Urinary Pharmacokinetics of Methamphetamine and Its Metabolite, Amphetamine Following Controlled Oral Administration to Humans

Insook Kim, PhD,‡ Jonathan M. Oyler, BA,*‡ Eric T. Moolchan, MD,* Edward J. Cone, PhD,† and Marilyn A. Huestis, PhD**

Abstract: Methamphetamine is widely abused for its euphoric effects. Our objectives were to characterize the urinary pharmacokinetics of methamphetamine and amphetamine after controlled methamphetamine administration to humans and to improve the interpretation of urine drug test results. Participants (n = 8) received 4 daily 10-mg (low) oral doses of sustained-release (*d*)-methamphetamine hydrochloride within 7 days. After 4 weeks, 5 participants received 4 daily 20-mg (high) oral doses. All urine specimens were collected during the study. Methamphetamine and amphetamine were measured by GC-MS/PCI. Maximum excretion rates ranged from 403 to 4919 μg/h for methamphetamine and 59 to 735 μg/h for amphetamine with no relationship between dose and excretion rate. The mean molar percentage of dose in the urine as total methamphetamine and amphetamine were 57.5 ± 21.7% (low dose) and 40.9 ± 8.5% (high dose). Mean urinary terminal elimination half-lives across doses were 23.6 ± 6.6 hours for methamphetamine and 20.7 ± 7.3 hours for amphetamine. Methamphetamine renal clearance across doses was 175 ± 102 mL/min. The mean amphetamine/methamphetamine percentage ratio based on the area under the urinary excretion–time curve increased over time from 13.4 ± 6.5% to 35.7 ± 26.6%. Slow urinary excretion results in drug accumulation and increases in detection time windows. Our findings also support the presence of an active renal excretion mechanism for methamphetamine.

Key Words: methamphetamine, amphetamine, urine, pharmacokinetics, excretion

(*Ther Drug Monit* 2004;26:664–672)

Methamphetamine, a sympathomimetic amine, produces potent central nervous system (CNS)-mediated stimulant, anorectic, and cardiovascular effects.[1,2] In the United States, it is a DEA Schedule II drug with limited therapeutic use for the treatment of attention deficit hyperactivity disorder, exogenous obesity, and narcolepsy. However, methamphetamine is mainly abused for its euphoric effect.

Methamphetamine is available in many forms and can be smoked, snorted, injected, or orally ingested.[3] When methamphetamine is orally administered, it is rapidly absorbed from the gastrointestinal tract and metabolized in the liver. The major routes of metabolism in humans are N-demethylation and aromatic hydroxylation to form amphetamine, a major active metabolite, and *p*-hydroxymethamphetamine, respectively. A minor route of metabolism is deamination. Caldwell et al[4] observed that 90% of a ^{14}C-labeled methamphetamine dose was excreted in urine over the first 4 days after oral administration. Parent drug (22%) and 4-hydroxymethamphetamine (15%) were the major analytes found in urine during the first 24 hours. Methamphetamine is excreted primarily in the urine in humans, and its excretion is pH dependent.[5–8] Under normal conditions, up to 43% of a dose is excreted as unchanged drug with 4%–7% as amphetamine in 24 hours.[8] This can be dramatically changed by adjusting urine pH. In acidic urine, up to 76% of the methamphetamine dose appears as parent drug, and 7% as amphetamine, in the first 24 hours; in alkaline urine, only 2% may be excreted as parent and 0.1% as amphetamine. Amphetamine also is a potent CNS stimulant,[9,10] and its urinary excretion is similarly affected by pH (1%–4% and 74% excretion in alkaline and acidic urine, respectively).[11]

Received for publication November 14, 2003; accepted May 17, 2004.

From the *Chemistry and Drug Metabolism Intramural Research Program, National Institute on Drug Abuse, NIH, Baltimore, MD; and †ConeChem Research, 441 Fairtree Drive, Severna Park, MD.

‡These authors contributed equally to this work.

This study was supported by National Institute on Drug Abuse Intramural Research Funds.

Abbreviations: CNS, central nervous system; HCl, hydrochloride; BSTFA, N,O-*bis* (trimethylsilyl)trifluoroacetamide; TMCS, trimethylchlorosilane; MTBSTFA, N-methyl-N-(*tert*-butyldimethylsilyl) trifluoroacetamide; TBDMCS, *tert*-butyldimethylchlorosilane; SPE, solid-phase extraction; $(dU/dt)_{max}$, peak urinary excretion rate; t_{max}, time of peak excretion rate; $t_{½}$, terminal elimination half-life; AURC, area under the urine excretion rate–time curve; Cl_R, renal clearance; D_{u24}, total amount of drug excreted in the urine for the first 24 hours after the first dose; AUC_{24}, area under the plasma concentration–time curve.

Reprints: Marilyn A. Huestis, PhD, National Institute on Drug Abuse/Intramural Research Program, NIH, Bldg C, Room 371, 5500 Nathan Shock Drive, Baltimore, MD 21224 (e-mail: mhuestis@intra.nida.nih.gov).

There are several pharmacokinetic studies of methamphetamine and its metabolites in plasma, oral fluid, or urine after controlled clinical administration.[6,7,12,13] Cook et al[7] studied methamphetamine pharmacokinetics after repeated daily oral doses. Challenge doses of 0.125 mg/kg (n = 6) and 0.25 mg/kg (n = 4) *S*-(+)-methamphetamine-d_3 hydrochloride (HCl) were orally administered to subjects before and after 13 days of subchronic oral dosing with 10 mg/d sustained-release *S*-(+)-methamphetamine·HCl (Desoxyn Gradumet®) to distinguish effects of subchronic administration on the elimination kinetics of a single methamphetamine dose. There were no statistically significant differences in pharmacokinetic parameters following subchronic administration of the low dose. However, with the high dose, the maximum plasma concentrations of methamphetamine-d_3 for the last dose (41.8 ± 1.7 ng/mL) were significantly higher than those for the first dose (37.2 ± 1.3 ng/mL). They also found that the renal clearance of methamphetamine was dependent on urine pH, urine flow, and dose and that the renal excretion of methamphetamine exceeded the average renal filtration rate, suggesting the presence of an active transport mechanism.

