The bioavailability of intranasal and smoked methamphetamine

Background: **Patients in harm-reduction treatment programs are switching from intravenous to other routes of methamphetamine (INN, metamfetamine) administration to avoid risks associated with needle use. Relatively little has been reported about the bioavailability of methamphetamine when smoked or used intranasally.**

Methods: **Eight experienced methamphetamine users were administered smoked or intranasal methamphetamine concurrently with an intravenous dose of deuterium-labeled methamphetamine. Plasma and urine concentrations were measured for calculation of bioavailability and other pharmacokinetic parameters by noncompartmental methods.**

Results: **Methamphetamine was well absorbed after smoking or intranasal administration, with bioavailabilities of 79% after intranasal administration and 67% of the estimated delivered dose or 37.4% of the absolute (pipe) dose after smoking. Maximum methamphetamine concentrations occurred at 2.7 and 2.5 hours after intranasal and smoked doses. The elimination half-life was similar for intravenous (11.4 hours), intranasal (10.7 hours), and smoked (10.7 hours) methamphetamine. Clearance (272 mL · h^{-1} · kg^{-1}), steady-state volume of distribution (4.2 L/kg), and mean residence time (16 hours) of the intravenous dose were similar to previously reported values. Dextroamphetamine (INN, dexamfetamine) half-life (all routes) was 16.2 hours. Methamphetamine and dextroamphetamine renal clearances (all routes) were about 100 and 1100 mL · h^{-1} · kg^{-1}, respectively.**

Conclusions: **Intranasal and smoked methamphetamine are well absorbed. Although intranasal or smoked routes may decrease the risk of transmission of blood-borne diseases, exposure to methamphetamine and the possibility of drug-related complications remain substantial. (Clin Pharmacol Ther 2003;74:475-86.)**

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Despite extensive illicit use[1-3] and risk-reduction programs suggesting that injection users switch to other routes of administration,[4] relatively little is known about the bioavailability of methamphetamine (INN, metamfetamine) when taken by intranasal or smoked routes. Case reports of toxic effects of intranasal[5-12] or smoked[13-16] methamphetamine have appeared. Smoked methamphetamine is widely abused,[17-19] but only one laboratory has characterized its pharmacokinetics.[20-22] Only one report has characterized the bioavailability of smoked methamphetamine.[21] Relatively little has been reported on the pharmacokinetics of intranasal methamphetamine, although case reports of adverse consequences have been published.[5,6,8-12] Methamphetamine sniffing or oral ingestion may lead to dependence as readily as intravenous use.[23] The increased popularity of methamphetamine smoking suggests that it has a high abuse liability as well.

In our experiment we used deuterium-labeled methamphetamine to enable simultaneous administration of labeled methamphetamine by the intravenous route and unlabeled methamphetamine by other routes for precise determination of bioavailability. Use of unlabeled and

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This work was supported by US Public Health Service grants DA12393 and DA00053 and contract No. N01DA-4-8306 awarded by the National Institute on Drug Abuse, National Institutes of Health, and carried out in part in the General Clinical Research Center at the University of California, San Francisco, with support of the Division of Research Resources, National Institutes of Health (grant 5 M01 RR-00079).

Received for publication April 28, 2003; accepted Aug 6, 2003.

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0009-9236/2003/$30.00 + 0

doi:10.1016/j.clpt.2003.08.002

labeled drug administered simultaneously eliminates the problems of day-to-day variability inherent when the drug is administered on separate days.[24] Deuterium labeling has been used to measure changes in pharmacokinetics[25] and pharmacodynamics[26] during repeated oral dosing of methamphetamine, but we are unaware of its use in the determination of methamphetamine absolute bioavailability. Before this bioavailability experiment, we compared the plasma levels of 5 mg of deuterium-labeled methamphetamine and 5 mg of nonlabeled methamphetamine after intravenous administration in 4 subjects. The plasma concentration–time curves were identical, indicating that deuterium labeling does not change the pharmacokinetics of methamphetamine. Given that the systemic intravenous dose is known and the clearance of both the labeled and nonlabeled methamphetamine is the same, we were able to calculate the bioavailability of the unknown smoked and intranasal systemic doses by using their respective area under the plasma concentration–time curves (AUCs) for calculation of dose (Dose = CL · AUC, in which *CL* is clearance).

METHODS

General design

Subjects were hospitalized at the General Clinical Research Center, University of California, San Francisco (San Francisco, Calif), on 2 occasions approximately 1 week apart. Subjects arrived the day before drug administration and remained as inpatients for 48 hours after dosing. With a terminal half-life for smoked and intravenous methamphetamine of about 12 hours,[21,27] 48 hours allowed collection of data while more than 90% of the drug was eliminated. Subjects were given either intranasal or smoked methamphetamine in a balanced crossover design along with a simultaneous intravenous dose of deuterated methamphetamine to calculate absolute bioavailability. They were discharged 48 hours after dosing and returned at 72 hours with the 48- to 72-hour urine collection and for other post–72-hour measures.

Subjects

Eight male nondependent methamphetamine users (according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) were recruited by newspaper advertisement or referral from previous subjects. All gave informed consent. Subjects were aged between 21 and 45 years and were within 30% of ideal body weight. Female users were welcome, but few called and none entered the study. Medical history, physical examination, complete blood cell count, blood chemical analysis, hepatitis C serologic result, and electrocardiogram excluded those with significant physical and psychiatric illness. The study was approved by the Committee on Human Research (institutional review board), University of California, San Francisco.

