Formal Written Submission to the U.S. Sentencing Commission

Re: Sentencing Guidelines for Offenses Involving Methamphetamine

Submitted by: John Mendelson, M.D., Chief Medical Officer, Ria Health, San Francisco, CA

Date: July 28, 2025

Introduction

Thank you for the opportunity to submit this formal testimony in support of the development of evidence-based federal sentencing guidelines for offenses involving methamphetamine possession and distribution. I am a Board-certified Internal Medicine physician with clinical and research expertise in the pharmacological effects and health risks of substances of abuse, including methamphetamine. I have conducted and published NIH-funded clinical trials involving the controlled administration of methamphetamine to human subjects with methamphetamine use disorder.

My research focuses on the pharmacokinetics, pharmacodynamics, and abuse potential of methamphetamine under varying dosing conditions and chemical compositions. These findings have direct relevance to the proportionality and scientific grounding of sentencing guidelines related to methamphetamine offenses.

Methamphetamine and Its Isomers

Methamphetamine is a potent central nervous system stimulant belonging to the phenethylamine class. It exists as two enantiomers: **dextro-methamphetamine (d-methamphetamine)** and **levo-methamphetamine (l-methamphetamine)**. These stereoisomers are mirror images but differ significantly in their physiological and psychological effects.

- **D-methamphetamine** is highly reinforcing and euphorigenic, and it induces substantial cardiovascular stimulation. It is the primary isomer involved in recreational abuse and is classified as a Schedule II controlled substance under the Controlled Substances Act.
- **L-methamphetamine**, by contrast, exhibits negligible euphoric properties, is not associated with substantial abuse liability, and is present in over-the-counter decongestants such as the Vicks® nasal inhaler (Mendelson et al., 2008).

Illicit methamphetamine products may consist of either isomer or a racemic (50:50) mixture, depending on the synthesis route. Thus, **the enantiomeric composition** critically influences a sample's potency, abuse liability, and public health risk.

Summary of Research Findings

Our most relevant NIH-funded study enrolled 12 individuals with methamphetamine use disorder. Using a double-blind, placebo-controlled crossover design, participants received intravenous doses of:

- D-methamphetamine (0.25 mg/kg and 0.5 mg/kg)
- L-methamphetamine (0.25 mg/kg and 0.5 mg/kg)
- Racemic methamphetamine (0.5 mg/kg)
- Placebo

We assessed:

- **Pharmacokinetic parameters**: plasma concentrations, elimination half-life, clearance, and volume of distribution
- **Pharmacodynamic outcomes**: heart rate, blood pressure, respiratory rate, and subjective experiences (e.g., drug liking and intoxication)
- **Monetary valuation**: participants' hypothetical willingness to pay per dose as a proxy for perceived street value and abuse potential (Mendelson et al., 2006)

Key Findings:

1. **Potency and Abuse Liability**: D-methamphetamine significantly increased cardiovascular activity and euphoric subjective ratings, with effects lasting up to six hours. L-methamphetamine, even at higher doses, produced only mild effects. Participants strongly preferred d-methamphetamine and were willing to pay more for it.

2. **Racemic Mixtures**: Racemic methamphetamine produced psychoactive and cardiovascular effects similar to pure d-methamphetamine, despite containing only 50% of the d-isomer—suggesting a non-linear or synergistic effect.

3. **Dilution Effects**: Mixtures with more than 50% l-methamphetamine were rated less desirable, had diminished cardiovascular effects, and had reduced hypothetical street value.

(Figure: Monetary valuation of d- and l-methamphetamine by participants — see attached study figures)

Implications for Federal Sentencing Policy

Current federal sentencing guidelines calculate offense levels based on total drug weight, without regard to isomeric composition. Our research shows this approach fails to reflect the pharmacological and public health impact of specific formulations.

Recommendations:

1. **Account for Isomeric Composition**: Sentencing guidelines should distinguish between d-, l-, and racemic methamphetamine in quantity calculations and severity assessments.
2. **Permit Downward Departures or Variances**: In cases involving predominantly l-isomer or diluted methamphetamine, courts should have discretion to apply downward sentencing adjustments.
3. **Mandate Isomeric Analysis in Forensic Testing**: Routine lab reporting of enantiomeric composition would enhance fairness and scientific accuracy in sentencing decisions.

Responses to Commission Questions

1. **Do differences in purity result in differences in effect or harm?**
   Yes. Differences in purity—particularly the ratio of d- to l-methamphetamine—affect both pharmacological effects and perceived value. More than 50% dilution with the l-isomer is generally needed before users detect a reduction in effect.
2. **Do chemical or pharmacological differences affect harm?**
   Yes. D-methamphetamine has much higher abuse potential and more pronounced physiological effects than l-methamphetamine.
3. **Do users select methamphetamine based on purity?**
   Not directly. However, they can recognize when a sample is highly diluted, and this affects repeat use and willingness to pay.
4. **Does the duration of effect vary by purity?**
   The available data are inconclusive. Duration seems more related to the isomeric composition than total purity.
5. **Do users change their dosage based on purity?**
   Generally, no. Unless the methamphetamine is significantly diluted, users tend to take consistent doses. Our study found that at least a 50% dilution is necessary for users to notice a change.
6. **Is harm correlated with purity?**
   Yes. Higher proportions of d-methamphetamine are associated with increased physiological harm. However, some adulterants may also increase toxicity independently.
7. **Can clinicians determine methamphetamine purity?**
   No. Clinicians treating individuals for methamphetamine use disorder do not have access to data on enantiomeric composition.

8. **Does treatment vary based on methamphetamine purity?**
   No. Treatment protocols are not customized based on the isomeric composition or purity.
9. **Does public health impact differ based on purity?**
   Likely not in a significant way, since overall use behavior tends to remain consistent regardless of purity.
10. **Do individual case differences in purity correlate with harm?**
    Yes, particularly where the d-isomer content is high, the risk of cardiovascular and psychiatric effects increases.

11–14. **Trafficking-Related Questions**
These questions fall outside my area of clinical and pharmacological expertise.

15. **How does methamphetamine compare to other drugs in terms of harm and lethality?**
    Methamphetamine is among the most toxic illicit drugs, now contributing to roughly 50% of fatal drug poisonings. However, legal substances like alcohol result in higher absolute mortality, causing an estimated 180,000 deaths annually in the U.S.

Conclusion

Scientific evidence clearly shows that methamphetamine's potency and abuse risk depend on its isomeric composition. Incorporating this pharmacological distinction into sentencing guidelines will improve fairness, reduce harm, and align policy with public health principles.

Thank you for the opportunity to contribute to the Commission's important work. I am available to provide additional data or testimony upon request.

References

1. Mendelson JE, McGlothlin D, Harris DS, Foster E, Everhart T, Jacob P 3rd, Jones RT. The clinical pharmacology of intranasal l-methamphetamine. *BMC Clin Pharmacol*. 2008;8:4. doi:10.1186/1472-6904-8-4.
2. Mendelson J, Uemura N, Harris D, Nath RP, Fernandez E, Jacob P 3rd, Everhart ET, Jones RT. Human pharmacology of the methamphetamine stereoisomers. *Clin Pharmacol Ther*. 2006;80(4):403–420. doi:10.1016/j.clpt.2006.06.013.

Attachments: - Full-text of relevant peer-reviewed studies - Curriculum Vitae of John Mendelson, M.D.

Figure showing monetary value of intravenous d- and l-methamphetamine [2]

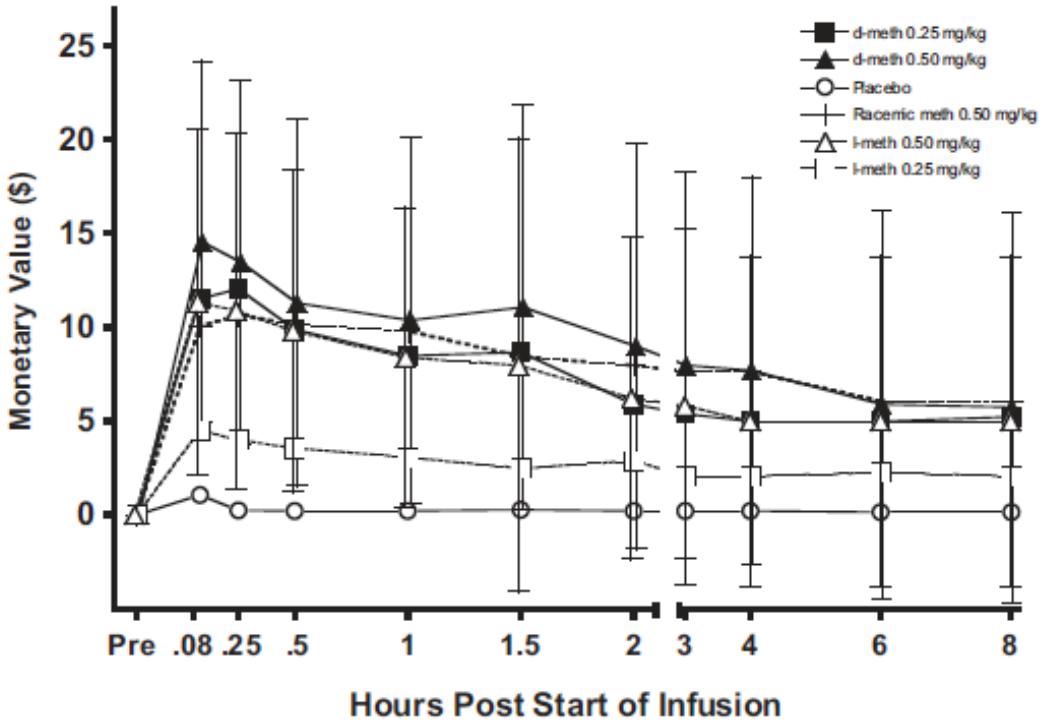

Fig 6. Mean visual analog scale subjective response for monetary value after *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. *Solid squares*, 0.25 mg/kg of *d*-methamphetamine; *open squares*, 0.25 mg/kg of *l*-methamphetamine; *solid triangles*, 0.5 mg/kg of *d*-methamphetamine; *open triangles*, 0.5 mg/kg of *l*-methamphetamine; *dashed lines*, racemic methamphetamine; *circles*, placebo. Mean data are shown (N = 12), except for 0.5 mg/kg of *d*- and *l*-methamphetamine, for which data are given as mean ± SD.