The objective of this study was to characterize the urinary pharmacokinetics of methamphetamine and its major metabolite, amphetamine, after controlled methamphetamine administration. These data are helpful in understanding potential mechanisms for drug toxicity and in improving interpretation of urine drug testing results used in drug treatment, emergency medicine, criminal justice, military, and workplace drug-testing programs.

MATERIALS AND METHODS

Chemicals and Reagents

Chemicals were obtained from the following sources: methamphetamine, amphetamine, [$^2H_{11}$]methamphetamine, [$^2H_{10}$]amphetamine, [Radian (now Cerilliant), Austin, TX]; N,O-*bis* (trimethylsilyl)trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (TMCS), N-methyl-N-(*tert*-butyldimethylsilyl) trifluoroacetamide (MTBSTFA) with 1% *tert*-butyldimethylchlorosilane (TBDMCS) (Pierce Chemical, Rockford, IL). Solid-phase extraction (SPE) columns (Clean Screen DAU, 200 mg, 10 mL) were obtained from United Chemical Technologies (Bristol, PA). Methanol, methylene chloride, 2-propanol, and acetonitrile were HPLC grade chemicals. All other chemicals were reagent grade.

Human Participants and Study Protocol

This study was approved by the National Institute on Drug Abuse Institutional Review Board. Participants were healthy volunteers with a history of stimulant and opioid use who provided informed consent and were paid for their participation. All participants were evaluated medically, physically, and psychologically before admission to the clinical ward. Participants were not physically dependent on drugs and medications with the possible exceptions of nicotine and caffeine. Four male and 4 female healthy volunteers participated in the controlled methamphetamine administration protocol. Of the 8 participants, 4 were African American, 2 were white, and 2 were Hispanic. Their mean age (±SD) was 35.3 ± 4.2 years (range 26.3–39.8 years) with a mean weight of 72.0 ± 17.6 kg (range 54.7–103.2 kg). Throughout the 10-week study, participants resided on the Intramural Research Program's secure research unit.

The first 2 weeks of the study served as a clearance phase to eliminate previously self-administered drugs. Participants (n = 8) received 4 daily 10-mg (low) sustained-release oral doses of methamphetamine · HCl (Desoxyn Gradumet) within 7 days. After a 4-week interval, 5 of 8 participants received 4 daily 20-mg (high) oral methamphetamine · HCl doses. Three participants did not receive the high-dose regimen because of personal choice or medical disqualification. All drug administrations were conducted under subject-blind conditions.

Urine Specimens

Urine specimens were collected in polypropylene bottles *ad libitum* up to 8 days following the last dose, and void volumes were recorded. Approximately 15 mL was aliquoted into polypropylene cryotubes and stored at −20°C until analysis. The pH (Diagnostic Reagent Inc. pH-Detect Assay®) and creatinine concentration (Diagnostic Reagent Inc. creatinine-Detect® Assay) of each specimen were measured on a Hitachi Modular-P Unit. Creatinine normalized values (ng methamphetamine/mg creatinine) were calculated by dividing the urinary methamphetamine or amphetamine concentration (ng/mL) by the creatinine concentration (mg/mL).

Analytic Procedure

Calibrators and controls were prepared from different commercially available drug lots in drug-free urine. Deuterated internal standards, [$^2H_{11}$]methamphetamine and [$^2H_{10}$]amphetamine, were employed to improve quantification. Calibration curves were prepared in duplicate at methamphetamine and amphetamine concentrations ranging from 1.25 to 1000 ng/mL. Duplicate control samples were prepared and analyzed with each sample batch at concentrations of 10, 100, and 250 ng/mL. Calibrator, control, and specimen samples were processed by SPE for methamphetamine and amphetamine according to a previously published method.[14–16] After SPE, extracted samples were derivatized with TBDMS followed by TMS.

Mass spectrometric data were acquired with a Hewlett-Packard 6890 gas chromatograph interfaced with a Hewlett-Packard 5973 mass selective detector in positive chemical ionization mode with methane as reactant gas, as previously reported.[15] The mass filter was operated in selected ion monitoring mode employing *m/z* 130, 136, 158, and 162 as

quantifying ions for methamphetamine, methamphetamine-d_{11}, amphetamine, and amphetamine-d_{10}, respectively. The limits of quantification of the method were 2.5 ng/mL for methamphetamine and amphetamine. Quantitative analysis was performed employing split curves ($r \geq 0.99$) with concentrations ranging from 2.5 to 100 and 100 to 1000 ng/mL. Control samples containing 10 and 100 ng of drug were analyzed with the 2.5–100 ng/mL curve, and 250-ng controls were analyzed with the 100 to 1000 ng/mL curves. Quantitative results for all controls across sample batches were within ±20% of their target concentrations.

Pharmacokinetic Analysis

The peak urinary excretion rate $[(dU/dt)_{max}]$ and time of peak excretion rate (t_{max}) were obtained from the urinary excretion rate (dU/dt) versus midpoint of time curves obtained for each participant after the oral administration of methamphetamine. Terminal elimination half-life ($t_{½}$) was calculated after the last dose using the formula, $t_{½} = \ln 2/\lambda$, where the elimination rate constant (λ) was calculated from the slope of the terminal portion of the semilogarithmic urinary excretion rate (μg/h) versus midpoint of time (h) curves. Area under the urine excretion rate–time curve $(AURC)_{0-\infty}$ was calculated by the linear trapezoidal rule from the first dose to infinity. $AURC_{1(24)}$ and $AURC_{4(24)}$ were calculated as partial AURCs for the first 24 hours after the first and last dose, respectively. Renal clearance (Cl_R) was calculated by a mode-independent method using the formula, $Cl_R = D_{u24}/AUC_{24}$. D_{u24} was obtained by summing the total amount of drug excreted in the urine for the first 24 hours after the first dose. AUC_{24} was determined from area under the plasma concentration–time curve for the first 24 hours after the first dose, as reported previously.[12] Pharmacokinetic parameters were derived by noncompartmental model with the use of WinNonlin Professional software (Ver. 3.3, Pharsight Co). Uniform weighting for all data points was used throughout the analysis.