Subjects had infrequent to moderate recent experience with methamphetamine (at least once in the previous 6 months) and were experienced with the intranasal, smoked, or intravenous route. None were exclusive oral methamphetamine users. All were tobacco smokers and used caffeine. They infrequently used other illicit drugs.

Synthesis of deuterated methamphetamine

S−(+)-[$^2H_3$]amphetamine was synthesized by a published method[28] and converted to S–(+)-[$^2H_3$]methamphetamine by formation of the *N*-formyl derivative and reduction with lithium aluminum hydride. The results demonstrated both chemical and enantiomeric purity. The deuterium label incorporation was calculated to be 99.1% [$^2H_3$]methamphetamine and 0.9% [$^2H_2$]methamphetamine. Acceptance criteria for drug identification were that the analyte had to extract from the biofluid, back-extract into acid and re-extract as the authentic substance, derivatize as the authentic analyte, exhibit the same retention time in capillary gas chromatography, ionize by isobutane chemical ionization–mass spectrometry, and yield the same ion as the ion used for quantitation.

Study procedures

Subjects were asked to abstain from drug and alcohol use, except for nicotine and caffeine, for 48 hours before hospital admission. On admission, subjects provided a urine sample for urine toxicology screening and urinalysis and a blood sample for general admission laboratory screening tests. An electrocardiogram was obtained, and subjects were asked about recent drug use. If no signs of medical illness or recent drug use were found, they proceeded with the study.

Intranasal dextromethamphetamine, 50 mg (base equivalent), as a 10% solution of the hydrochloride salt in isotonic sodium chloride solution was delivered as a fine mist to the nasopharynx by use of two 0.25-mL Accuspray syringes (Becton Dickinson Pharmaceutical Systems, Franklin Lakes, NJ). On the basis of an estimated bioavailability of at least 30%, a dose of 50 mg was chosen, because a 15-mg intravenous dose was the lowest dose of methamphetamine that could be reliably subjectively distinguished from placebo in our laboratory. This nasal dose was expected to produce subjec-

tive effects but would still be within a safe range if a higher bioavailability resulted.

The 40 mg of smoked dextromethamphetamine (base equivalent) was delivered with 2 doses smoked 10 minutes apart so that dosing could be terminated if subjects showed greater than expected sensitivity to the first dose. Each smoked dose consisted of 2 deep, untimed inhalations from a borosilicate glass pipe (fabricated from a 20-mL scintillation vial [Fisher brand; Fisher Scientific International Inc, Hampton, NH]) containing 20 mg of methamphetamine with 7 inches of glass tubing attached. The pipe was temperature-controlled by placing it in a snugly fitted well drilled in a 17-lb aluminum brick electrically heated to 265°C ± 10°C. The large thermal mass of the brick approximated the oil bath used in the experiment of Cook et al.[21] This temperature was chosen as sufficient to produce vaporization but low enough to minimize pyrolysis.[20] The delivered dose was calculated from the difference between the weight of the pipe before and after smoking. The dose contained in the pipe was based on (1) the intravenous 15-mg minimum dose required for subjective data, (2) the estimated bioavailability through the smoked route (about 90% according to a previous report[21]), and (3) an estimate of the delivered dose of about one half the pipe dose.[21] We thought this dose would produce measurable subjective effects but was within a safe dosage range if an unexpectedly higher bioavailability was present. A 10-mg dose of d-methamphetamine-d_3 (in which d_3 indicates deuterated) was infused at a constant rate intravenously for 15 minutes while the intranasal or smoked doses were administered. Vital signs and psychiatric status were monitored for several hours after drug administration.

Plasma samples for methamphetamine and d-amphetamine assay were obtained at 5 minutes before infusion and at 10, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, and 72 hours after the start of the methamphetamine infusion. Plasma samples were stored at −20°C until assayed.

After methamphetamine dosing, urine was collected in fractions from 0 to 4 hours, 4 to 24 hours, 24 to 48 hours, and 48 to 72 hours (with the last period sample collected on an outpatient basis). A 0- to 24-hour sample was constructed by pooling urine remaining after removal of two 20-mL aliquots from each timed specimen for measurement of pH and then frozen at −70°C until analyzed.

Physiologic measures. Heart rate and blood pressure were measured with a cardiovascular monitor (Escort II, Model 20300; Medical Data Electronics, Arleta, Calif). Rate-pressure product, an index of myocardial oxygen consumption and cardiac work, was calculated as the product of systolic blood pressure and heart rate. Respiratory rate was measured by counting the number of inhalations per minute.

Physiologic measures were obtained before dosing, continuously during the infusion (recorded at 10 minutes and 15 minutes after the beginning of dosing for statistical purposes), every 15 minutes until 1 hour after dosing, and at 1.5, 2, 3, 4, 5, 6, 8 12, 18, 24, 36, and 48 hours. Heart rate and blood pressure were always obtained with the subject recumbent for at least 5 minutes.

Subjective measures. Verbally rated measures on a scale of methamphetamine intoxication and craving for methamphetamine ranging from 0 to 100 were obtained with each physiologic measurement. Visual analog scales, administered with a handheld computer and obtained with each vital sign measurement, were good drug effect, bad drug effect, desire for methamphetamine, and methamphetamine quality. These 100-mm scales were labeled with 0 indicating "none" and 100 indicating "most ever."