BMC Clinical Pharmacology

Research article

The Clinical Pharmacology of Intranasal l-Methamphetamine

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Abstract

Background: We studied the pharmacology of l-methamphetamine, the less abused isomer, when used as a nasal decongestant.

Methods: 12 subjects self-administered l-methamphetamine from a nonprescription inhaler at the recommended dose (16 inhalations over 6 hours) then at 2 and 4 (32 and 64 inhalations) times this dose. In a separate session intravenous phenylephrine (200 μg) and l-methamphetamine (5 mg) were given to define alpha agonist pharmacology and bioavailability. Physiological, cardiovascular, pharmacokinetic, and subjective effects were measured.

Results: Plasma l-methamphetamine levels were often below the level of quantification so bioavailability was estimated by comparing urinary excretion of the intravenous and inhaled doses, yielding delivered dose estimates of 74.0 ± 56.1, 124.7 ± 106.6, and 268.1 ± 220.5 μg for ascending exposures (mean 4.2 ± 3.3 μg/inhalation). Physiological changes were minimal and not dose-dependent. Small decreases in stroke volume and cardiac output suggesting mild cardiodepression were seen.

Conclusion: Inhaled l-methamphetamine delivered from a non-prescription product produced minimal effects but may be a cardiodepressant.

Background

There are two enantiomers of methamphetamine: dextrorotatory (d) methamphetamine and levorotatory (l) methamphetamine. The d-isomer is commonly abused and is available by prescription (DEA Schedule II), but unknown to most physicians the l-isomer is sold over-the-counter and is the active ingredient of the Vicks® Vapor Inhaler (spelled levmetamfetamine by the manufacturer, Procter & Gamble, Cincinnati, OH) [1,2]. Each Vicks inhaler contains about 50 mg of l-methamphetamine, and earlier estimates suggested delivered daily doses between 1.9 to 7.2 mg of drug when used as directed [3]. The over-the-counter (OTC) vasoconstrictor nasal decongestant phenylpropanolamine (PPA) was associated with

an increased risk of hemorrhagic stroke in young women that led to it being voluntarily withdrawn from the market [4]. Ephedra, another component of OTC nasal decongestants may also increase the risk of cardiovascular adverse events [5]. Methamphetamine is a sympathomimetic vasoconstrictor that increases blood pressure and myocardial oxygen consumption [6].

Despite the widespread use of OTC nasal decongestants, there is surprisingly little published data on their pharmacologic effects. Thus, physicians may encounter patients using l-methamphetamine but have little data on risks and drug exposure. To date, there are no published data on the pharmacology of intranasal l-methamphetamine. The complications of OTC decongestants, although severe, are exceedingly rare. Because adverse events of these drugs are uncommon, observational studies are unlikely to delineate mechanisms of action or toxicity. Measures that assess cardiovascular, and pharmacokinetic variables could assist in predicting risk and defining mechanisms of action.

The effects of l-methamphetamine on cardiac function are not yet defined. In this study we used impedance cardiography to measure the effects of methamphetamine-induced vasoconstriction on vascular resistance and cardiac work. Because people using the inhaler are likely to exercise (indeed one Olympic athlete lost a medal due to Vicks inhaler use before his race) [7], interactions between exercise and intranasal methamphetamine were assessed. Understanding the effects of intranasal l-methamphetamine contained in the Vicks® Inhaler is important due to the associated cardiovascular risks of other OTC nasal decongestants. In addition, establishing the relative and absolute bioavailability of l-methamphetamine in the Vicks® Inhaler would aid in a further assessment of risk. In this study, we examined the pharmacokinetic, cardiovascular, and subjective effects of l-methamphetamine. Doses were delivered using an easily available non-prescription product – the Vicks® Vapor Inhaler.

Methods

Subject selection

Twelve subjects with a mean age of 38 (range 28 to 51 years old) participated in the study. Subjects were recruited through advertisements, and were included if they were normotensive, between 18 to 65 years, had a normal physical examination, EKG, blood and urine chemistries and had no nasal pathology that might alter the absorption of l-methamphetamine.

Subjects were excluded if they had used nasal decongestants within the last three months, were dependent on any drugs other than caffeine or nicotine or had structural abnormalities of the heart seen during a preliminary stress echocardiogram. Women were required to have a negative serum pregnancy test (Unilab, San Jose, California) before each session. Subjects were not dependent on methamphetamine, alcohol or other illicit drugs using DSM-IV-R criteria.

Because the Vicks® Inhaler is an OTC product, prior experience with methamphetamine was not necessary. Informed consent was obtained and subjects were paid for their participation. The study was approved by the UCSF IRB.

Study design

Inhaled l-methamphetamine was self administered from the commercially available Vick's® Inhaler using a 3 session, ascending dose, open-label study design with sessions separated by at least 1 week. Dosing was starting at the manufacturer's recommended dose of 2 inhalations per nostril every 2 hours. Within each session 4 dosing periods occurred with periods separated by 2 hours; all dosing within a session occurred over 8 hours. In the first session subjects received 4 inhalations per period. Thus, over 8 hours a total of 16 inhalations were given. In the second and third sessions, the inhaler was administered with the same 2 hour dose period but at 2 and 4 times the recommended dose. In these sessions a total of 32 and 64 inhalations were given. Inactive ingredients in the Vicks inhaler include bornyl acetate, camphor, lavender oil, menthol and methyl salicylate. Subjects were admitted as inpatients to the UCSF General Clinical Research Center (GCRC) for approximately 36 hours.

Following administration of 3 ascending dose inhalations, a fourth session was conducted to contrast the effects of a prototypic alpha agonist phenylephrine, (Gensia Sicor Pharmaceuticals, Irvine, CA) with those produced by inhaled methamphetamine and to administer a parenteral dose of l-methamphetamine that would allow determination of absolute bioavailability. A similar phenylephrine challenge procedure has been safely used to measure hemodynamic response in hypertensive patients maintained off all antihypertensive medication for 2 weeks [8]. The phenylephrine response test was performed by giving an intravenous phenylephrine bolus dose of 100 μg. If the initial dose did not produce a 15 mm rise in systolic blood pressure within 15 minutes, a second 200 μg dose was given at 30 minutes. Two hours after the last phenylephrine dose, a slow (over 15 minutes) intravenous infusion of 5 mg of l-methamphetamine was administered to establish absolute bioavailability. The l-methamphetamine was prepared from the free base obtained from Sigma (St. Louis, MO) under FDA IND 58,189. We had planned to quantify relative bioavailability by extracting and quantifying the residual l-methamphetamine content from the inhalers.

However, the amount of l-methamphetamine in new inhalers was highly variable (between 50 and 75 mg) and, given the small delivered doses, we were not able to obtain sufficiently accurate inhaler weights before and after dosing to allow estimation of delivered doses.

Subjects were requested to abstain from both nicotine and caffeine for approximately 12 hours before each dosing and from alcohol for 48 hours prior to dosing. Subjects were excluded from participation if they had a positive qualitative urine test for abused drugs prior to dosing or reported use of nicotine, caffeine or alcohol with the above windows; no subjects were excluded for positive qualitative urinalysis or caffeine, nicotine or alcohol use within specified time limits. No caffeine was allowed until stress echocardiograms were completed. No smoking was permitted during the hospital stay; nicotine patches were offered to all smokers. Vicks® Inhalers from a single batch were used for each subject; all inhalers were purchased from a single pharmacy.

Measures

Physiological measures

Blood pressure, heart rate, skin and core temperature, and respiratory rate were measured using a non-invasive automatic device (Escort II 300 Patient Monitor, Medical Data Electronics, Arleta, Calif.) at 15 minutes before and 5, 15, 30 and 60 minutes within each period; and 2, 4, 8, 18, 24, and 30 hours after the last period to assess safety. For Session 4, before and after intravenous phenylephrine and l-methamphetamine, vital signs were measured at 5-minute intervals until they returned to baseline, then hourly for 8 hours, and then at 8-hour intervals until discharge.

Echocardiography and stress-echocardiograph

2D echo-Doppler examination was performed at the time of enrollment to ensure normal cardiac structure and function. To determine if l-methamphetamine produces alterations in myocardial contractility with changes in vascular resistance, a treadmill stress echocardiogram was performed 15 minutes following the last period, except after the methamphetamine infusion (session 4) where the echo was done at 30 minutes. Subjects exercised to general fatigue or until asked to stop. Stress ECG results were defined as abnormal if there was ≥ 1.0-mm ST-segment depression measured at 80 ms after the J point in 2 contiguous leads during peak stress or immediately after recovery.

Stress echocardiographic measurements were made at baseline and 50%, 70%, and 85% of maximal heart rate. The cardiovascular variables measured by stress echocardiography included systolic blood pressure, heart rate, cardiac output, stroke volume, ejection fraction, systolic wall stress, septal wall thickness, posterior wall thickness, and left-ventricular internal diameter. Measurements obtained approximately 15 minutes before exercise, and immediately following exercise (85% of maximal heart rate) were used in final analyses. Echocardiographic data was analyzed offline (ProSolv CardioVascular Analyzer with DICOM software).

Impedance cardiography

Impedance cardiographic measures of stroke volume and ejection times were obtained before and at 15 minutes and 2 hours within each period. Blood pressure and heart rate were simultaneously obtained. From these variables, systemic vascular resistance, left cardiac work, left ventricular ejection time, and cardiac output were determined using a dedicated commercially available system (Cardiodynamics) consisting of a personal computer with customized data processing software, a transmitting unit with four pairs of electrodes for analyses of the thoracic impedance field.

Biological samples

Blood samples

For Sessions 1 to 3, 5-ml plasma samples for methamphetamine and metabolites were obtained 15 minutes after inhalations (theoretical peak) and 5 minutes before the next series of inhalations (theoretical trough), and then 4, 8, 18, 24, and 30 hours after the last inhaled dose. For Session 4, samples were obtained before and at 30 minutes, 1, 2, 4, 8, 18, 24, and 30 hours after methamphetamine. Samples were placed on ice immediately after collection. Samples were obtained through an in-dwelling venous catheter using sterile technique.

Urine samples

All urine was collected for the time from admission to just prior to dosing and from 0–12 hours, 12–24 hours, and 24–36 hours after the beginning of dosing.

Assays

Plasma and urine l-methamphetamine concentrations were determined according to a previously described gas chromatography-mass spectrometry method [9].