RESULTS

Urinary Excretion of Methamphetamine and Amphetamine

Mean (±SD) methamphetamine peak concentrations were 6137 ± 2402 ng/mL (range 3091–10,905 ng/mL) for the low dose and 11,267 ± 5113 ng/mL (range 5092–18,468 ng/mL) for the high dose, as previously reported.[15] Mean amphetamine peak concentrations were 1147 ± 820 ng/mL (range 370–2872 ng/mL) and 2943 ± 2052 ng/mL (range 1195–5992 ng/mL) for low and high doses, respectively.

A total of 881 urine specimens were collected from 8 participants throughout the 10-week study. Each participant provided an average of 110 ± 45 (range 69–168) specimens. Urinary pH ranged from 5.0 to 10.3 (overall mean, pH = 7.0 ± 1.0; median, pH = 7.0). An inverse correlation was found between urinary methamphetamine and amphetamine concentrations and urine pH ($P \leq 0.002$) following the low and high methamphetamine doses (Fig. 1).

Mean urinary creatinine concentrations were 106.1 ± 87.8 (range 6–591 mg/dL; median 85.5 mg/dL) and 141.3 ± 127.4 mg/dL (range 6–726 mg/dL; median 91.0 mg/dL) for the low and high doses, respectively. Urinary excretion curves and time to maximum excretion also were generated from methamphetamine and amphetamine concentrations normalized to urinary creatinine concentrations. These parameters were compared between the nonnormalized and creatinine-normalized data following the first methamphetamine dose (data not shown). No significant differences were found in urinary excretion and the time to maximum concentration between nonnormalized and normalized data following the first dose.

Initial excretion rates for methamphetamine ranged from 5.8 to 93.0 μg/h and 25.4 to 189.0 μg/h following low and high doses, respectively. For the first 24 hours after the first low and high doses, mean peak urinary excretion rates for methamphetamine were 674 ± 571 μg/h (range 107–1379 μg/h) at a mean time of 9.8 ± 7.0 hours and 299 ± 197 μg/h (range 141–600 μg/h) at a mean time of 9.2 ± 8.3 hours, respectively. For the first 24 hours after the last low and high doses, the mean peak methamphetamine urinary excretion rates were 601 ± 440 μg/h (range 208–1207 μg/h) at a mean time of 8.1 ± 7.0 hours (range 7.9–23.8 hours) and 609 ± 363 μg/h (range 249–870 μg/h) at a mean time of 11.5 ± 7.0 hours (range 6.8–23.5 hours). Peak urinary excretion rates over the collection period (from the first dose to 8 days after the last dose) ranged from 403 to 4919 μg/h and 428 to 1181 μg/h for low and high doses, respectively.

Initial excretion rates for amphetamine ranged from 0.2 to 7.1 μg/h for the low dose and 1.9 to 10.6 μg/h for the high dose. For the first 24 hours after the first low and high doses, the mean peak urinary excretion rates for amphetamine were 62 ± 42 μg/h (range 19–149 μg/h) at a mean time of 16.1 ± 7.8 hours and 26 ± 7 μg/h (range 18–36 μg/h) at a mean time of 12.7 ± 4.5 hours, respectively. For the first 24 hours after the last low and high doses, the mean peak urinary excretion rates for amphetamine were 182 ± 251 μg/h (range 31–735 μg/h) occurring at a mean time of 10.8 ± 7.7 hours (range 1.3–23.8 hours) and 92 ± 28 μg/h (range 57–131 μg/h) at a mean time of 15.5 ± 6.5 hours (range 7.7–23.5 hours). Peak urinary excretion of amphetamine over the collection period (from the first dose to 8 days after the last dose) ranged from 59 to 735 μg/h and from 85 to 287 μg/h for low and high doses, respectively.

Figure 2 illustrates urinary excretion rates and cumulative amount versus midpoint time curves for methamphetamine and amphetamine from participant W, who had 4 consecutive daily oral doses of 10 mg and 4 nonconsecutive daily oral doses of 20 mg methamphetamine. The average molar percentage of dose excreted in the urine as total methamphet-