Assays. Plasma and urine deuterated and nondeuterated d-methamphetamine and d-amphetamine were analyzed in our laboratory by methods developed there.[29] The methods allow simultaneous determination of methamphetamine and amphetamine (INN, amfetamine) and its deuterium-labeled analogs (methamphetamine-d_3 and amphetamine-d_3) by use of combined gas chromatography–mass spectrometry. Stable isotope–labeled analogs used as internal standards are easily distinguished from both unlabeled methamphetamine and methamphetamine-d_3. This method has sensitivity, precision, and accuracy suitable for measuring pharmacokinetic parameters in human studies. To determine interday precision and accuracy, we carried out 13 different runs, with duplicate quality-control samples at each of 5 concentrations. For intraday precision and accuracy data, we analyzed a run consisting of a full complement of 9 calibration standards, along with 10 replicates of each quality-control plasma concentration. The acceptance criterion was that the calculated average concentration should be within 15% of the spiked value.

For plasma, intraday precision and accuracy for methamphetamine-d_0 and methamphetamine-d_3 ranged from 4.3% coefficient of variation (CV) and 93.5% accuracy at 1 ng/mL to 2.4% CV and 102.3% accuracy at 250 ng/mL. Interday precision and accuracy for methamphetamine-d_0 and methamphetamine-d_3 ranged from 13.5% CV and 104.9% accuracy at 1 ng/mL to 3.5% CV and 98.5% accuracy at 250 ng/mL. Intraday precision and accuracy for amphetamine-d_0 and

amphetamine-d_3 ranged from 5.9% CV and 97.3% accuracy at 0.5 ng/mL to 2.5% CV and 99.5% accuracy at 25 ng/mL. Interday precision and accuracy for amphetamine-d_0 and amphetamine-d_3 ranged from 8.6% CV and 99.5% accuracy at 0.5 ng/mL to 4.9% CV and 97.6% accuracy at 25 ng/mL.

For urine, intraday precision and accuracy for methamphetamine-d_0 and methamphetamine-d_3 ranged from 4.4% CV and 108.3% accuracy at 10 ng/mL to 3.8% CV and 105.2% accuracy at 10,000 ng/mL. Interday precision and accuracy for methamphetamine-d_0 and methamphetamine-d_3 ranged from 11.7% CV and 100.2% accuracy at 10 ng/mL to 1.0% CV and 99.7% accuracy at 250 ng/mL. The limit of quantitation for methamphetamine-d_0 and methamphetamine-d_3 was 10 ng/mL. Intraday precision and accuracy for amphetamine-d_0 and amphetamine-d_3 ranged from 10.8% CV and 109.6% accuracy at 1 ng/mL to 2.4% CV and 102.4% accuracy at 1000 ng/mL. Interday precision and accuracy for amphetamine-d_0 and amphetamine-d_3 ranged from 13.8% CV and 95.6% accuracy at 1 ng/mL to 1.6% CV and 100.4% accuracy at 1000 ng/mL. The limit of quantitation for amphetamine-d_0 and amphetamine-d_3 was 1 ng/mL.

Pharmacokinetic analysis

Methamphetamine and amphetamine plasma concentration–time data were analyzed by noncompartmental methods,[30] with the program WinNonlin, version 3.0 (Pharsight Corp, Mountain View, Calif). Except for predose samples, sample concentrations less than the lower limit of quantitation were treated as missing data points and were not used in the analysis. Maximum plasma concentration (C_{max}) and peak time to maximum plasma concentration (t_{max}) were calculated with a computerized WinNonlin algorithm and confirmed by visual inspection. AUCs were calculated by use of the linear trapezoidal rule up to the maximum concentration and thereafter by use of the logarithmic trapezoidal rule.[31] AUC was calculated to the last measurable plasma concentration [AUC(0-t_{last}), in which t_{last} was the time of the last measurable concentration]. The remaining area was extrapolated to infinity by dividing the last measurable concentration by the terminal exponential rate constant (λ_z). Summing these 2 segmented areas yielded the AUC profile from time 0 to infinity [AUC(0-∞)]. Terminal exponential half-life ($t_{1/2}$) and λ_z values were calculated from log-linear regression of terminal phase data points [$t_{1/2} = (\ln[2])/\lambda z$], in which the terminal phase was determined from visual inspection of the plasma concentration–time profiles. Clearance (CL), terminal exponential volume of distribution (V_z), steady-state volume of distribution (V_{ss}), and mean residence time (MRT) values were calculated by use of standard mathematic relationships.[30] The MRT was calculated by an equation compensating for the 15-minute time period during which the deuterated methamphetamine was intravenously infused.

Visual inspection of the plasma and urinary excretion data for both methamphetamine and amphetamine indicated that renal clearance (CL_r) could best be calculated by using only the 0- to 24-hour data. Consequently, renal clearance was calculated from the following relationship: Urine amount from 0 to 24 hours/AUC from 0 to 24 hours. The fraction of methamphetamine eliminated by renal excretion was calculated as renal clearance (CL_r)/CL.

Absolute methamphetamine bioavailability (F) from the nasal and smoked routes was calculated from the following equation, with the use of plasma data[30]: F = [Intravenous CL × Extravascular AUC(0-∞)]/Extravascular dose.