Subjective measures

Visual Analog Scales were administered (Sessions 1 to 3) 15 minutes before the first period, at 5 and 30 minutes within each period, and then 4, 8, 18, and 30 hours after the last l-methamphetamine dose. In Session 4, tests were administered 15 minutes before the phenylephrine dose and then 0.5, 1.5, 4, 8, 18, and 30 hours after the first phenylephrine dose. Items included Visual Analog Scale ratings of "any drug effect," "good drug effect," "bad drug effect," "nasal stuffiness," "nasal dryness," "headache," and "dizziness." Visual analog ratings were performed by

asking the subject to place a vertical mark along a 100 mm line with 0 defined as "none" and 100 as the "most ever."

Statistical analysis

Group comparisons with PC-SAS's general linear model procedure (SAS Institute Inc., Release 6.04 Edition, Cary, N.C., 1990) and with multifactor repeated-measures analysis of variance were done with SAS (UNIX) or Super ANOVA (Macintosh) software applications. Physiologic data were transformed to change scores (post-treatment minus pre) and analyzed by repeated measures analysis of variance (ANOVA). Each session had 4 dosing periods. Within each period the mean value of the identical time points were calculated and used in the analysis. After a significant F-test, pair-wise comparisons were performed using the least squares means analysis. Effects were considered statistically significant at $p \leq 0.05$. Data is presented as mean (SD).

Results

Methamphetamine concentrations

Plasma methamphetamine and amphetamine concentrations were often below the limit of quantification (< 5 ng/ml). Thus, absolute bioavailability and pharmacokinetic variables could not be calculated. Measurable quantities were excreted in the urine with maximum levels at the highest dose (4× the recommended dose), showing a dose response to inhalations. Peak amounts excreted in urine occurred between 12–24 hours and then decreased significantly during the 24–36 hour collection (Figure 1).

We estimated the dose delivered by comparing urinary excretion from the three inhalation conditions with the iv condition. Total methamphetamine excretion (0–36 hours) was 40.7 (30.9) μg, 68.6 (58.6) μg, and 147.4 (121.2) μg for the 16, 32 and 64 inhalation conditions. It was 2749.5 (499.6) μg following the 5 mg IV dose. Assuming similar distribution and elimination of inhaled and intravenous doses, estimated delivered nasal doses for each session are 74.0 (56.1) μg, 124.7 (106.6) μg, and 268.1 (220.5) μg, respectively. The estimated delivery of a single inhalation is approximately 4.2 (3.3) μg per inhalation (range 0.8–14.3 μg/inhalation). Following inhalations approximately 4% of the dose was excreted as l-amphetamine (corrected for difference in molecular weight); after intravenous dosing approximately 3% of the dose was excreted as l-amphetamine.

Physiological measures

Most physiological variables did not change in a clear dose-dependent manner. For example, systolic blood pressure increased by 11.8 (16.2) and 12.3 (20.5) mmHg ($p = 0.02$) in the 16 and 32 but fell by 1.2 (16) mmHg 64 inhalation conditions. Mean peak diastolic blood pressure increased by 7 to 9 mmHg ($p = 0.04$) with no difference between doses. Across time, core temperature increased by ∼0.1°C in the 16 and 32 inhalation conditions and decreased by ∼0.1°C in the 64 inhalation condition ($p = 0.02$). In the 64-inhalation condition respiratory rate increased by 0.4 (1.68) ($p = 0.02$) breaths per minute; no hyperthermia or respiratory distress was seen in any condition. Peak respiratory rate increased by a clinically insignificant 3 (2.5) breaths per minute in the 32-inhalation condition ($p = 0.03$). No significant increases in heart rate were seen.

The intravenous methamphetamine dose did not alter cardiovascular parameters – mean (SD) peak responses were 2.9 (9.3) mmHg, 7.4 (12.5) mmHg, and 0.42 (4.4) breaths/min in systolic and diastolic blood pressure, and respiratory rate, respectively. In contrast to the results seen in hypertensives, the phenylephrine doses (100 and 200 μg) produced no significant changes in blood pressure or heart rate (Table 1). Interestingly, the 16 and 32 inhalation conditions produced substantially more robust effects on systolic blood pressure than the much larger intravenous l-methamphetamine and phenylephrine doses. All three inhalation conditions increased diastolic blood pressure more than phenylephrine or intravenous l-methamphetamine. Mean peak changes in physiological variables are shown in Table 1.

Stress echocardiography

Intranasal l-methamphetamine did not alter the effect of exercise on most cardiovascular measures. Exercise produced expected increases in cardiac output ($p < 0.001$), ejection fraction ($p < 0.001$), heart rate ($p < 0.001$), systolic wall stress ($p = 0.002$), and systolic blood pressure ($p \leq 0.001$) and expected decreases in end-systolic left ventricular internal diameter ($p = 0.01$). The cardiac response to exercise was not affected by any inhaler dose level except for septal wall thickeness (SWT), which increased significantly only after the highest inhaler dose. This difference is most likely due to a single outlier. Echocardiographic measurements are shown in Table 2.

Impedance cardiography

Significant differences were seen in a few cardiovascular parameters at 15 minutes post dose. Inhaled l-methamphetamine decreased stroke volume by 3.9 to 6 mls/beat ($p = 0.01$). Heart rate fell slightly by ∼1 to 2 beats/per minute. These small decreases in heart rate and stroke volume decreased cardiac output (CO) by ∼0.5 l/min ($p = 0.02$). Systemic vascular resistance (SVR) increased in all conditions by 106 to 137 dynes*sec*cm^5 (1190 dynes*sec*cm^5, 1259 dynes*sec*cm^5, and 1278 dynes*sec*cm^5 for 16, 32 and 64 inhaler doses, $p = 0.004$). However, this was a small absolute increase of less than 10%. The increase in SVR is probably compensating

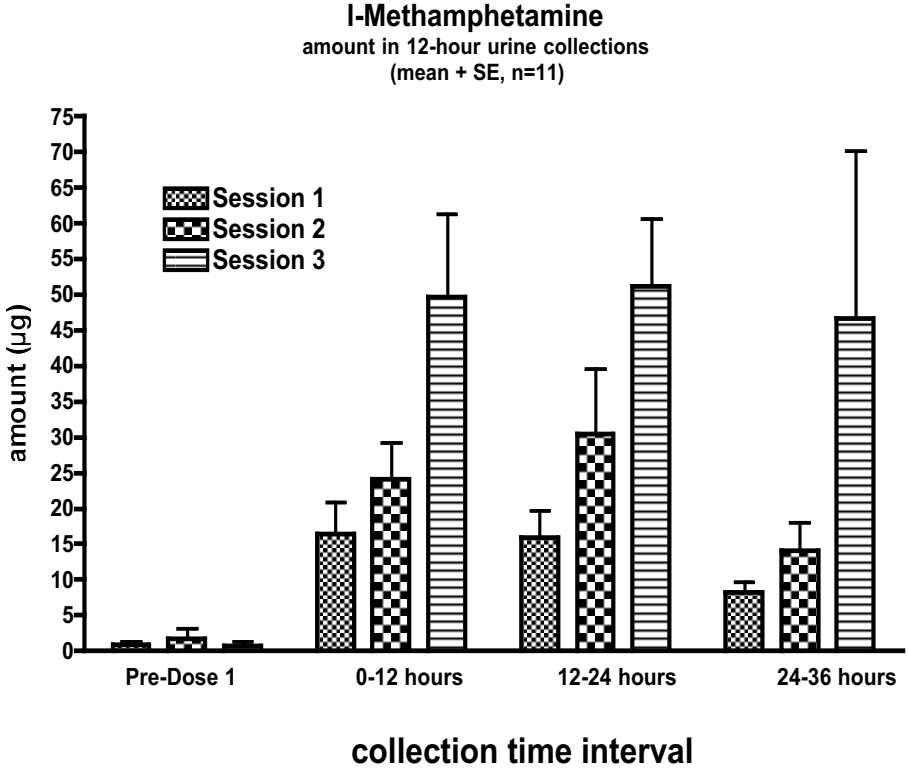

Figure 1
Methamphetamine and amphetamine concentrations excreted in the urine from 0–12, 12–24, and 24–36 hours. Values are means (SE). N = 11.

for the decrease in CO, and was not accompanied by an increase in blood pressure.

At two hours post-dose, many parameters were significantly different from pre-dose conditions. In response to l-methamphetamine, stroke volume remained 1.6 to 6.2 mls/beat below baseline ($p = 0.02$). Heart rate increased by 4 to 5 beats/min ($p = 0.003$). Therefore, cardiac output returned to approximately pre-dose values. Diastolic blood pressure increased slightly by ~2 mmHg ($p = 0.01$). A decrease of ~12 ms occurred in left ventricular ejection time possibly resulting from the increase in heart rate. No significant differences were found between conditions; parameters are shown in Table 3. These results suggest that l-methamphetamine has mild cardiodepressant actions that initiate compensatory increases in heart rate and systemic vascular resistance.

Subjective ratings

The subjective effects of inhaled l-methamphetamine were modest. In all three inhaler conditions VAS peak ($p < 0.01$) and overall ($p = 0.001$) ratings of "Any Drug Effect increased, indicating that subjects noted a drug effect. However, other ratings were inconsistent. VAS "Bad Drug Effect," ($p = 0.01$) and "Dizziness" ($p = 0.002$) both significantly increased across time with no significant differences between inhaler conditions but peak effects were trivial and non-significant. The 64 inhalation condition increased peak "Good Drug Effect" ($p = 0.001$) but only to 9.7 (13.0) on a 0–100 VAS scale. The 64 inhalation condition increased VAS "headache" ($p = 0.01$) but again the effect was modest [12.7 (17.0)]. Interestingly, the parenteral phenylephrine and l-methamphetamine produced less subjective effects than the inhaled l-methamphetamine doses. Mean peak changes are shown in Table 4.

Discussion

l-Methamphetamine delivered through the Vicks® Inhaler was well tolerated and produced minimal pharmacodynamic effects, even at 4 times the maximum recommended dose. Dose dependent but small increases in systolic and diastolic blood pressure were seen. Impedance cardiography results suggest that l-methamphetamine may actually depress cardiac function. There were no effects of increasing l-methamphetamine dose on stress echocardiography. Small increases in visual analog "Good Drug Effect" were seen (from a mean of 5.8 to 9.7)

Table 1: Peak Changes in Physiological Variables in Response to Inhaled l-Methamphetamine, IV phenylephrine and IV l-methamphetamine.