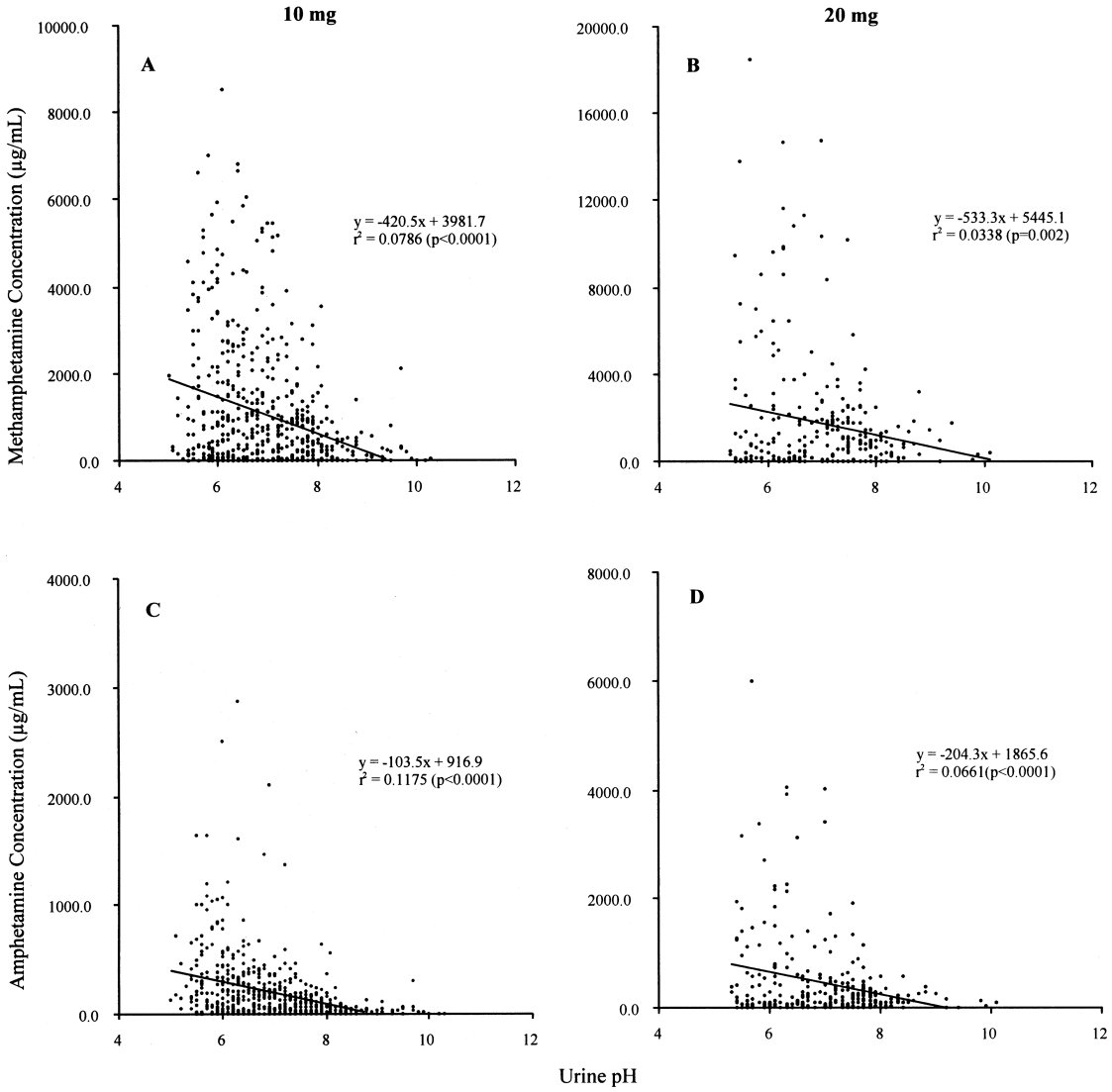

FIGURE 1. Correlation between urinary methamphetamine and amphetamine concentrations and pH. A and B, Methamphetamine urine concentrations after 4 daily oral administrations of 10 and 20 mg sustained-release methamphetamine hydrochloride, respectively. C and D, Amphetamine urine concentrations after 4 daily oral administrations of 10 and 20 mg sustained-release methamphetamine hydrochloride, respectively. The regression was calculated by least-squares regression analysis.

amine and amphetamine up to 8 days after the last dose was 57.5 ± 21.7% for the low dose and 40.9 ± 8.5% for the high dose.

Methamphetamine Urinary Pharmacokinetics

The slope of the line defined by 4 to 14 consecutive terminal excretion phase points after the last drug administration was used to estimate terminal elimination $t_{½}$ for each participant. The mean methamphetamine $t_{½}$ was 22.6 ± 7.2 hours (range 15.3–34.9 hours) and 25.2 ± 6.0 hours (range 17.8–32.7 hours) for low and high doses, respectively (Table 1). The mean methamphetamine t_{max} over the first 24 hours following the first dose was 9.8 ± 7.0 hours and 9.2 ± 8.3 hours for the low and high doses, respectively. Mean t_{max} following the last administration was 20.3 ± 19.7 hours for the low dose and 11.5 ± 7.0 hours for the high dose. The mean methamphetamine $AURC_{0-\infty}$ was 21,700 ± 7859 h · µg/h for the low dose (range 10,771–36,526 h · µg/h) and 23,346 ± 5508 h · µg/h for the high dose (range 17,625–31,303 h · µg/h). There was no dose response in AURC or in the mean total amount of methamphetamine excreted in urine. The mean ratio of $AURC_{4(24)}/AURC_{1(24)}$ for methamphetamine was greater than 1 (a mean of 1.6 ± 0.9 for the low dose, a mean of 2.0 ± 0.5 for the high dose). At the high dose, the increase in $AURC_{4(24)}$ for