Statistical analysis

Data were analyzed by repeated-measures ANOVA. Treatment conditions (smoked or intranasal methamphetamine) and observation times (hours after dosing) were considered within-subject factors. Change scores (postdose minus predose values) were used in the analysis. After a significant F test, pairwise comparisons were performed by use of least squares means analysis. Effects were considered statistically significant at $P = .05$. Data were adjusted for sphericity by use of the Huynh-Feldt adjustment factor. Huynh-Feldt–corrected significance values are reported.

RESULTS

Comparison of deuterated versus nondeuterated methamphetamine plasma levels

Before this experiment, 4 male subjects with a mean (±SD) age of 34 ± 9 years were given 10 mg of a 50/50 mixture of deuterium-labeled and nonlabeled d-methamphetamine intravenously for 15 minutes by infusion pump. There was no significant difference between deuterated and nonlabeled plasma concentrations over time (Fig 1).

Subjects

Eight male subjects completed the study. Their mean age was 40 years (range, 31-45 years). Self-reported ethnicity was as follows: 1 black, 1 Hispanic, 4 non-Hispanic white, and 2 mixed (Hispanic and non-Hispanic white). Average methamphetamine use

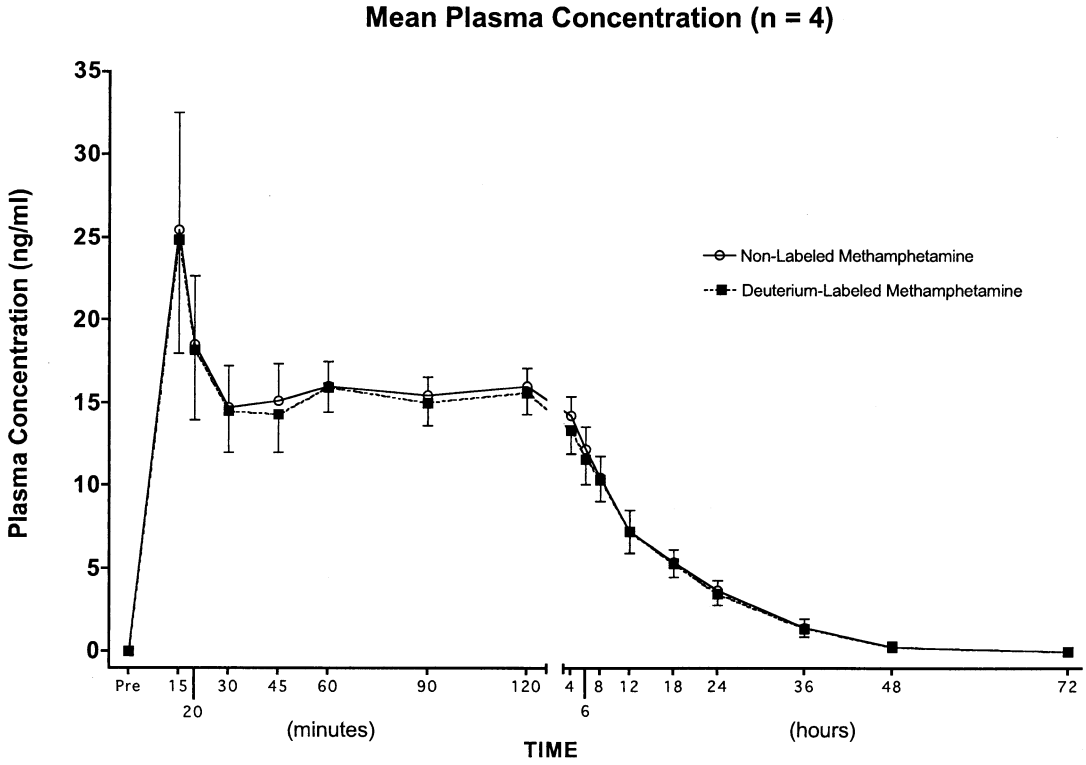

Fig 1. Mean plasma concentrations after 5 mg deuterium-labeled methamphetamine and 5 mg nonlabeled methamphetamine in preliminary study (n = 4).

ranged from 3 times a week to 3 times a year. All subjects had had experience using methamphetamine with all 3 routes except for one, who had no intravenous experience.

Pharmacokinetic measures

The mean pharmacokinetic parameters for methamphetamine and amphetamine are shown in Tables I through VI and Fig 2. Intranasal or smoked administration resulted in similar $t_{1/2}$, V_{ss}, and CL. However, with 1 outlier excluded, t_{max} occurred earlier with the smoked route ($P < .03$). The fraction of methamphetamine excreted in the urine varied considerably, from about 10% to 90%. Calculated methamphetamine renal clearance was about 10% of that for amphetamine. If we assume that (1) methamphetamine is completely metabolized by the liver, (2) availability to the liver is unity, (3) the blood-to-plasma concentration ratio is unity, (4) linear kinetics prevail, and (5) hepatic blood flow is 25 mL $\cdot$ min^{-1} $\cdot$ kg^{-1}, the hepatic extraction ratio was approximately 19%.

Subjects were able to extract a mean ($\pm$SD) dose of 22.2 $\pm$ 8.4 mg methamphetamine from the 40 mg in the 2 pipes. However, this ranged from 11.3 to 36.4 mg (28%-91%) extracted. Mean absolute bioavailability of intranasal methamphetamine was approximately four fifths (79%). Smoked bioavailability was one third (37%) based on the dose loaded into the pipe (40 mg) and two thirds (67%) based on the estimated delivered dose after correction for drug remaining in the delivery system after smoking (mean, 22.2 mg). Bioavailability was significantly higher ($P < .02$) for the intranasal route than for the smoked route based on the original doses but was not statistically significantly different based on the estimated delivered dose ($P < .1$).