Measure	16 Inhalations	32 Inhalations	64 Inhalations	PE_1	PE_2	IV l-Meth	Overall P-Value
Systolic Blood Pressure (mmHg)	11.8 (16.2)‡§||**	12.3 (20.5)‡§||**	- 1.2 (16.0)	0.9 (10.1)	1.4 (9.8)	2.9 (9.3)	0.03
Diastolic Blood Pressure (mmHg)	8.7 (8.9)||**	6.6 (9.9)||	9.0 (12.4)||**	1.9 (8.3)	-2 (10.2)	7.4 (12.5)||	0.04
Heart Rate (beats/min)	1.3 (12.3)	4.2 (19.2)	2.3 (14.3)	2.8 (9.7)	-4.2 (7.9)	- 0.33 (8.4)	0.62
Respiratory Rate (breaths/min)	0.17 (4.3)	3 (2.5)*§||**	2.4 (3.5)§||	- 1.9 (4.8)	-1.5 (3.3)	0.42 (4.4)	0.003
Core Temperature (°C)	0.13 (0.8)	- 0.32 (0.9)	0.21 (0.9)	- 0.19(0.6)	0.08 (0.4)	0.09 (0.2)	0.41

Data presented as mean (SD).
PE_1 = phenylephrine dose 1; PE_2 = phenylephrine dose 2; IV l -Meth = IV l-methamphetamine
* = significantly greater than 16 inhalations
† = significantly greater than 32 inhalations
‡ = significantly greater than 64 inhalations
§ = significantly greater than PE_1
|| = significantly greater than PE_2
¶ significantly greater than IV l-methamphetamine
** = significantly greater than baseline

but increases of a similar magnitude in ratings of "Bad Drug Effect," and "Dizziness" were also seen, suggesting a low abuse liability in these non-drug using subjects.

Delivered doses from the inhaler are small and produce correspondingly low plasma concentrations. Using an in-vitro system, data available in the PDR and the Federal Register suggests that [3,10], adults who inhale twice in each nostril every two hours may expect a total inhaled dose of 1.9 – 7.2 mg l-methamphetamine in a 24-hour period, or 40 μg to 150 μg per 800 mls of air. However, published source data are not cited and none could be found after an extensive literature search. Using similar dosing assumptions to the PDR we estimate that about 0.2 mg per 24 hours [4.2 (3.3) μg/inhalation] is delivered. Therefore, our estimate is 10-fold less, probably due to differences in the technique used to deliver inhaled dose. Our estimate is based on the renal excretion of l-methamphetamine following controlled dosing in humans, which may have caused considerable variability in our estimates. Heavy use of the inhaler can produce substantial urinary methamphetamine concentrations, some greater than 2000 ng/ml with concentrations up to 6000 ng/ml reported [11]. Poklis (1995) treated 6 subjects either hourly for 3 days or every 2 hours for 5 days while awake. Use of the inhaler every 2 hours did not produce positive urine tests but when administered hourly two subjects had urinary concentrations of 1530 and 1560 ng/ml [12].

The small changes seen on most cardiovascular measures appear to be of little clinical significance. Peak increases in systolic blood pressure of approximately 12 mmHg did occur in some cases in the 16 and 32 inhaler condition. In the 64-inhalation condition systolic blood pressure fell, suggesting a biphasic cardiovascular response to l-methamphetamine. Morgan's report (1979) that the cardiovascular system is more affected by l-amphetamine than d-amphetamine may lead one to expect a similar or greater cardiovascular response from the l-methamphetamine contained in the Vicks® inhaler [13]. However, a 20% fall in mean arterial pressure was seen after 1 mg/kg l-methamphetamine in Sprague-Dawley rats [14]. This was

Table 2: Change in Cardiovascular Variables in Response to Exercise After Vicks Inhalation and IV l-Methamphetamine As Measured by Stress Echocardiography. Data presented as mean (SD).

Measure	16 Inhalations	32 Inhalations	64 Inhalations	IV l-Meth	Overall P-Value (time)	Overall P-Value (dose)
Cardiac Output (l/min)	3.1 (2.0)	2.4 (2.2)	2.5 (2.5)	3.8 (2.3)	< 0.001	0.10
Heart Rate (beats/min)	73.5 (26.7	66.3 (21.5)	64.5 (22.9)	76.9 (16.8)	< 0.001	0.17
Systolic Blood Pressure (mmHg)	41.3 (18.7)	41.6 (42.6)	52.0 (13.9)	57.6 (11.6)	< 0.001	0.35
Stroke Volume (ml)	3.3 (13.2)	2.5 (13.4)	2.1 (13.9)	-0.02 (7.3)	0.41	0.90
LV Internal Diameter (cm)	-2.6 (2.9)	-2.1 (3.5)	-1.8 (4.1)	-2.0 (4.6)	0.01	0.96
Ejection Fraction (%)	8.9 (5.8)	7.8 (7.6)	6.3 (6.4)	9.9 (6.5)	< 0.001	0.62
Systolic Wall Stress(kdynes/cm^2)	64.5 (62.8)	51.7 (61.6)	41.7 (79.3)	81.7 (90.6)	0.002	0.42
Posterior Wall Thickness (cm)	- 0.58 (1.4)	0.67 (1.3)	0.25 (0.97)	0.08 (1.5)	0.49	0.20
Septal Wall Thickness (mm)	0.08 (0.79)	0.08 (1.5)	2.0 (3.1)	0.25 (0.97)	0.05	0.04

Responses are post-exercise minus pre; wall thicknesses measurements are end-systolic
LV = Left Ventricular
p-values are based on overall p-values across time and dose.

Table 3: Change in Cardiovascular Variables in Response to Inhaler Condition and IV l-Methamphetamine as Measured by Impedance Cardiography.

Measure	16 Inhalations	32 Inhalations	64 Inhalations	IV l-Meth	Overall P-Value (time)	Overall P-Value (dose)
Cardiac Output (l/min)						
15 minutes	-0.53 (0.66)	-0.46 (1.3)	-0.56 (0.52)	-0.01 (0.54)	0.02	0.67
2 Hours	0.0 (0.67)	0.05 (1.6)	0.31 (0.77)	0.28 (1.0)	0.32	
Heart Rate (beats/min)						
15 Minutes	-2.6 (4.9)	-2.1 (5.8)	-1.7 (5.9)	1.0 (5.8)	0.38	0.60
2 Hours	4.3 (6.0)	5.4 (11.3)	4.3 (7.7)	6.1 (9.5)	0.003	
Systolic Blood Pressure (mmHg)						
15 Minutes	1.0 (12.5)	-1.2 (6.6)	-3.0 (6.4)	4.8 (9.0)	0.76	0.09
2 Hours	1.8 (7.9)	-0.17 (7.0)	3.1 (6.9)	5.9 (6.9)	0.06	
Diastolic Blood Pressure (mmHg)						
15 Minutes	0.50 (7.5)	1.4 (6.7)	1.2 (6.4)	4.3 (8.8)	0.09	0.23
2 Hours	2.2 (4.2)	2.6 (6.5)	1.2 (4.9)	6.5 (8.1)	0.007	
Stroke Volume						
15 Minutes	-3.9 (7.3)	-4.9 (16.0)	-6.0 (6.4)	-1.0 (5.4)	0.008	0.66
2 Hours	-5.4 (6.6)	-6.2 (17.5)	-1.6 (7.8)	-0.67 (6.4)	0.02	
Systemic Vascular Resistance (dynes*sec*cm^5)						
15 Minutes	106.0 (168.9)	137.1 (388.5)	129.1 (169.5)	48.8 (112.7)	0.004	0.89
2 Hours	47.2 (140.2)	72.0 (441.7)	-10.2 (204.0)	12.3 (127.2)	0.36	
Left CardiacWork						
15 Minutes	-0.51 (1.0)	-0.48 (1.6)	-0.59 (0.64)	0.44 (0.93)	0.21	0.12
2 Hours	0.22 (0.91)	0.23 (2.1)	0.53 (0.78)	1.1 (1.5)	0.03	
LV Ejection Time						
15 Minutes	-0.75 (12.4)	-4.8 (16.4)	-12.4 (19.1)	-0.25 (10.4)	0.19	0.54
2 Hours	-11.8 (16.4)	-12.1 (26.8)	-11.8 (19.9)	-6.4 (26.5)	0.005	

Data presented as mean (SD).
IV-l-meth-IV l-methamphetamine; p-value (time)-compared to baseline vs. 15 minutes and 2 hours post-dose

accompanied by a 35% increase in cerebral vascular resistance and a 40% decrease in cerebral blood flow. d-Methamphetamine is usually a potent sympathomimetic alpha agonist and vasoconstrictor where systolic and diastolic blood pressure increase significantly with slight decreases in heart rate consistent with a baroreceptor response [6,15-17]. In contrast, our studies showed that these effects did not occur in response to inhaled or intravenous l-methamphetamine [16].

The small declines in stroke volume and cardiac output at 15 minutes within each period suggest that l-metham-

Table 4: Peak Changes in VAS Subjective Variables in Response to Inhaled l-Methamphetamine, IV phenylephrine and IV l-methamphetamine.

Measure	16 Inhalations	32 Inhalations	64 Inhalations	PE_1	PE_2	IV l-Meth	Overall P-Value
Any Drug Effect	9.0 (13.9)§‖**	7.3 (10.5)§‖**	9.8 (7.9)§‖¶**	1.5 (2.1)	1.7 (2.4)	4.5 (8.6)	0.001
Bad Drug Effect	6.8 (13.7)	2.8 (4.6)	4.9 (5.0)	0.33 (0.9)	1.1 (0.79)	5.3 (10.7)	0.07
Dizziness	9.3 (14.0)§‖¶**	6.5 (6.4)¶**	9.0 (13.5)§‖¶**	1.5 (2.9)	0.92 (2.2)	-0.67 (5.7)	0.004
Good Drug Effect	5.8 (13.0)‖**	5.7 (10.5)**	9.7 (13.0)§‖¶**	0.42 (2.9)	0.25 (1.5)	2.7 (4.7)	0.005
Headache	5.1 (18.1)	4.8 (5.1)‖	12.7 (17.0)§‖¶**	-0.08 (1.7)	1.8 (3.3)	-3.8 (13.4)	0.02
Nasal Dryness	5.2 (16.2)	3.3 (9.6)	4.1 (9.9)	-0.75 (2.1)	-0.50 (1.7)	-0.42 (2.7)	0.20
Nasal Stuffiness	1.1 (16.9)	2.8 (4.8)	1.4 (6.7)	0.50 (4.4)	-1.6 (3.6)	0.42 (1.2)	0.88

Data presented as mean (SD).
PE_1 = phenylephrine dose 1; PE_2 = phenylephrine dose 2; IV l -Meth = IV l-methamphetamine
*= significantly greater than 16 inhalations
† = significantly greater than 32 inhalations
‡ = significantly greater than 64 inhalations
§ = significantly greater than PE1
|| = significantly greater than PE2
¶ significantly greater than IV l-methamphetamine
** = significantly greater than baseline

phetamine may have some cardiodepressant effects, similar to those seen by Abassi [14]. Heart rate did not change significantly but SVR increased by ~10%, maintaining blood pressure. All subjects in this study were young and had normal cardiovascular function. For people with compromised ventricular function the negative inotropic effects of inhaled l-methamphetamine could become clinically significant; to date no reports of heart failure associated with l-methamphetamine have been reported. In contrast to the nasal decongestants removed from the market the product containing l-methamphetamine modestly increased blood pressure. However, the ~12 mmHg maximal increases seen are unlikely to produce medical complications in young, otherwise healthy people.