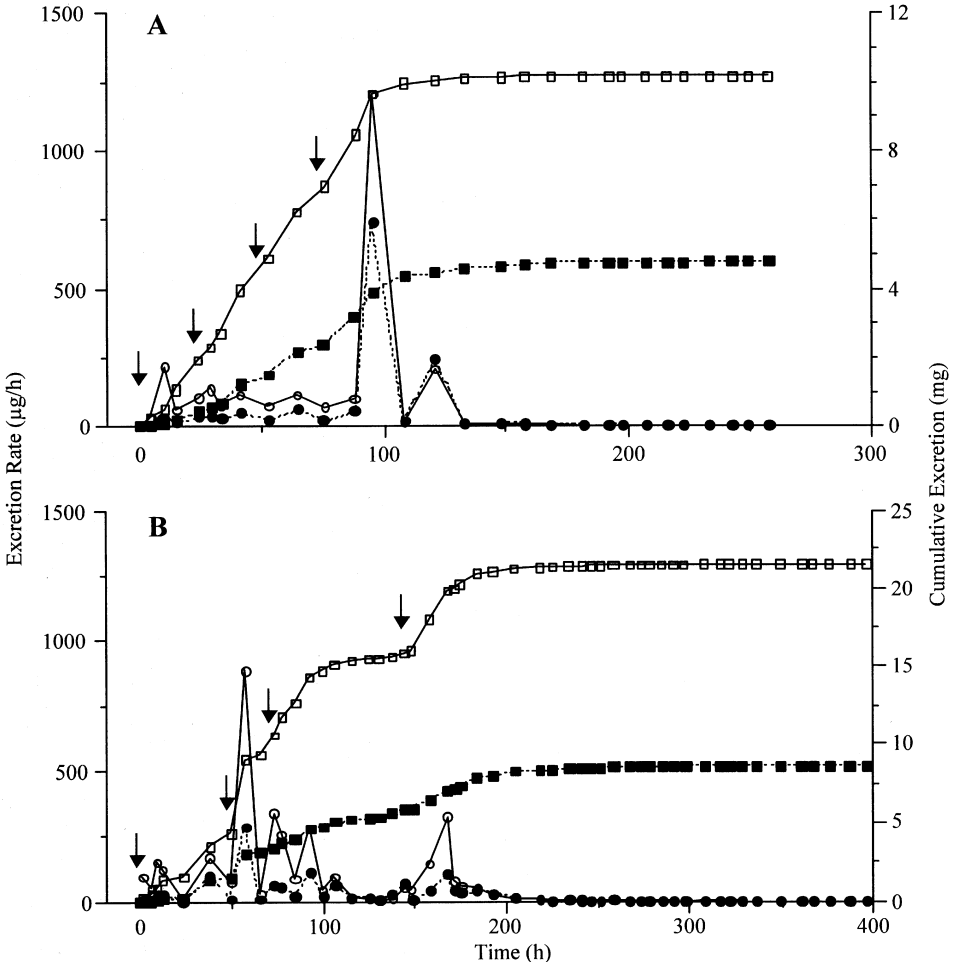

FIGURE 2. Urinary excretion rate and cumulative excretion amount versus midpoint time plots for methamphetamine and its metabolite, amphetamine, in participant W after 4 consecutive daily oral administrations of 10 mg (A) and 4 nonconsecutive daily oral administrations of 20 mg (B) of sustained-release methamphetamine hydrochloride. Urinary excretion rate for methamphetamine (◯) and for amphetamine (●); cumulative excretion amount for methamphetamine (□) and for amphetamine (■). Arrows indicate methamphetamine hydrochloride administration.

methamphetamine was statistically significant ($P < 0.02$) as compared with the $AURC_{1(24)}$, suggesting drug accumulation. Some pharmacokinetic parameters for methamphetamine from participants Z and AA were not available because of missing data. Methamphetamine mean renal clearance was calculated from the total amount of methamphetamine excreted in urine over the first 24 hours and the methamphetamine plasma AUC for the first 24 hours as reported previously[12] and was 214 ± 120 mL/min for the low dose and 120 ± 33 mL/min for the high dose.

Amphetamine Urinary Pharmacokinetics

The mean urinary terminal elimination $t_{½}$ of amphetamine was 19.8 ± 7.3 hours for the low dose and 22.0 ± 8.0 hours for the high dose (Table 2). Some pharmacokinetic parameters for amphetamine from participants Y and AA were not available because of missing data. The mean amphetamine t_{max} over the first 24 hours following the first methamphetamine dose was 16.1 ± 7.8 hours and 12.7 ± 4.5 hours for the low and high doses, respectively. Mean t_{max} following the last administration was 24.5 ± 19.0 hours for the low dose and 23.6 ± 16.9 hours for the high dose. Mean amphetamine $AURC_{4(24)}/AURC_{1(24)}$ ratios of 2.9 ± 2.8 and 2.7 ± 1.5 for the low and high doses, respectively, were higher than those of methamphetamine. Mean molar amphetamine/methamphetamine $AURC_{1(24)}$ percentage ratio was 13.4 ± 6.5% (range 5.4%–25.2%); however, the mean molar percentage ratio of amphetamine/methamphetamine $AURC_{4(24)}$ increased to 22.7 ± 16.1%. The mean percentage ratio of amphetamine/methamphetamine AURC from the time of the last dose to the time when the analytes were no longer detectable was 34.7 ± 27.5%.

DISCUSSION

This study was designed to characterize the urinary pharmacokinetics of methamphetamine and its metabolite, amphetamine in humans and to evaluate whether renal excretion was limited following controlled oral administration of sustained-release methamphetamine. There was no attempt to control urinary pH. Our urine specimens (n = 881) had a pH range of 5.0 to 10.3. Normal urine pH range is 4.6–8.0 when

TABLE 1. Urinary Pharmacokinetic Parameters for Methamphetamine in Individual Participants after Controlled Methamphetamine Oral Administration

Subject	Dose (mg)	t_{max}* (h)	$(dU/dt)_{max}$† (μg/h)	Dose in urine‡ (%)	pH (range)	Half-life (h)	Cl_R§ (mL/min)	$AURC_{0-\infty}$‖ (h · μg/h)	$AURC_{1(24)}$¶ (h · μg/h)	$AURC_{4(24)}$# (h · μg/h)
S	10	11.0	1193	91.5	7.0 ± 1.3 (5.0–9.9)	31.8	351	36,526	6710	5400
	20	11.5	1098	43.1	7.0 ± 1.1 (5.3–9.9)	26.4	126	31,303	4115	8572
V	10	0.7	403	30.1	7.1 ± 0.9 (5.7–10.2)	17.2	72	10,771	1648	2407
W	10	23.8	1207	31.6	6.8 ± 0.7 (5.7–9.8)	15.3	371	23,916	2172	6686
	20	23.5	327	33.5	7.4 ± 0.9 (5.7–9.8)	28.4	137	25,854	1899	3593
X	10	48.0	817	45.2	6.4 ± 0.6 (5.5–8.1)	34.9	192	18,517	4371	4730
Y	10	46.1	1560	37.1	6.2 ± 0.8 (5.4–8.2)	16.1	70	22,438	1472	2092
	20	7.8	249	25.0	6.3 ± 0.9 (5.4–9.2)	20.1	116	1,763	2241	4645
Z	10	4.5	851	54.6	7.4 ± 1.0 (5.6–10.3)	20.9	N/A**	21,989	2845	7682
AA	10	N/A	N/A	38.8	7.6 ± 1.0 (6.1–9.7)	21.6	204	N/A	3610	N/A
	20	7.7	499	29.8	7.3 ± 0.8 (5.6–10.1)	20.6	155	2,295	4398	5395
BB	10	7.9	208	50.0	6.8 ± 0.7 (5.6–8.0)	22.6	241	17,745	3835	3387
	20	6.8	870	26.8	6.7 ± 0.8 (5.3–8.0)	32.7	67	19,002	2314	6392
Mean ± SD	10	20.3 ± 19.7	891 ± 474	47.3 ± 19.8	7.0 ± 1.0 (5.0–10.3)	22.6 ± 7.2	214 ± 120	21,700 ± 7859	3333 ± 1719	4627 ± 2124
	20	11.5 ± 7.0	608 ± 363	31.6 ± 7.2	7.0 ± 1.0 (5.3–10.1)	25.1 ± 6.0	120 ± 33	23,346 ± 5508	2994 ± 1168	5919 ± 1895

