMA.

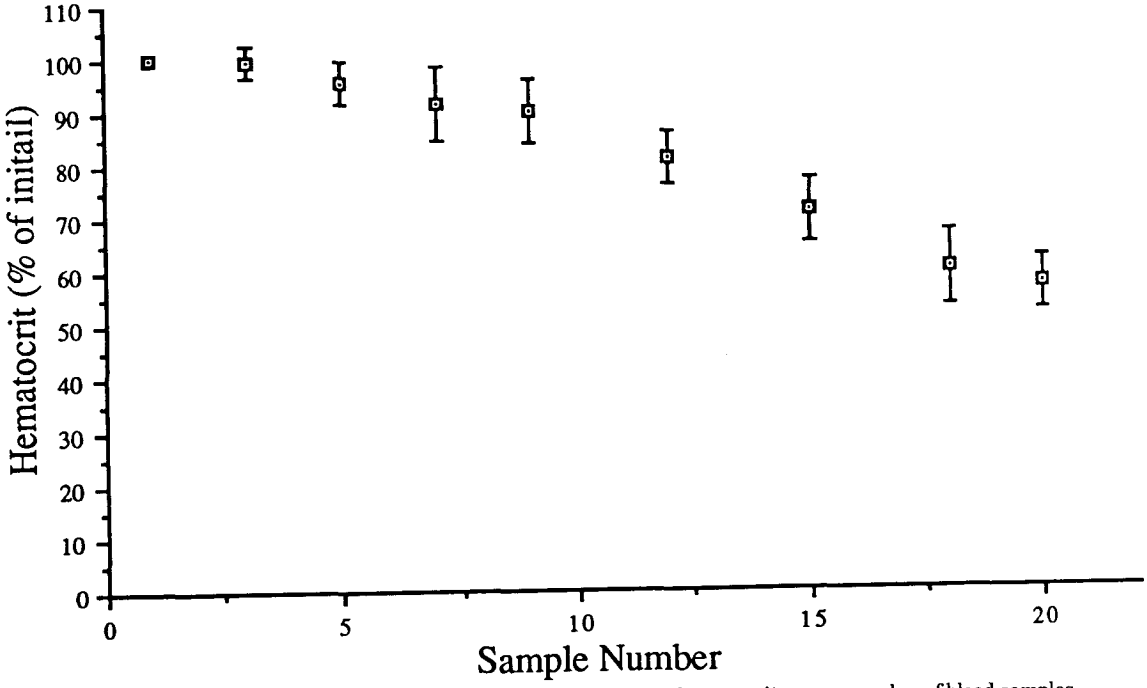

Fig. 3. Mean (±standard deviation, $N = 4$) decrease in rat hematocrit versus number of blood samples collected. The blood sampling protocol was identical to that used in pharmacokinetic studies.

TABLE 3. Urinary excretion of stereoisomers of MDA and MDMA following an intravenous dose of 20 mg/kg racemic MDMA[a]

Animal No.	% Excreted as (−)-(R)-MDMA	% Excreted as (+)-(S)-MDMA	% Excreted as (−)-(R)-MDA	% Excreted as (+)-(S)-MDA
1	9.5	5.0	2.0	3.6
2	32.5	18.8	4.0	8.8
3	20.1	12.4	2.9	4.8
4	17.2	11.5	3.2	4.7
Average	20.0	12.0	3.0	5.5
±SD	10.0	6.0	0.8	2.3

[a]All entries represent the percent of dose excreted.

(−)-(R)-MDA, and higher peak concentrations of (+)-(S)-MDMA existed for the subcutaneous route.

The terminal half-life was calculated on the assumption that this was a first-order process. Log concentration vs time plots of the elimination phase were linear indicating that the first-order process assumption was valid. Noncompartmental formulas were used to calculate volume of distribution and systemic clearance.[14,15] The intravenous data were also fit with a two compartment pharmacokinetic model (data not shown). The distribution half-life calculated using the two compartment model varied considerably between animals (range 2 to 26 minutes), but was not significantly different between the enantiomers of MDMA.

The hematocrit data demonstrated that at the end of the time course (12 h, 20 samples) there was a significant decrease in the percentage of red blood cells. The pharmacokinetic study was repeated at the 20 mg/kg intravenous dose using 9 sampling points instead of 20, to determine if the decrease in hematocrit effected the terminal half-life. An unpaired t test was used to compare the mean terminal half-lives obtained using 20 and 9 sample collections. The terminal half-life was not significantly different between these two groups suggesting that the decrease in hematocrit was not influencing the pharmacokinetics of MDMA.

The most interesting difference between the two routes of administration was in the volume of distribution. The volume of distribution for the intravenous route was 3 to 4 times larger than that for identical doses given by the subcutaneous route. This suggests that MDMA is being concentrated at a site in the body when given by the intravenous route or that a first pass effect is occurring. A first pass effect which usually does not occur with intravenous injection is possible in this case, considering the anatomy of the rat. The tail vein drains into one of the ileac veins. The iliac veins merge to form the caudal vena cava. The caudal vena cava enters the liver[16] subjecting drugs to metabolism. Differences in volume of distribution between routes of

administration are larger for (+)-(S)-MDMA, which is known to be metabolized more extensively than the (−)-(R)-MDMA (see Table 3), supporting the theory of a first pass effect.

Stereoselective formation of (+)-(S)-MDA relative to (−)-(R)-MDA appears to be a result of metabolism. The subcutaneous absorption rate constants and the intravenous distribution half-lives were not significantly different between the two isomers of MDMA suggesting that stereoselective absorption and distribution are not responsible for the observed stereoselective pharmacokinetics. Several explanations are possible for the greater amounts of (+)-(S)-MDA formed. These include (1) stereoselective demethylation preferentially forming the (+)-(S)-isomer, (2) demethylation of both isomers of MDMA followed by further metabolism of the (−)-(R)-isomer of MDA, (3) metabolism of (−)-(R)-MDMA by a route other than N-demethylation, and (4) inversion of (−)-(R)-MDMA and/or inversion of (−)-(R)-MDA to the corresponding (+)-(S)-isomer.

The preferential formation of (+)-(S)-MDA is consistant with the behavioral effects of MDMA. N-Demethylation is a major route of metabolism of methamphetamine in rats and humans.[17–19] Prior to these studies it was speculated that N-demethylation could not be a major route of metabolism of MDMA because the metabolite formed, MDA, would cause hallucinations, which do not occur with MDMA.[20] With a closer look at the discriminative properties of the stereoisomers of MDA others concluded that N-demethylation of MDMA was possible if this pathway was stereoselective for the (+)-(S)-isomer.[21] The quantitative analysis of the enantiomers of MDMA and MDA demonstrated that more of the (+)-(S)-MDMA is metabolized by N-demethylation than is the (−)-(R)-MDMA. This result is consistent with observations reported by others showing more (+)-(S)-amphetamine was excreted than (−)-(R)-amphetamine when animals were dosed with racemic methamphetamine.[22] The stereoselective N-demethylation demonstrated in this study is consistent with metabolism of methamphetamine and explains why MDMA is not hallucinogenic-like even though MDA is a major metabolite.

Metabolism of MDMA by N-demethylation produces a neurotoxic metabolite. The preferential formation of (+)-(S)-MDA possibly contributes to the stereoselectivity of the neurotoxicity of MDMA, but the exact role this metabolism plays in the degeneration of 5-HT neurons observed following administration of MDMA is unknown.

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