Pharmacodynamic measures

Meaningful comparisons of drug effects between routes and description of intensity and course of effects were confounded by the intravenous dose and by unequal delivered doses between routes. Adjusted for bioavailability, the mean intranasal dose was approximately 40 mg (79% of 50 mg) and the smoked dose was approximately 15 mg (bioavailability of 37% $\times$ 40-mg dose). Therefore the intravenous dose of 10 mg turned out to be a substantial proportion of the total doses

Table I. Methamphetamine-d_3 plasma pharmacokinetic parameters after 10 mg deuterated methamphetamine administered intravenously by constant-rate intravenous infusion (15 minutes)

Concomitant dosing	C_{max} *(ng/mL)*	t_{max} *(h)*	$AUC(0\text{-}t_{last})$ *(ng · h/mL)*	$AUC(0\text{-}\infty)$ *(ng · h/mL)*	AUC_{ext} *(%)*
With 50 mg intranasal methamphetamine-d_0	37.7 ± 15.0	3.55 ± 8.27	491 ± 194	523 ± 206	6.20 ± 2.13
With 40 mg smoked methamphetamine-d_0	41.2 ± 16.9	1.00 ± 0.641	478 ± 150	514 ± 169	6.49 ± 2.21

Data are presented as mean ± SD.
C_{max}, Maximum plasma concentration; t_{max}, time of C_{max}; AUC(0-t_{last}), area under plasma concentration–time curve from time 0 until time of last measurable plasma concentration; AUC(0-∞), area under plasma concentration–time curve from time 0 to infinity; AUC_{ext}, extrapolated area from time of last measurable plasma concentration to infinity (expressed as a percent), λ_z, terminal exponential rate constant; $t_{1/2}$, terminal exponential half-life; CL, clearance; V_z, terminal exponential volume of distribution; V_{ss}, steady-state volume of distribution; MRT, mean residence time.

Table II. Methamphetamine-d_0 plasma pharmacokinetic parameters after methamphetamine-d_0 administered intranasally or smoked (simultaneously with 10 mg intravenous deuterated methamphetamine by constant-rate intravenous infusion over 15 minutes)

Route	C_{max} *(ng/mL)*	t_{max} *(h)*	$AUC(0\text{-}t_{last})$ *(ng · h/mL)*	$AUC(0\text{-}\infty)$ *(ng · h/mL)*
Intranasal 50 mg	113 ± 23.1	2.66 ± 1.16	1950 ± 576	2000 ± 599
Smoked 40 mg	50.9 ± 24.7	2.47 ± 3.91	775 ± 522	801 ± 526

Data are presented as mean ± SD.
F, Absolute bioavailability (expressed as a percent).

Table III. Amphetamine-d_3 plasma pharmacokinetic parameters after 10 mg deuterated methamphetamine administered intravenously by constant-rate intravenous infusion (15 minutes)

Concomitant dosing	C_{max} *(ng/mL)*	t_{max} *(h)*	$AUC(0\text{-}t_{last})$ *(ng · h/mL)*	$AUC(0\text{-}\infty)$ *(ng · h/mL)*
Intranasal 50 mg	1.85 ± 0.50	18.8 ± 5.95	63.1 ± 22.2	73.8 ± 17.8
Smoked 40 mg	2.00 ± 0.874	16.8 ± 5.75	66.8 ± 35.2	80.0 ± 34.0

Data are presented as mean ± SD.

Table IV. Amphetamine-d_0 plasma pharmacokinetic parameters after methamphetamine administered intranasally or smoked (simultaneously with 10 mg intravenous deuterated methamphetamine by constant-rate intravenous infusion over 15 minutes)

Route	C_{max} *(ng/mL)*	t_{max} *(h)*	$AUC(0\text{-}t_{last})$ *(ng · h/mL)*	$AUC(0\text{-}\infty)$ *(ng · h/mL)*
Intranasal 50 mg	9.12 ± 2.39	17.3 ± 5.95	344 ± 102	371 ± 104
Smoked 40 mg	3.71 ± 2.88	15.3 ± 5.12	129 ± 115	148 ± 122

Data are presented as mean ± SD.

(about one fifth [10/50 mg] to two fifths [10/25 mg]). In addition, the absorbed intranasal dose was about twice the delivered smoked dose. Perhaps not surprisingly, there were no significant differences in physiologic and subjective effects between conditions (intranasal versus smoked).

The time course of several subjective effects is shown in Fig 3. The reported intoxication levels of about one half of the "most ever" used are consistent with the level produced by the amount typically used outside the laboratory based on patient reports. Intranasally administered methamphetamine produced a mean (±SD) increase in systolic blood pressure from a baseline of 121 ± 10 mm Hg to a peak of 141 ± 13 mm Hg, in diastolic blood pressure from 76 ± 7 mm Hg to 86 ± 7 mm Hg, and in heart rate from 73 ± 9 beats/min

λ_z (L/h)	$t_{1/2}$ (h)	CL (mL · h^{-1} · kg^{-1})	V_z (L/kg)	V_{ss} (L/kg)	MRT (h)
0.0628 ± 0.0158	11.8 ± 3.59	272 ± 73.3	4.38 ± 0.948	4.30 ± 0.930)	16.6 ± 4.34
0.0661 ± 0.0159	11.0 ± 2.68	271 ± 70.8	4.12 ± 0.641	4.02 ± 0.607	15.5 ± 3.55