*Time to maximum urinary excretion rate after the last dose.
†Maximum urinary excretion rate after the last dose.
‡Total amount from the first dose to last sample ≥ LOQ.
§Renal clearance calculated by the formula, $Cl_R = D_{u24}/AUC_{24}$. D_{u24} was obtained by summing the total amount of drug excreted in the urine for the first 24 hours after the first dose. AUC_{24} is the area under the plasma concentration–time curve for the first 24 hours after the first dose.
‖Area under the urine excretion rate–time curve from the time of the first dose to infinity.
¶Area under the urine excretion rate–time curve for the first 24 hours after the first dose.
#Area under the urine excretion rate–time curve for the first 24 hours after the last dose.
**Data were not available.

urine was collected directly from the bladder.[17] Of 881 urine specimens, 110 (12.5%) were above the normal pH range. Urine specimens from 7 of 8 participants had at least some specimens with urine pH outside the normal range (Table 1). According to Elliot et al,[18] urine pH is affected by both circadian rhythms and food intake. Although urinary pH fluctuated, there were no significant differences between the mean and median urinary pH following the low (mean pH = 7.0 ± 1.0; median pH = 6.9) and high methamphetamine doses (mean pH = 7.0 ± 1.0; median pH = 7.1).

According to the Urine Specimen Validity Testing Guidelines,[19] if the creatinine concentration is below 20 mg/dL and the specific gravity is less than 1.003, a urine specimen is defined as a "diluted" specimen. In our data, the creatinine concentration range was 6–726 mg/dL, with 62 urine specimens (7.0%; from 4 of 8 participants) having a creatinine concentration between 6 and 19 mg/dL.

In this study, urinary methamphetamine and amphetamine concentrations were inversely dependent on urine pH ($P \leq 0.002$) (Fig. 1). This finding lends further support for the pH effect on urinary methamphetamine and amphetamine excretion.[5,7,20] Beckett et al[5,20] reported reabsorption of methamphetamine and amphetamine in the kidney dependent on urinary pH. The more alkaline the urine, the higher the un-ionized drug concentration and subsequent reabsorption, yielding decreased excretion rates. Decreased excretion rates are important because retention of methamphetamine and amphetamine in the body also increases the duration of pharmacological effects. According to Cook et al,[7] renal clearance of oral methamphetamine was dependent on renal flow (expressed as urine volume per hour) and inversely dependent on urine pH. In addition, the mean elimination rate may decrease with increasing dose, suggesting that the pharmacokinetics of methamphetamine may be dose-dependent because of saturated excretion in the kidney.

Previous studies documented the primary methamphetamine metabolites found in human urine.[4–7] In the current study, the mean percentages of total dose excreted as parent drug were 47.3 ± 19.8% (10-mg regimen) and 31.6 ± 7.2% (20-mg regimen). Additionally, 10.2 ± 4.1% (10-mg regimen) and 9.3 ± 3.5% (20-mg regimen) were excreted as amphetamine (mole%) over 8 days. These results are in close agreement with other investigators' findings in spite of different dosing regimens and administration routes. At a similar low dose of 11 mg (+)- or (−)-methamphetamine,[5] 27%–67% of the dose was excreted as parent and 3%–10% as the metabolite amphetamine in the first 48 hours. After smoked (an average inhaled dose of 21.8 ± 0.3 mg) and intravenous (15.5 mg) ad-

TABLE 2. Mean Urinary Pharmacokinetic Parameters for Amphetamine from Individual Participants after Controlled Methamphetamine Oral Administration

Subject	Dose (mg)	t_{max}* (h)	$(dU/dt)_{max}$† (μg/h)	Dose in urine‡ (%)	Half-life (h)	$AURC_{0-\infty}$§ (h · μg/h)	$AURC_{1(24)}$‖ (h · μg/h)	$AURC_{4(24)}$¶ (h · μg/h)
S	10	1.3	193	16.4	16.7	5,606	604	545
	20	51.8	144	8.7	13.6	5,519	341	463
V	10	9.9	122	7.9	15.1	2,540	303	841
W	10	23.8	735	16.3	30.7	14,084	425	3763
	20	23.5	104	14.8	28.5	10,103	332	1492
X	10	48.0	486	9.8	24.3	4,458	513	1007
Y	10	46.4	677	9.1	N/A#	N/A	318	364
	20	14.6	57	10.2	14.6	6,571	566	1647
Z	10	34.5	40	5.9	12.3	2,179	180	605
AA	10	N/A	N/A	6.4	12.8	N/A	194	N/A
	20	7.7	81	6.1	21.6	4,044	312	266
BB	10	7.9	46	9.3	26.4	3,041	390	603
	20	20.5	85	6.5	31.5	4,067	328	1210
Mean ± SD	10	24.5 ± 19.0	328 ± 299	10.2 ± 4.1	19.8 ± 7.3	5,318 ± 4,482	366 ± 148	1104 ± 1191
	20	23.6 ± 16.9	94 ± 32	9.3 ± 3.5	22.0 ± 8.0	6,061 ± 2,497	375 ± 107	1016 ± 619

*Time to maximum urinary excretion rate after the last dose.
†Maximum urinary excretion rate after the last dose.
‡Total amount from the first dose to last sample ≥ LOQ.
§Area under the urine excretion rate–time curve from the time of the first dose to infinity.
‖Area under the urine excretion rate–time curve for the first 24 hours after the first dose.
¶Area under the urine excreation rate–time curve for the first 24 hours after the last dose.
#Data were not available.

ministration of *S*-(+)-methamphetamine HCl in humans (n = 6),[6] 36.8 ± 4.3% (mean ± SE) and 45.0 ± 9.5% of the dose were excreted as parent drug, respectively, and 6.9 ± 0.9% and 7.1 ± 1.0% of the molar dose was excreted as amphetamine.