The response to exercise was not affected by l-methamphetamine. Even at 4 times the recommended dose, intranasal l-methamphetamine did not alter the effects of exercise. For instance, as measured by impedance cardiography changes in cardiac output (0.5 l/min) and stroke volume (5 mls) in the 32 and 64 inhalation conditions were small. Athletes that may use this product would unlikely have enhanced cardiovascular performance, even at high doses.

Recently, we reported on isomeric differences between d- and l methamphetamine in humans [16]. d-Methamphetamine produces larger and more sustained cardiovascular and subjective effects than identical doses (0.5 mg/kg and 0.25 kg/kg i.v. over 1 minute) of l-methamphetamine, suggesting that the enantiomers act through different pharmacologic mechanisms. In this study, intranasal l-methamphetamine generally did not produce clinically significant cardiovascular effects. Small increases in visual analog ratings of "Any Drug Effect" indicate that subjects perceived effects and small increases in "Bad Drug Effect" and "Dizziness" suggest non-drug users do not find inhaling l-methamphetamine pleasurable. The 64-inhalation condition produced a small (change score of ~6) increase in "Good Drug Effect" suggesting a low potential for abuse even though occurrences of inhaler abuse is reported in the literature [1,18,19]. Larger doses of intravenous l-methamphetamine are psychoactive and may have some abuse potential in methamphetamine users [16].

Stroke is a serious but rare complication of nasal decongestant use. The risk of stroke after phenylpropylalinine (a related nasal decongestant now off the market) was greatest in those just initiating use and may be related to the development of tolerance with repeated use [4]. Methamphetamine is an indirectly acting sympathomimetic amine that potentiates the presynaptic release and blocks reuptake of catecholamine neurotransmitters (norepinephrine and dopamine), thus activating the sympathetic nervous system [20-22]. However, sustained exposure to high doses of methamphetamine results in depletion of monoamine [22-25]. Infrequent users of the intranasal l-methamphetamine (people with a cold) may have more catecholamine stores compared to chronic methamphetamine abusers, and could have a greater pharmacodynamic response to small doses of l-methamphetamine. According to Zhu et al. (2000) stroke is the most common cause of sudden death in first time methamphetamine users [26]. Our results suggest this adverse event should be uncommon with inhaled l-methamphetamine.

There are several limitations to our study. The lack of a placebo limits our ability to assess the importance of the small increases in blood pressure seen. Similar diurnal changes in blood pressure may have occurred without l-methamphetamine. We only studied normotensive people; results in hypertensives might differ. Normotensives may be more resistant to alpha agonist stimuli; in this study they had minimal responses to both intravenous l-methamphetamine and phenylephrine. Hypertensives might show more cardiovascular effects after a sympathomimetic amine like l-methamphetamine, and possibly be at greater risk for cardiovascular adverse events.

In summary, the low doses of inhaled l-methamphetamine delivered from the Vicks inhaler produced little cardiovascular effects in healthy people, even when given in amounts much larger than recommended. Over time, changes in blood pressure and heart rate were clinically insignificant. Significant peak increases in systolic blood pressure did occur, however, a biphasic response was seen since systolic blood pressure fell following the highest inhaler dose. The clinically significance of this finding requires further study. Stroke volume and cardiac output decreased but systemic vascular resistance increased suggesting a compensatory mechanism to maintain blood pressure. Overall, the results indicate that inhaled l-methamphetamine at these doses appears to be a slight cardiodepressant. A straightforward dose-dependence did not occur on most measures. The mild subjective changes suggest that l-methamphetamine, at least when delivered from a widely available non-prescription product, is well tolerated and has a low potential for abuse.

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Human pharmacology of the methamphetamine stereoisomers

Objective: **To help predict the consequences of precursor regulation, we compared the pharmacokinetics and pharmacodynamics of the methamphetamine (INN, metamfetamine) stereoisomers.**

Methods: **In this study 12 methamphetamine abusers received intravenous *d*-methamphetamine (0.25 and 0.5 mg/kg), *l*-methamphetamine (0.25 and 0.5 mg/kg), racemic methamphetamine (0.5 mg/kg), or placebo with the use of a 6-session, double-blind, placebo-controlled, balanced crossover design. Pharmacokinetic measures (including area under the plasma concentration–time curve [AUC], elimination half-life, systemic clearance, apparent volume of distribution during the elimination phase, and apparent bioavailability) and pharmacodynamic measures (including heart rate, blood pressure, respiratory rate, and visual analog scale ratings for "intoxication," "good drug effect," and "drug liking") were obtained.**

Results: **Pharmacokinetic parameters for the individual enantiomers given separately were similar, with dose-proportional increases in AUC and maximum plasma concentration. After racemate administration, the AUC for *d*-methamphetamine was 30% smaller than that for *l*-methamphetamine ($P = .0085$). The elimination half-lives were longer for *l*-methamphetamine (13.3-15.0 hours) than for *d*-methamphetamine (10.2-10.7 hours) ($P < .0001$). Compared with placebo, *d*-methamphetamine (0.25 mg/kg, 0.5 mg/kg, and racemic) increased the heart rate ($P < .0001$), blood pressure ($P < .0001$), and respiratory rate ($P < .05$), and this increase lasted for 6 hours. The peak heart rate changes after racemic methamphetamine and 0.5 mg/kg *d*- and *l*-methamphetamine were similar (18.7 ± 23.4 beats/min, 13.5 ± 18.5 beats/min, and 10.7 ± 10.2 beats/min, respectively), but racemic methamphetamine and 0.5 mg/kg *d*-methamphetamine increased systolic blood pressure more than 0.5 mg/kg *l*-methamphetamine (33.4 ± 17.8 beats/min and 34.5 ± 18.9 beats/min, respectively, versus 19.5 ± 11.3 beats/min; $P < .01$). *l*-Methamphetamine, 0.5 mg/kg, was psychoactive, producing peak intoxication (46.0 ± 35.3 versus 30.3 ± 24.9) and drug liking (47.7 ± 35.1 versus 28.6 ± 24.8) ratings similar to 0.5 mg/kg *d*-methamphetamine, but the effects of *l*-methamphetamine dissipated more quickly (approximately 3 hours versus 6 hours). The effects of 0.25 mg/kg *l*-methamphetamine were similar to those of placebo. Racemic methamphetamine was similar to *d*-methamphetamine with regard to most pharmacodynamic measures.**

Conclusion: **The pharmacokinetics of the methamphetamine enantiomers are similar, but there are substantial pharmacodynamic differences between the isomers. At high doses, *l*-methamphetamine intoxication is similar to that of *d*-methamphetamine, but the psychodynamic effects are shorter-lived and less desired by abusers. Racemic and *d*-methamphetamine have similar effects and would be expected to have comparable abuse liabilities. (Clin Pharmacol Ther 2006;80:403-20.)**

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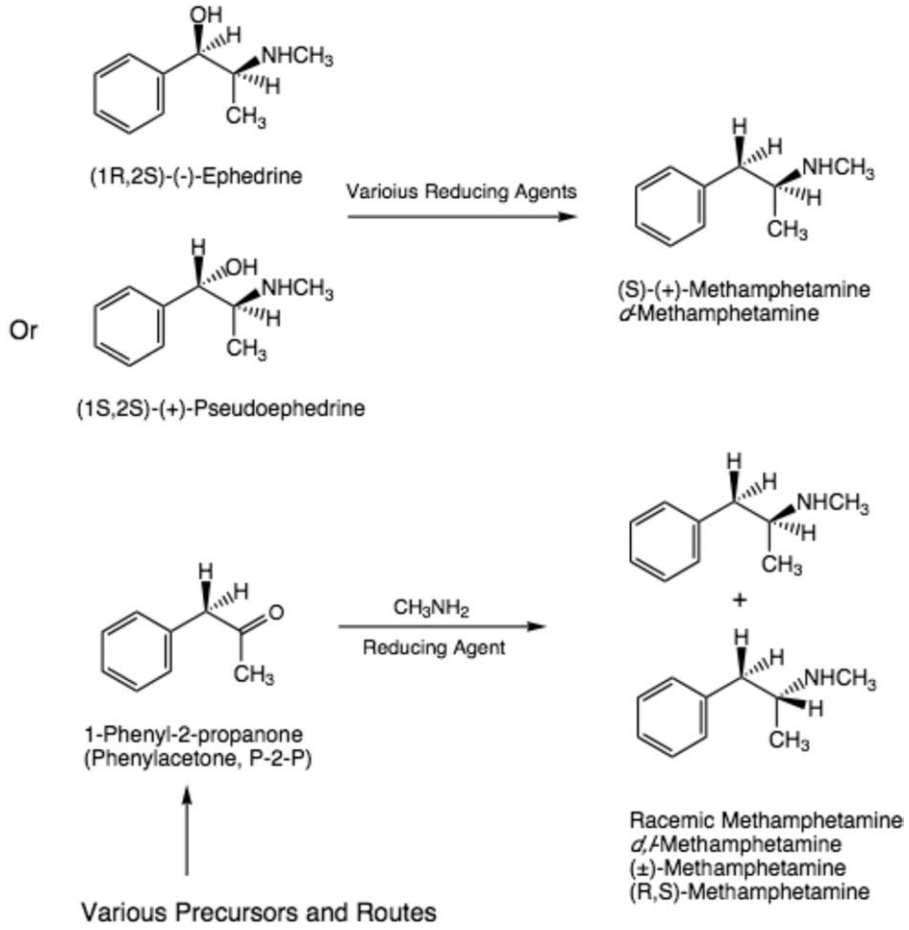

Fig 1. Various precursors and routes of synthesis for *d*-methamphetamine and racemic methamphetamine.