AUC_{ext} (%)	λ_z (L/h)	$t_{1/2}$ (h)	F
2.72 ± 1.09	0.0672 ± 0.0134	10.7 ± 2.39	79.4 ± 13.1
3.89 ± 2.30	0.0676 ± 0.0146	10.7 ± 2.11	37.4 ± 14.2

AUC_{ext} (%)	λ_z (L/h)	$t_{1/2}$ (h)	Plasma AUC(0-∞) ratio: Amphetamine/methamphetamine (%)
16.3 ± 15.2	0.0479 ± 0.0153	16.2 ± 6.35	15.5 ± 5.79
18.8 ± 15.3	0.0437 ± 0.0125	16.9 ± 4.37	16.1 ± 5.55

AUC_{ext} (%)	λ_z (L/h)	$t_{1/2}$ (h)	Plasma AUC(0-∞) ratio: Amphetamine/methamphetamine (%)
7.63 ± 6.65	0.0509 ± 0.0150	15.2 ± 6.42	19.3 ± 6.01
14.3 ± 8.78	0.0460 ± 0.0148	16.3 ± 4.45	17.8 ± 6.23

to 94 ± 13 beats/min. Smoked methamphetamine produced a mean (±SD) increase in systolic blood pressure from 121 ± 10 mm Hg to a peak of 137 ± 11 mm Hg, in diastolic blood pressure from 73 ± 10 mm Hg to 83 ± 8 mm Hg, and in heart rate from 76 ± 10 beats/min to 106 ± 19 beats/min.

DISCUSSION

Deuterium labeling allowed simultaneous administration of a known systemic dose of deuterated intravenous drug along with unlabeled intranasal or smoked methamphetamine to facilitate calculation of absolute bioavailability. In addition, simultaneous administra-

Table V. Ratio of amphetamine to methamphetamine renal clearance values determined from data from 0 to 24 hours

	Amphetamine CL_r ($mL \cdot h^{-1} \cdot kg^{-1}$)	*Methamphetamine CL_r ($mL \cdot h^{-1} \cdot kg^{-1}$)*	*Amphetamine/ methamphetamine CL_r ratio*
IV with nasal	1240 ± 825	97.4 ± 51.9	13.0 ± 6.19
IV with smoked	1270 ± 1030	94.4 ± 53.7	12.3 ± 4.72
Nasal	957 ± 586	102 ± 55.1	9.75 ± 3.83
Smoked	1120 ± 907	98.9 ± 55.9	10.5 ± 3.59

Data are presented as mean ± SD.
CL_r, Renal clearance; IV, intravenous.

Table VI. Methamphetamine percent of dose excreted in urine and related parameters

Route of administration	*Amount in urine from 0 to 24 h (ng)*	*AUC(0–24) ($ng \cdot h/mL$)*	*CL_r ($mL \cdot h^{-1} \cdot kg^{-1}$)*	*CL ($mL \cdot h^{-1} \cdot kg^{-1}$)*	*Percent dose excreted in urine (CL_r/CL)*
IV nasal	2,700,000 ± 1,250,000	380 ± 89.5	97.4 ± 52	284 ± 59.0	36.4 ± 18.4
IV smoked	2,740,000 ± 1,420,000	396 ± 95.1	94.4 ± 53.7	271 ± 70.8	34.4 ± 17.0
Nasal	11,300,000 ± 5,770,000	1,510 ± 306	102 ± 55.1	284 ± 59.0*	39.3 ± 24.5
Smoked	3,840,000 ± 1,920,000	613 ± 362	98.9 ± 55.9	271 ± 70.8*	36.0 ± 17.7

Data are presented as mean ± SD.
AUC(0-24), Area under plasma concentration–time curve from 0 to 24 hours.
*Intravenous CL used.

tion in pharmacokinetic experiments eliminates inconsistent effects produced by unknown factors on different days. However, a disadvantage is that it is complicated to interpret physiologic and subjective data from simultaneous administration if the intravenous dose makes up a substantial portion of the total dose, because pharmacodynamic effects cannot be separated by deuterium labeling. In retrospect, we should have used a much lower traced dose for the intravenous dose.

This is the first report of the bioavailability of intranasal methamphetamine. Methamphetamine was readily available (mean, 79%). This information may be of interest to patients, health care providers, and toxicologists.

Smoked methamphetamine had mean bioavailability values based on delivered dose of 67% and 37% when calculated on the basis of total pipe dose. The bioavailability of the delivered dose was less than that reported by Cook et al,[21] who found a bioavailability of 90% with a similar delivered dose. It is possible that the higher pipe temperature (approximately 300°C) or slightly different smoking technique used in that study enhanced absorption. It is likely that experienced pipe users might be able to increase the dose delivered, although, with the common method of holding the pipe over a flame, variable and indeterminate loss to pyrolysis is likely. Nevertheless, most users would likely get a pipe dose bioavailability of between 37% and 67%, perhaps in the higher part of that range with good smoking and heating technique, because they would not be limited to 2 puffs per pipe and could better experiment with smoking techniques to optimize delivery. Depending on the actual amount of drug delivered by smoking, this might still be significantly less than the amount available from insufflation according to our findings (although results from the study by Cook et al suggest that smoking could deliver more). However, drug-dependent persons are less concerned with plasma levels than they are with obtaining the initial intoxication effects ("rush") that are commonly reported as more prominent with the smoked route than with snorting.[32] Patients who have switched to intranasal use because of concern about the health risks of the intravenous and smoked routes or for other reasons are likely to be less concerned with differences in bioavailability, because methamphetamine is relatively inexpensive and dosage adjustments are easy.