We also found that the percentage of dose excreted as methamphetamine was 54.3 ± 46.3% higher for the 10-mg dose as compared with the 20-mg dose. This is comparable to the 56%–66% higher percentage excretion of parent drug for the 0.125 mg/kg dose as compared with a 0.25 mg/kg dose observed by Cook et al.[7] In that study, 54% of the 0.125 mg/kg (low) dose and 35% of the 0.25 mg/kg (high) dose were excreted in urine on day 1. After 14 daily doses of methamphetamine, the same trend was observed (50% of the low dose and 30% of the high dose).

We also compared renal clearance with total body clearance. Using our previous plasma data collected in the same participants,[12] total body clearance was 537 ± 228 mL/min for 24 hours after the first low dose and 558 ± 264 mL/min for the first high dose. In this study, renal clearances over the same 24-hour period after the low and high doses were 214 ± 120 and 120 ± 33 mL/min (overall mean 175 ± 102 mL/min), which were 40.6 ± 23.3% and 25.0 ± 13.0% of total body clearance, respectively. In addition, methamphetamine renal clearance in our study (overall mean 175 ± 102 mL/min) was similar to a previously reported renal clearance of 164 mL/min by Cook et al.[7] Both renal clearances were greater than the reported glomerular filtration rate (~125 mL/min).[21] These results lend further support for an active transport mechanism in renal excretion of methamphetamine and demonstrate that this important detoxification mechanism might become saturated with only moderate doses.

We reported previously an overall mean methamphetamine and amphetamine plasma t_{max} of 6.3 ± 3.0 hours and 13.1 ± 6.0 hours, respectively, following initial administration of a single 10- or 20-mg dose.[12] Over the same time period, the mean methamphetamine urinary t_{max} values were similar at 9.8 ± 7.0 and 9.2 ± 8.3 hours (overall mean 9.4 ± 7.2 hours) and for amphetamine at 16.1 ± 7.8 and 12.7 ± 4.5 hours (overall mean 14.8 ± 6.7 hours) for low and high doses, respectively. The mean methamphetamine urinary t_{max} values after the last dose were 20.3 ± 19.7 hours for the low dose and 11.5 ± 7.0 hours for the high dose (Table 1), which were somewhat higher than those reported by Cook et al (3–6 hours),[7] most likely because of the difference in methamphetamine absorption kinetics of the gelatin capsule formulation versus the sustained-release formulation used in this study. The mean amphetamine urinary t_{max} values of 24.5 ± 19.0 and 23.6 ± 16.9 hours following the last administration of low and high doses, respectively, also

were comparable to those reported by Cook et al (6–24 hours).[7] Substantial intra- and intersubject variability in t_{max} also was observed.

We found mean terminal elimination half-lives of methamphetamine of 22.6 ± 7.2 hours and 25.1 ± 6.0 hours, and for amphetamine 19.8 ± 7.3 and 22.0 ± 8.0 hours for the low and high doses, respectively. These methamphetamine and amphetamine mean urinary terminal elimination $t_{½}$ were in close agreement with those of the Cook et al study.[7] They reported mean urinary excretion rate constants for methamphetamine of 0.0314 ± 0.0022 (SEM) to 0.0674 ± 0.0207 $hour^{-1}$ (mean $t_{½}$ ranges of 10.3 to 22.1 hours when using the ln2/λ) and an overall mean urinary excretion rate constant for amphetamine of 0.025 ± 0.003 (SEM) $hour^{-1}$ ($t_{½}$ of ~27.7 hours).

The overall mean urinary amphetamine/methamphetamine $AURC_{1(24)}$ percentage ratio of 13.4 ± 6.5% was lower than the 21 ± 25% and 24 ± 11% we previously reported for plasma and oral fluid ratios in the same participants, respectively.[12] The overall mean amphetamine/methamphetamine AURC percentage ratio increased over time with $AURC_{4(24)}$ percentage ratios of 22.7 ± 16.1% ($P < 0.05$) and 34.7 ± 27.5% ($P < 0.05$) from the time of the last dose to the time when the drug was no longer detectable in urine. The $AURC_{0-\infty}$ percentage ratio from the first administration of each dose until drug was no longer measurable averaged 24.7 ± 13.9%. In the Cook et al studies,[6,7] the peak urinary concentrations of amphetamine occurred later (6–24 hours) than those of the parent drug (3–6 hours) following subchronic oral doses and increased to 50% of the methamphetamine concentration during a 24 to 47 hour collection period after the 0.125 and 0.250 mg/kg doses. They also reported an increase in the urinary amphetamine/methamphetamine ratio over time after smoked and intravenous methamphetamine.[6]

Because methamphetamine frequently is repeatedly administered (binge use), it is important to study the effects of methamphetamine after multiple dosing. Comer et al[22] evaluated subjective effects after 5 or 10 mg of oral methamphetamine administered twice a day for 3 consecutive days (n = 7). These investigators reported "good drug effects" on the first day of methamphetamine administration; however, tolerance to these positive effects occurred, and negative effects, "bad drug effect," "dizzy," and "flu-like symptoms" appeared by the third day of drug administration. Perez-Reyes et al[1] reported that tolerance did not develop to the "high" subjective effect, but the magnitude of heart rate acceleration decreased on day 15 following single daily doses of 10 mg methamphetamine for 13 consecutive days. This indicates that daily subchronic exposure to methamphetamine resulted in tolerance to its tachycardic effects; however, there were no differences in plasma methamphetamine concentrations, indicating that the tolerance was pharmacodynamic rather than pharmacokinetic in nature. Most pharmacokinetic parameters did not change significantly after subchronic oral administration; however, plasma elimination rate, plasma maximum concentration, and AUC were significantly different after the 0.25 mg/kg dose as compared with the 0.125 mg/kg dose.[7] In the current study, the mean methamphetamine $AURC_{4(24)}/AURC_{1(24)}$ ratio was 1.9 ± 0.7, indicating methamphetamine accumulation, possibly caused by relatively slow absorption of the sustained-release preparations (supported by the relatively late urinary t_{max} of 11–20 hours) and long urinary elimination $t_{½}$ (overall mean of 23.6 ± 6.6 hours).