Methamphetamine (INN, metamfetamine) and amphetamine (INN, amfetamine) have a chiral center, and the drugs may be abused as single isomers or a mixture, depending on the drug product or source. To decrease methamphetamine abuse, many precursors are now controlled substances, including pseudoephedrine. Although *d*-methamphetamine is the isomer that is usually abused, other synthetic pathways via unregulated precursors can be used to make racemic and *l*-methamphetamine. In the United States illicit methamphetamine is predominately distributed as the *d*-isomer. Whether the pure isomer or a racemic mixture is encountered depends on the synthesis used by illicit manufacturers (usually referred to as clandestine laboratories). This, in turn, is controlled by the availability of precursors. Before 1980, most illicit methamphetamine was synthesized by reductive amination of phenylacetone (also called phenyl-2-propanone) with methylamine, which yields a racemic mixture of methamphetamine isomers (Fig 1). In 1980 the US Drug Enforcement Administration made phenylacetone a Schedule II substance. Consequently, operators of clandestine laboratories began to use an alternate route to produce methamphetamine using ephedrine and, more recently, pseudoephedrine as the starting material. This route yields pure *d*-methamphetamine, and thus, today, most of the "street methamphetamine" in the United States is the *d*-isomer.[1]

The situation may be changing again because there are attempts to reduce the availability of ephedrine. In the United States ephedra is no longer available (because of adverse effects of the drug and its use as a methamphetamine precursor), and 20 states are considering or have enacted legislation restricting the availability of over-the-counter (OTC) cold medicines containing pseudoephedrine.[2] If these precursors become

less available, the phenylacetone route, which yields racemic methamphetamine, would likely be used, because there are many synthetic methods for the preparation of phenylacetone. There is evidence that this may be occurring,[3,4] and the availability of racemic methamphetamine may be increasing. If precursor regulation decreases the availability of *d*-methamphetamine but increases the manufacture of racemic methamphetamine, the toxic consequences of drug misuse may also change. Therefore it is important to understand the pharmacologic effects of racemic methamphetamine before policy changes produce unanticipated health outcomes. Although several studies have characterized the pharmacologic features of *d*-methamphetamine, the effects of racemic and *l*-methamphetamine in humans are relatively unexplored.[5,6] The levorotatory isomer of methamphetamine is present in the OTC Vicks Vapor Inhaler (Procter & Gamble, Cincinnati, Ohio) (containing 50 mg *l*-methamphetamine but called levmetamfetamine by the manufacturer). The dextrorotatory isomer of methamphetamine is marketed as Desoxyn (Abbott Laboratories, North Chicago, Ill) for the treatment of attention deficit disorder and narcolepsy.

Pharmacologic differences between the amphetamine enantiomers were recognized early in the 20th century.[7] In general, the *d*-isomers of amphetamine and methamphetamine are 2 to 10 times more potent in producing central nervous system (CNS) stimulation than the corresponding *l*-isomers.[8-10] However, in one study *l*-amphetamine produced relatively more cardiovascular activation than *d*-amphetamine.[11] If *l*-methamphetamine behaves like *l*-amphetamine, with relatively more cardiovascular stimulation and less CNS stimulation, then severe adverse events could actually increase if racemic methamphetamine becomes the dominant illicit form. In contrast, if *l*-methamphetamine attenuates CNS effects, the abuse potential of racemic methamphetamine may be less than that of *d*-methamphetamine. In rodents *d*-methamphetamine is more potent than *l*-methamphetamine in stimulating dopamine release,[12,13] suggesting a lower abuse potential of racemic or *l*-methamphetamine.

Data in humans on the pharmacokinetic differences between methamphetamine isomers are limited. Some evidence suggests that the metabolism of methamphetamine enantiomers is different in humans compared with animals. In humans the *l*-enantiomers of both amphetamine and methamphetamine are eliminated more slowly than the *d*-isomers. The half-life of *d*-amphetamine is 7 $\pm$ 1.2 hours versus 11 $\pm$ 2.1 hours for *l*-amphetamine,[14] and the values are approximately 5 hours and 6 hours for *d*- and *l*-methamphetamine, respectively.[15] However, the latter study involved only 2 subjects. In contrast, the clearance of *l*-methamphetamine in rats is greater than that of *d*-methamphetamine.[16]

It has been suggested in the literature that *d*-methamphetamine is metabolized more extensively than *l*-methamphetamine in humans.[17,18] After the administration of racemic methamphetamine in 4 subjects, the urinary excretion of *d*-methamphetamine was lower and the urinary excretion of *d*-amphetamine was greater than that for the corresponding *l*-isomers.[17] One interpretation is that *d*-methamphetamine is metabolized more rapidly than the *l*-isomer. Taken together, these results suggest that the *l*-enantiomer might accumulate more rapidly with repeated dosing of the racemate, a possibility if abusers self-administer for the greater subjective effects of the *d*-isomer.[1,19]

Studies have not directly compared the pharmacokinetics of methamphetamine enantiomers using modern techniques, and the limited data that do exist are based on urinary excretion studies in a small number of subjects. In this study we characterize the plasma pharmacokinetics and pharmacodynamics of *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine in humans. We use these data to help predict the consequences of precursor regulation.

METHODS

Subjects

Twelve male intravenous methamphetamine users (mean age, 32 $\pm$ 7 years) participated in the study. The subjects were not dependent on methamphetamine, alcohol, or other illicit drugs according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria; none was seeking treatment for methamphetamine-related problems. Inclusion criteria were as follows: aged 21 to 45 years; in good physical health as judged by medical examination, laboratory tests (including hematologic, hepatic, and renal serum chemical analysis), urinalysis, and electrocardiogram; within 15% of ideal body weight as defined by current health insurance table standards; and self-reported intravenous methamphetamine use from once weekly to once or twice every 6 weeks. Although not excluded, no women were recruited. Those subjects with significant medical or psychiatric illnesses; treatment of substance abuse in the last 12 months; current dependence on any drug (except caffeine or nicotine) according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria; use of any medication that could affect the ability to complete the study or alter drug kinetics; and a history of sensitivity to study

medications were excluded from the study. Serum hepatitis C status and human immunodeficiency virus status were not assessed. Written informed consent was obtained from all subjects. The Committee on Human Research, University of California, San Francisco, San Francisco, Calif, approved the study protocol. The study was carried out in accordance with the Declaration of Helsinki.

Study design

A 6-session, double-blind, placebo-controlled, Latin-square, balanced crossover design was used. Single intravenous doses of *d*-methamphetamine, *l*-methamphetamine, racemic methamphetamine, or placebo were administered over a period of 1 minute via infusion pump control into a forearm vein. Intravenous doses were aseptically prepared by the UCSF School of Pharmacy investigational pharmacist from 10-mg/mL methamphetamine isomer stock solutions sterilized by use of Millipore filters (Millipore, Bedford, Mass) compounded by the School of Pharmacy, University of California, San Francisco. Investigational drugs were obtained from a commercial source (Sigma-Aldrich, St Louis, Mo) and recrystallized in our laboratories. The purity, chemical identity, and sterility were established before human use as outlined in Investigational New Drug 58,189. Each calculated aliquot was diluted with sterile 0.9% sodium chloride to a final volume of 10 mL to maintain the study blind. Saline solution alone served as the placebo.

The drugs and doses (all intravenous) were as follows: *d*-methamphetamine, 0.25 mg/kg; *d*-methamphetamine, 0.5 mg/kg; *l*-methamphetamine, 0.25 mg/kg; *l*-methamphetamine, 0.5 mg/kg; racemic methamphetamine, 0.5 mg/kg (0.25 mg/kg *d*-methamphetamine plus 0.25 mg/kg *l*-methamphetamine); and placebo (0.9% sodium chloride).

The subjects were admitted as inpatients to the General Clinical Research Center on the evening before the experimental session and remained there for 48 hours after methamphetamine administration. Experimental sessions were performed at the Drug Dependence Research Center laboratories (Langley Porter Psychiatric Institute, University of California, San Francisco). The subjects were asked to abstain from drug and alcohol use (except for caffeine and nicotine) for 48 hours before admission. They participated in all 6 experimental sessions approximately 1 week apart. On admission, they provided a blood sample for laboratory tests, as well as a urine sample for urinalysis and toxicology screening. Evidence of recent illicit drug use or short-term illness delayed the study session.

After baseline measurements were obtained, *d*-methamphetamine, *l*-methamphetamine, racemic methamphetamine, or placebo (normal saline solution) was administered intravenously. Pharmacodynamic measurements and plasma for analysis of pharmacokinetic parameters were obtained over the next 48 hours.

Blood collection

A plastic catheter was inserted into an arm vein, and 7.5 mL of whole blood was collected before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours after dosing.

Methamphetamine and amphetamine: Stereoselective assay

After administration of *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine, corresponding active metabolites were determined by use of an enantioselective assay. A chiral capillary gas chromatography column (beta-DEXcst; Restek, Bellefonte, Pa) resulted in good separation of the trifluoroacetyl derivatives of both enantiomers. We developed a gas chromatography–mass spectrometry method for the determination of methamphetamine and amphetamine enantiomers in plasma using this column. The analytes were extracted from plasma by a liquid-liquid extraction procedure (ethyl acetate/heptane [4:1]) and converted to the trifluoroacetyl derivatives with trifluoroacetylimidazole. Methamphetamine-d_{14} and amphetamine-d_{11} were used as internal standards. Standard curves were linear over the range of 0.5 to 500 ng/mL in plasma. The limits of quantification for the assay method were 1 ng/mL for the methamphetamine and amphetamine enantiomers.

Pharmacokinetic analysis

The plasma concentration–time profiles for *d*-methamphetamine, *l*-methamphetamine, and amphetamine were analyzed by use of the pharmacokinetic data analysis program WinNonlin Professional (version 3.1, Pharsight, Mountain View, Calif). The area under the plasma concentration–time curve up to the time of the last measurable plasma concentration ($AUC_{0\text{-}t}$) of methamphetamine and amphetamine was calculated by use of the linear trapezoidal rule. The AUC to infinity was determined by extrapolation of $AUC_{0\text{-}t}$ by use of the terminal rate constant (λ), which was calculated by log-linear regression of the terminal linear phase of the plasma concentration–time curves. The elimination half-life ($t_{½}$) was calculated by use of the following equation: $t_{½} = \ln 2/\lambda$.