Harm reduction encompasses a wide variety of approaches to decreasing risk associated with drug use.[4] One potential impact of these findings in the treatment planning of patients in harm-reduction programs would

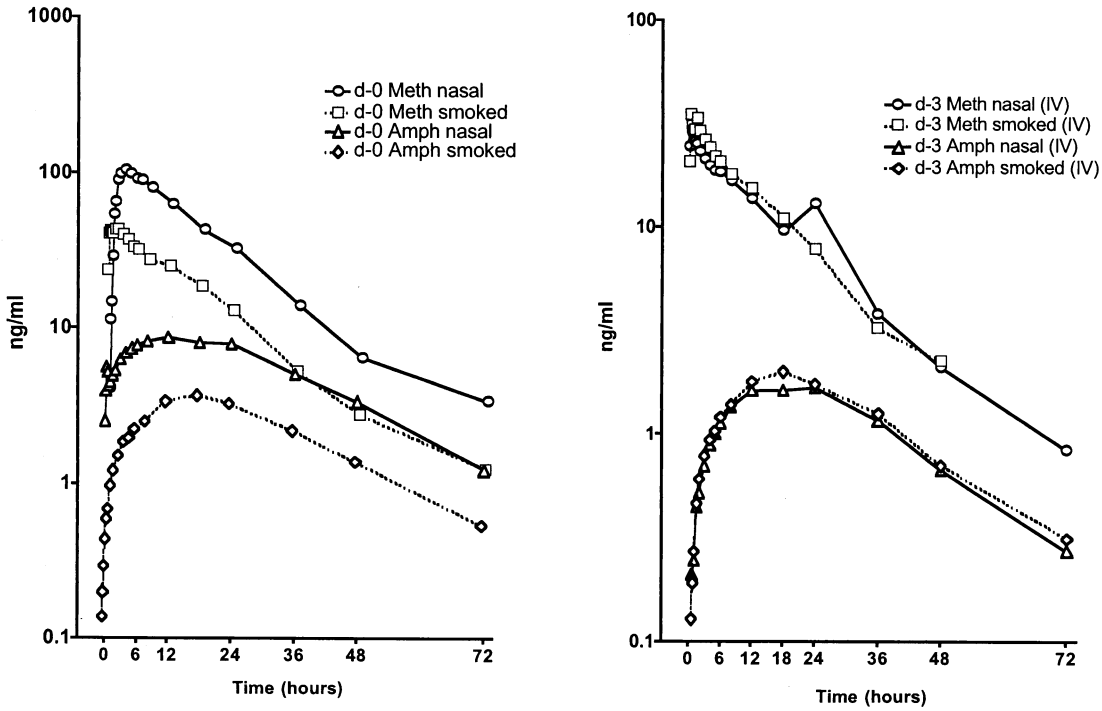

Fig 2. Mean methamphetamine and amphetamine plasma concentrations (n = 8). d-0, From smoked or intranasal methamphetamine; d-3, from intravenously (IV) administered methamphetamine. *Error bars* represent SE.

be that education about the bioavailabilities of other routes might help with risk assessment. Some patients might be under the impression that, because the rush or high from snorting is less than that from the intravenous or smoking routes, they are really using a much smaller dose. However, after snorting, sustained plasma levels only slightly lower than the level from intravenous use (79%) would likely produce longer-term problems almost as severe as would the same amount injected. Knowledge of intranasal bioavailability would help to more accurately assess risk.

Several pharmacokinetic parameters for smoked and intravenous methamphetamine were similar to those reported by Cook et al.[21] The mean AUC(0-∞) in our study was about 20% less than that of Cook et al, consistent with their greater bioavailability finding. Amphetamine excreted in the urine in their study was approximately 15% to 20% that of methamphetamine on a molar basis, similar to the uncorrected ratio of the AUCs in our study. Renal clearance of amphetamine, in contrast, was about 10 times that of methamphetamine. Because methamphetamine renal clearance decreases with dose[25] and the ratio of plasma concentrations of amphetamine to methamphetamine increases over time, this ratio might also vary depending on the methamphetamine dose or the period of urine collection. The fraction of methamphetamine excreted in the urine and the ratio of amphetamine to methamphetamine renal clearance fluctuated considerably. This may be in part because we did not control for urine pH because of infrequent measurement and its instability. Urine pH has been shown to be correlated with and to greatly influence renal excretion of methamphetamine.[25,33]

Our subjective effects data suggest that the methamphetamine doses administered in this study were in the range of doses used outside of a laboratory setting. Mean subjective "high" (approximately 50) for the smoked dose in our study was slightly higher than that reported by Perez-Reyes et al[22] (approximately 35), as might be expected with our concurrent administration of the intravenous dose. In our study and that of Perez-Reyes et al, significant increases in blood pressure and heart rate followed methamphetamine. We included no placebo condition, so subject expectations may have influenced subjective responses. Because the intravenous dose contributed a significant proportion of the total doses for both intranasal and smoked methamphetamine conditions, the intravenous dose confounds de-