This study provides pharmacokinetic data on the urinary excretion of methamphetamine and its metabolite, amphetamine, following controlled oral administration. Based on these data, methamphetamine was largely excreted as parent drug in urine with smaller amounts of amphetamine. Long terminal elimination half-lives of methamphetamine and amphetamine in urine result in accumulation and an increased detection window for drug exposure. The renal clearance of methamphetamine was higher than the glomerular filtration rate, suggesting an active transport system for methamphetamine excretion in the kidney. Although there is evidence of tolerance to some drug effects, the limited renal excretion, accumulation, and possible reabsoption of methamphetamine into the body, especially after repeated administrations, might increase the chance of drug toxicity. These controlled drug administration data should aid clinicians and toxicologists in understanding limitations in the urinary excretion of methamphetamine, perhaps contributing to drug toxicity and also aiding in the interpretation of urine drug tests for methamphetamine.

ACKNOWLEDGMENTS

We would like to thank the staff of the Department of Forensic Toxicology, Armed Force Institute of Pathology, and Deborah Price of our staff for technical assistance with pH and creatinine measurements and Natalie Eddington for pharmacokinetic consultation.

REFERENCES

1. Perez-Reyes M, White WR, McDonald SA, et al. Clinical effects of daily methamphetamine administration. *Clin Neuropharmacol*. 1991;14:352–358.
2. *Physicians' Desk Reference.* Desoxyn Tablets. *Physicians' Desk Reference.* Oradell, NJ: Medical Economics, 2003:441–442.
3. Leshner AI. Methamphetamine. *NIDA Community Drug Alert Bull.* 1998:1–3.
4. Caldwell J, Dring LG, Williams RT. Metabolism of [^{14}C]methamphetamine in man, the guinea pig and the rat. *Biochem J*. 1972;129:11–22.
5. Beckett AH, Rowland M. Urinary excretion of methylamphetamine in man. *Nature*. 1965;206:1260–1261.
6. Cook CE, Jeffcoat AR, Hill JM, et al. Pharmacokinetics of methamphetamine self-administered to human subjects by smoking *S*-(+)-methamphetamine hydrochloride. *Drug Metab Dispos*. 1993;21:717–723.
7. Cook CE, Jeffcoat AR, Sadler BM, et al. Pharmacokinetics of oral methamphetamine and effects of repeated daily dosing in humans. *Drug Metab Dispos*. 1992;20:856–862.
8. Baselt RC. ed. *Disposition of Toxic Drugs and Chemicals in Man, 2nd ed*. Davis: Biomedical Publications, 1978:488–490.

9. Kraemer T, Maurer HH. Determination of amphetamine, methamphetamine and amphetamine-derived designed drugs or medicaments in blood and urine. *J Chromatogr*. 1998;713:163–187.
10. Caldwell J. The metabolism of amphetamines in mammals. *Drug Metab Rev*. 1976;5:219–280.
11. Moffat AC, Jackson JV, Moss MS, et al. eds. *Clarke's Isolation and Identification of Drugs*. London: The Pharmaceutical Press, 1996:349–351.
12. Schepers RJF, Oyler JM, Joseph RE Jr, et al. Methamphetamine and amphetamine pharmacokinetics in oral fluid and plasma after controlled oral methamphetamine administration to human volunteers. *Clin Chem*. 2003; 49:121–132.
13. Gunne LM, Anggard E. Pharmacokinetic studies with amphetamines—relationship to neuropsychiatric disorders. *J Pharm Biopharmac*. 1973;1: 481–495.
14. Cone EJ, Weddington WW Jr. Prolonged occurrence of cocaine in human saliva and urine after chronic use. *J Anal Toxicol*. 1989;13:65–68.
15. Oyler JM, Cone EJ, Joseph RE Jr, et al. Duration of detectable methamphetamine and amphetamine excretion in urine after controlled oral administration of methamphetamine to humans. *Clin Chem*. 2002;48:1703–1714.
16. Oyler J, Darwin WD, Preston KL, et al. Cocaine disposition in meconium from newborns of cocaine-abusing mothers and urine of adult drug users. *J Anal Toxicol*. 1996;20:453–462.
17. Ballantyne B, Marrs TC, Syversen T. *General and Applied Toxicology*. New York: Grove's Dictionaries, 1999:332.
18. Elliott JS, Shart RF, Lewis L. Urinary pH. *J Urol*. 1959;81:339–343.
19. SAMHSA's Workplace Resource Center. Urine Specimen Validity Testing: Evaluation of the Scientific Data Used to Define Specimen as Substituted. *http://workplace.samhsa.gov/ResourceCenter/r381.htm.* Accessed 2004.
20. Beckett AH, Rowland M. Urinary excretion kinetics of amphetamine in man. *J Pharm Pharmacol*. 1965;17:628–638.
21. Shargel L, Yu A. eds. *Applied Biopharmaceutics & Pharmacokinetics*. Stamford, CT: Appleton & Lange, 1999:326–328.
22. Comer SD, Hart CL, Ward AS, et al. Effects of repeated oral methamphetamine administration in humans. *Psychopharmacology (Berl)*. 2001; 155:397–404.