Systemic clearance (CL) and apparent volume of distribution during the elimination phase (V_d) were calculated by use of the following formula: CL = Dose/AUC and V_d = CL/λ, respectively. AUC ratios were compared with estimates of the apparent "exposure" of the *d*- and *l*-enantiomers. This method is similar to that used for establishing the relative bioavailability of 2 formulations. The apparent relative exposure to *d*- and *l*-methamphetamine and amphetamine was defined as follows:

$$\text{Exposure (\%)} = \left(\frac{\text{AUC d-enantiomer}}{\text{AUC l-enantiomer}}\right) \times 100$$

The analyses were performed separately for both doses (0.25 and 0.5 mg/kg) of *d*-methamphetamine and *l*-methamphetamine and the racemate. The mean plasma AUC ratios were presented with 90% confidence intervals (CIs). On the basis of logic similar to that used previously, had this CI been contained entirely within the range from 80% to 125%, this would have been consistent with demonstrating "exposure bioequivalence" in terms of AUC.

Pharmacodynamic measures

Physiologic measures. Heart rate and systolic and diastolic blood pressure were measured with an automated noninvasive electronic device (Escort II+, model 20301; Medical Data Electronics, Arleta, Calif). The rate-pressure product was calculated as systolic blood pressure multiplied by heart rate. The respiratory rate was counted manually. The skin temperature and tympanic (core) temperature were measured by use of thermocouples on an index finger and adjacent to the tympanic membrane (Mallinckrodt Mon-a-therm, model 6500; Mallinckrodt Medical, St Louis, Mo). All measures were obtained before dosing and at 0.08, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours after dosing. Blood and urine samples were collected for pharmacokinetic analysis and determination of methamphetamine and metabolite levels.

Subjective measures. Verbal ratings of global intoxication (on a scale ranging from 0 to 100) were obtained at the same time intervals as the physiologic measures, with 0 representing no drug effect and 100 representing the highest level of intoxication. Visual analog scales were used to rate other subjective effects from 0 ("none") to 100 ("most ever") for "any drug effect," "good drug effect," "drug liking," "bad drug effect," "intoxication," and "high" and were obtained before dosing and at 0.5, 1, 1.5, 3, 4, 5.5, 8, 12, and 24 hours after dosing. The Profile of Mood States was used to assess subjective mood changes on specific subscales for tension-anxiety, depression-dejection, anger-hostility, vigor, confusion, and fatigue.[20] Subjects rated the presence and intensity of symptoms on a scale ranging from 0 to 4, where 0 indicates "no effect" and 4 indicates "extremely strong." Ratings were obtained before dosing and at 0.5, 1.5, 4, 12, 24, and 48 hours after dosing.

The Beck Depression Inventory and the State-Trait Anxiety Inventory were used to measure symptoms of anxiety and depression.[21,22] These were obtained before dosing and at 2 and 48 hours after dosing. The Buss Aggression Scale was used to evaluate anger, hostility, and verbal and physical aggression[23] and was obtained before dosing and at 3 and 24 hours after dosing. A monetary value was obtained for each dose at baseline and at 0.08, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours after dosing, and it ranged from $0 to $20. The monetary value was the value in dollars if the dose was purchased illicitly.

Statistical analysis

For each pharmacokinetic parameter, the mean, SD, and 95% CI were calculated for both doses (0.25 mg/kg and 0.5 mg/kg) of *d*- and *l*-methamphetamine and the racemate. The effect of dosing conditions on the pharmacokinetics of *d*- and *l*-methamphetamine and the active metabolite (amphetamine) was analyzed by use of repeated-measures ANOVA. Dosing conditions were considered independent factors in the ANOVA model. The AUC, CL, $t_{½}$, and V_d for *d*- and *l*-methamphetamine and the AUC and $t_{½}$ for *d*- and *l*-amphetamine, as well as the amphetamine/methamphetamine AUC ratios of both enantiomers, were the dependent factors.

Pharmacodynamic data across time were analyzed by repeated-measures ANOVA. Treatment conditions and observation times were considered within-subject factors. Change scores (postdose values minus predose values) were used in these analyses. Peak scores for all subjective and physiologic variables were also analyzed by repeated-measures ANOVA.

When a significant F test was observed, post hoc comparisons were conducted by use of the Fisher least significant difference or Scheffé test. Missing data, which accounted for less than 1% of the data, were replaced by the group mean at that specific time point. Effects were considered statistically significant at $P \leq .05$.

RESULTS

Subjects

Twelve male intravenous methamphetamine users (mean age, 32.3 ± 7.4 years [range, 23-43 years]) completed the study. The mean weight and height were 73.5 ± 7.0 kg (range, 68.2-90.9 kg) and 177.6 ± 6.1 cm (range, 165-185 cm), respectively. On the basis of self-reported ethnicity, there were 9 white subjects and 3 black subjects.

Tolerability of methamphetamine

No serious adverse events occurred during the study, and all doses of methamphetamine were well tolerated. No clinically significant changes in electrocardiography, physical examination, vital signs, biochemical tests, or hematologic parameters were evident.

Pharmacokinetic results

The mean plasma concentration–time profiles are shown in Fig 2. Plasma levels of methamphetamine peaked immediately after administration and were detectable 36 to 48 hours after dosing. Estimated pharmacokinetic parameters are listed in Table I. No methamphetamine was detected just before drug administration.

The mean AUC values for methamphetamine after separate enantiomer doses were similar between *d*- and *l*-methamphetamine. The mean plasma AUC ratios of the *d*- and *l*-enantiomers were 0.910 (90% CI, 0.837-0.983) and 0.894 (90% CI, 0.821-0.967) for the 0.25-mg/kg dose and 0.5-mg/kg dose, respectively. This illustrates that the apparent "exposure" of *d*-methamphetamine to *l*-methamphetamine is almost 90% with regard to methamphetamine AUC. However, the AUC for *l*-methamphetamine was 30% greater ($P = .0085$) than that for *d*-methamphetamine after the racemic dose of methamphetamine (Fig 2, *B*). The mean plasma AUC ratio of racemic methamphetamine was 0.679 (90% CI, 0.622-0.736), which did not meet the criteria for exposure bioequivalence.

Mean maximum plasma concentration (C_{max}) values were similar among *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. The mean C_{max} ratios of the *d*- and *l*-enantiomers were 1.215 (90% CI, 1.044-1.385), 1.086 (90% CI, 0.974-1.199), and 1.008 (90% CI, 0.970-1.047) for the 0.25-mg/kg, 0.5-mg/kg, and racemic doses, respectively. Both the AUC and C_{max} for methamphetamine after the 0.5-mg/kg doses were approximately 2-fold higher than those for the corresponding 0.25-mg/kg doses, suggesting linear pharmacokinetics within our experimental dose range.

The clearance of *d*-methamphetamine was greater than that of *l*-methamphetamine after racemic methamphetamine ($P < .0001$). However, the clearance values for both *d*- and *l*-enantiomers were similar across the 2 dose levels (0.25 and 0.5 mg/kg) when each isomer was given separately.

The mean V_d was 3.73 to 4.17 L/kg across all dosing conditions and was not significantly different between the 2 enantiomers ($P = .2206$). The difference in clearance (*d*-isomer > *l*-isomer) found after administration of racemic methamphetamine can be explained by the difference in elimination half-lives of each enantiomer. In general, the half-lives for *d*-methamphetamine were shorter than those for *l*-methamphetamine ($P < .0001$). After the 0.5-mg/kg dose of *d*- and *l*-methamphetamine, the half-lives were 10.3 ± 2.6 and 13.3 ± 3.5 hours, respectively ($P = .0049$). The mean half-life of *l*-methamphetamine was slightly longer after racemic administration.

After intravenous dosing, the active metabolites of methamphetamine, *d*- and *l*-amphetamine, were detectable in plasma and peaked 12 to 18 hours after dosing. The elimination of *d*- and *l*-amphetamine was slower than that of methamphetamine (Fig 3). The AUC and C_{max} values for *d*- and *l*-amphetamine were considerably smaller than those for the parent drug (Table I and Fig 3). The AUC ratios for amphetamine to methamphetamine were significantly higher for the *d*-enantiomer (0.16-0.17) than for the *l*-enantiomer (0.03-0.04). The AUC for *d*-amphetamine was 4- to 7-fold greater than that for *l*-amphetamine within the same dose levels; the *d*- and *l*-enantiomers did not show exposure bioequivalence in terms of the amphetamine AUCs. The $t_{½}$ ranged between 33.0 and 65.0 hours but showed great variability.

Pharmacodynamic measures

Physiologic measures. Compared with placebo, all doses containing *d*-methamphetamine (0.25 mg/kg, 0.5 mg/kg, and racemic) significantly increased systolic and diastolic blood pressure, heart rate, and rate-pressure product (all $P < .0001$), as well as respiration rate ($P < .05$), across time (Fig 4). The 0.25-mg/kg and 0.5-mg/kg doses of *l*-methamphetamine significantly increased heart rate and rate-pressure product ($P < .01$), yet 0.25 mg/kg of *l*-methamphetamine had no effect on blood pressure ($P = .32$).