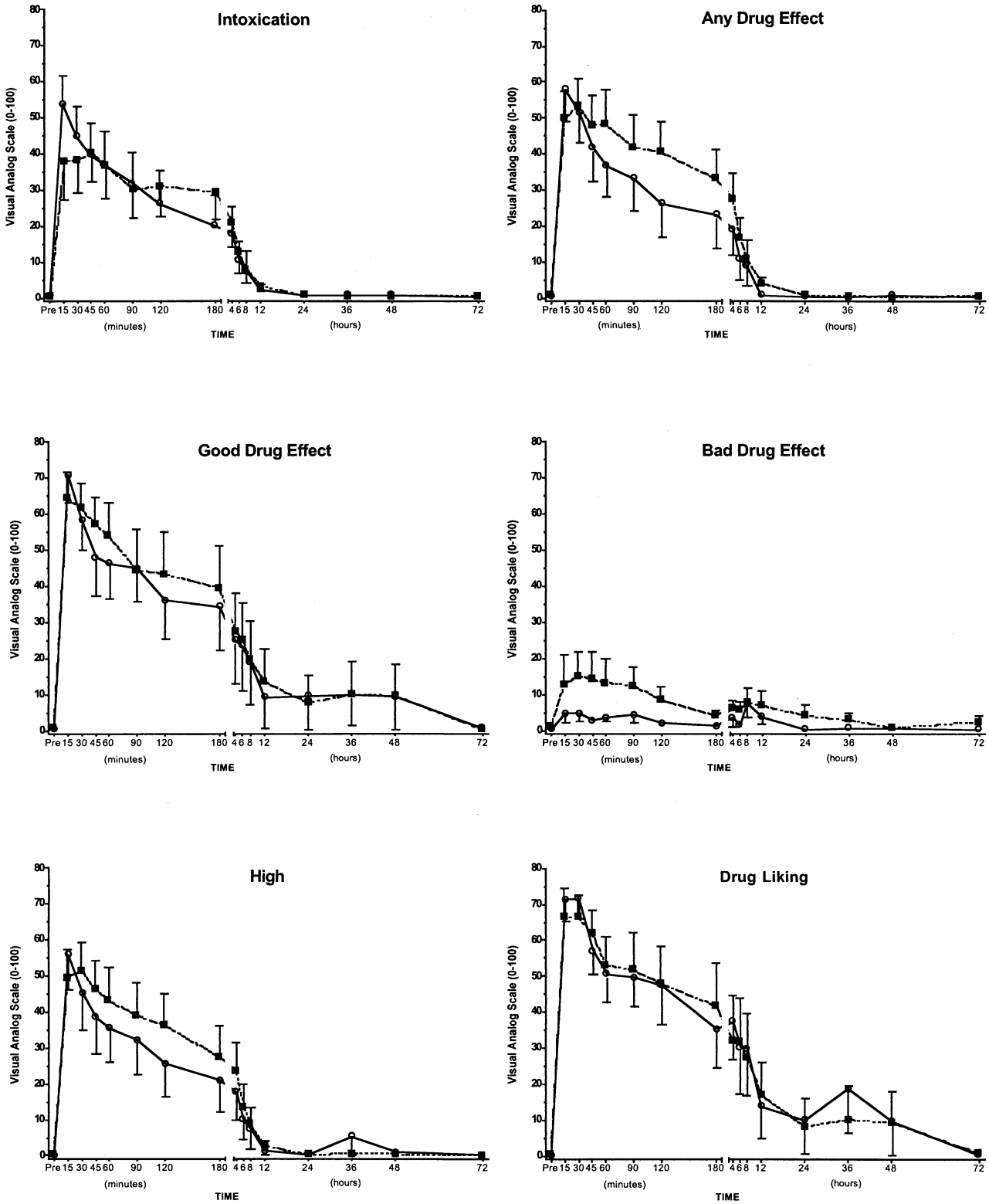

Fig 3. Mean subjective effects (n = 8) of 40 mg smoked methamphetamine or 50 mg intranasal methamphetamine (with 10 mg intravenous methamphetamine) as measured by visual analog scales (range, 0-100). *Circles*, Smoked methamphetamine; *squares*, intranasal methamphetamine. *Error bars* represent SE.

scriptions of the physiologic and subjective effects comparisons in the 2 conditions. In addition, the different doses were delivered by the 2 routes. The absence of significant differences in pharmacodynamic effects between conditions suggests the total doses administered may have been roughly equivalent or that both conditions had reached a dose threshold for the expression of most physiologic and subjective effects. However, caution is appropriate when one interprets comparisons in pharmacodynamic data between administration routes in this study because of the confounding factors of unequal doses and the concurrent intravenous dose.

In conclusion, a substantial proportion of methamphetamine is available from smoked (67%) or intranasal (79%) administration. This information may be useful in risk assessment and planning treatment strategies for those who have changed the route of use but have not stopped using methamphetamine.

We thank Nora Chiang, PhD, National Institute on Drug Abuse Medication Development Division Project Officer; Scott Fields, PharmD, University of California, San Francisco, investigational pharmacist; Tina Melby, Emilio Fernandez, Rajneesh Nath, Catherine Chin, Ellen Herbst, Boris Heifets, and the staff of the General Clinical Research Center at the University of California, San Francisco, for assistance in conducting the study; and Kaye Welch for administrative and editorial assistance.

The authors have no financial or personal relationships that could be perceived as influencing the described research.

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