Racemic methamphetamine produced increases in heart rate, blood pressure, and rate-pressure product similar to those of 0.5 mg/kg *d*-methamphetamine across time. Compared with corresponding doses of *l*-methamphetamine, all doses containing *d*-metham-

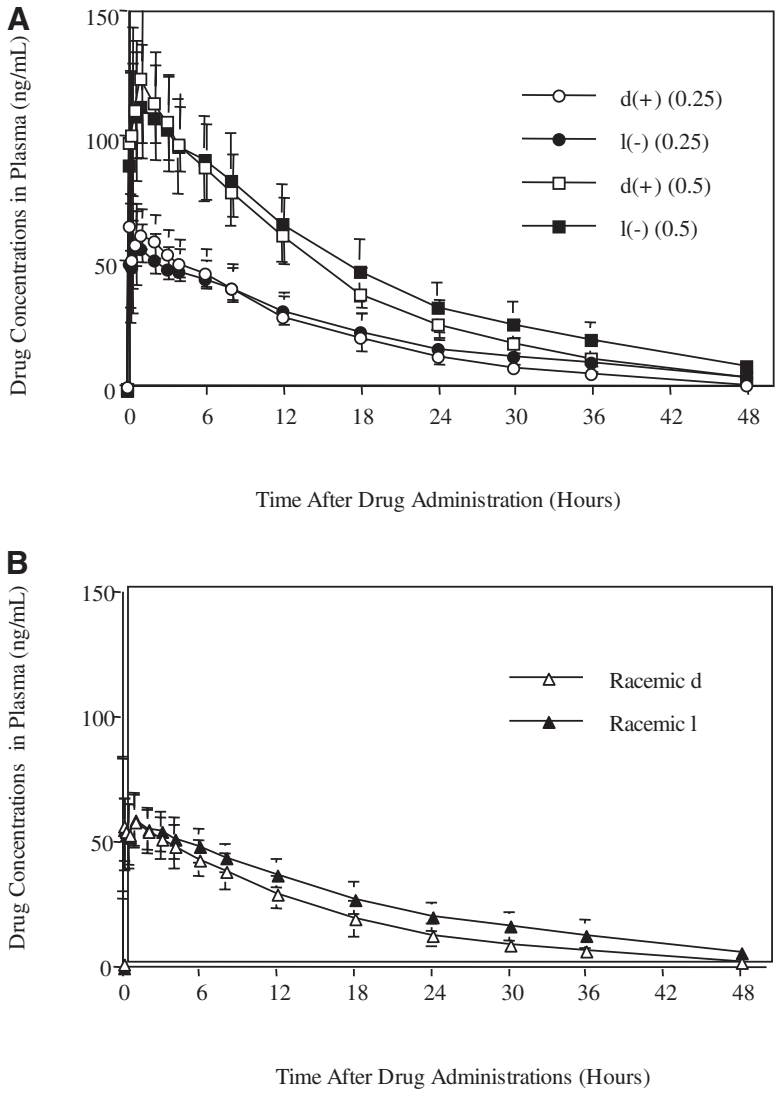

Fig 2. A, Mean plasma concentration–time curves for *d*- and *l*-methamphetamine after 0.25 and 0.5 mg/kg of the corresponding form of methamphetamine (intravenously). *Open circles*, 0.25 mg/kg of *d*-methamphetamine; *solid circles*, 0.25 mg/kg of *l*-methamphetamine; *open squares*, 0.5 mg/kg of *d*-methamphetamine; *solid squares*, 0.5 mg/kg of *l*-methamphetamine. Data are given as mean ± SD (N = 12). **B**, Mean plasma concentration–time curves for *d*- and *l*-methamphetamine after 0.5-mg/kg dose of racemic methamphetamine (*d*-methamphetamine/*l*-methamphetamine [1:1]). *Open triangles*, *d*-Methamphetamine; *solid triangles*, *l*-methamphetamine. Data are given as mean ± SD (N = 12).

phetamine produced greater and longer-lasting cardiovascular effects. For example, doses containing 0.25 mg/kg of *d*-methamphetamine produced larger and more sustained increases in cardiovascular activation than the 0.5-mg/kg *l*-methamphetamine dose. In all conditions blood pressure, heart rate, and rate-pressure product peaked at approximately 5 to 15 minutes after dosing. However, the values of these measures returned to baseline between 2 and 4 hours after either dose of *l*-methamphetamine. In contrast, the effects of *d*-methamphetamine persisted for up to 6 hours (Fig 4).

Peak systolic and diastolic blood pressure and rate-pressure product were significantly greater than with placebo for all conditions except 0.25 mg/kg of

Table I. Pharmacokinetic parameters for *d*- and *l*-methamphetamine and its metabolite amphetamine

	Dose	
Parameter	*d-Methamphetamine, 0.25 mg/kg*	*l-Methamphetamine, 0.25 mg/kg*
Methamphetamine		
$AUC_{0\text{-}t}$ (48 h) (ng · h/mL)	965.2 ± 189.7 (844.7-1085.7)	1072.2 ± 207.6 (940.3-1204.1)
$AUC_{0\text{-}\infty}$ (ng · h/mL)	1010.3 ± 210.2 (876.7-1143.8)	1190.7 ± 287.7 (1007.9-1373.5)
C_{max} (ng/mL)	76.7 ± 25.3 (60.6-92.8)	65.4 ± 18.1 (53.9-76.9)
CL ($L \cdot h^{-1} \cdot kg^{-1}$)	0.257 ± 0.053 (0.224-0.291)	0.221 ± 0.05 (0.189-0.252)
$t_{½}$ (h)	10.2 ± 2.3 (8.8-11.7)	13.6 ± 3.8 (11.2-16.0)
V_d (L/kg)	3.73 ± 0.94 (3.13-4.33)	4.15 ± 0.76 (3.66-4.63)
Amphetamine $AUC_{0\text{-}t}$ (ng · h/mL)	150.9 ± 75.4 (103.0-198.8)	32.1 ± 21.6 (13.4-45.8)
C_{max} (ng/mL)	4.8 ± 2.1 (3.4-6.1)	1.2 ± 0.8 (0.7-1.6)
$t_{½}$ (h)	32.5 ± 21.1 (18.4-46.7)	64.6 ± 41.2 (26.5-102.7)
Amphetamine/methamphetamine AUC ratio	0.163 ± 0.079 (0.118-0.207)	0.029 ± 0.019 (0.019-0.040)

$AUC_{0\text{-}t}$, Area under plasma concentration–time curve up to time of last measurable plasma concentration; $AUC_{0\text{-}\infty}$, area under plasma concentration–time curve extrapolated to infinity; C_{max}, maximum plasma concentration; CL, systemic clearance; $t_{½}$, elimination half-life; V_d, apparent volume of distribution during elimination phase; AUC, area under plasma concentration–time curve; N/A, not applicable.

l-methamphetamine ($P < .01$) (Fig 4 and Table II). Racemic methamphetamine and 0.5 mg/kg of *d*-methamphetamine increased mean peak systolic pressure values by 33 ± 18 mm Hg and 34 ± 19 mm Hg, respectively. In contrast, 0.25 and 0.5 mg/kg of *l*-methamphetamine only increased mean peak systolic blood pressure values by 14 ± 9 mm Hg and 19 ± 11 mm Hg, respectively ($P < .05$). Differences in peak heart rate were less marked between conditions. All doses of *d*- and *l*-methamphetamine lowered skin temperature more than placebo ($P < .05$). Core temperature was not significantly different between conditions.

Subjective measures. With regard to the visual analog scales, compared with placebo, the administration of 0.25 and 0.5 mg/kg of *d*-methamphetamine, 0.5 mg/kg of *l*-methamphetamine, and racemic methamphetamine significantly increased the verbal intoxication rating ($P < .0001$), as well as visual analog scale ratings of "intoxication," "any drug effect," "drug liking," "good drug effect," "high," and "bad drug effect" ($P < .01$), across time (Fig 5). No significant difference was found between 0.25 mg/kg of *l*-methamphetamine and placebo.

Racemic methamphetamine was similar to 0.25 mg/kg of *d*-methamphetamine with regard to all subjective measures and 0.5 mg/kg with regard to "intoxication" (verbal rating) (Fig 5) and monetary value (Fig 6). For several of these measures ("intoxication," "any drug effect," and "drug liking"), the 0.5-mg/kg *l*-methamphetamine dose produced significantly smaller effects compared with 0.5 mg/kg of *d*-methamphetamine ($P < .0001$) and racemic methamphetamine ($P < .05$). Its effect was also less than that of 0.25 mg/kg of *d*-methamphetamine for "drug liking" ($P < .01$). The effects of *l*-methamphetamine approached baseline at approximately 3 hours after dosing (Fig 5), whereas doses containing *d*-methamphetamine remained intoxicating for up to 6 hours. Interestingly, despite less intoxication with *l*-methamphetamine, both enantiomers had similar monetary value (Fig 6).

The peak effects for all doses containing *d*-methamphetamine (0.5 mg/kg, 0.25 mg/kg, and racemic) and 0.5 mg/kg of *l*-methamphetamine on "any drug effect," "drug liking," "good drug effect," and "high" were greater than those for placebo ($P < .05$). However, with the exception of the placebo and 0.25-mg/kg *l*-methamphetamine doses, few significant differences were found among the peak effects of the other doses (Table II). Subjects found that all doses of *d*-methamphetamine and the high dose of *l*-methamphetamine had monetary value and were willing to pay a mean of $10.70 to $14.60 per dose. In contrast, low-dose *l*-methamphetamine was worth no more than placebo.

With regard to the Profile of Mood States, no significant differences were found between conditions on any of the subscales across time, although condition-by-time interactions were significant ($P < .0001$) for the arousal, elation, fatigue, friendliness, positive mood, and vigor scales. After 0.25 and 0.5 mg/kg of *l*-methamphetamine, ratings on the majority of these scales reached a trough at approximately 1.5 hours after dosing, whereas ratings after 0.25 and 0.5 mg/kg of *d*-methamphetamine and racemic methamphetamine

Dose			
d-Methamphetamine, 0.5 mg/kg	*l-Methamphetamine, 0.5 mg/kg*	*d-Methamphetamine, (racemic [1:1])*	*l-Methamphetamine (racemic [1:1])*
1887.2 ± 335.1 (1674.3-2100.1)	2156.9 ± 452.0 (1869.7-2444.0)	937.6 ± 223.6 (795.5-1079.7)	1230.5 ± 239.0 (1078.6-1382.3)
1978.1 ± 374.7 (1740.0-2216.7)	2368.1 ± 524.1 (2035.0-2701.2)	990.7 ± 254.1 (829.3-1152.1)	1406.6 ± 350.3 (1184.1-1629.2)
131.9 ± 24.4 (116.3-147.4)	125.9 ± 30.7 (106.4-145.7)	68.9 ± 20.7 (55.8-82.0)	68.7 ± 21.6 (55.0-82.4)
0.259 ± 0.039 (0.234-0.284)	0.221 ± 0.048 (0.19-0.251)	0.266 ± 0.058 (0.229-0.302)	0.188 ± 0.046 (0.158-0.217)
10.3 ± 2.6 (8.7-11.9)	13.3 ± 3.5 (11.1-15.6)	10.7 ± 2.6 (9.0-12.4)	15.0 ± 4.6 (12.0-17.9)
3.80 ± 1.05 (3.14-4.47)	4.17 ± 1.25 (3.38-4.96)	3.97 ± 0.90 (3.40-4.54)	3.85 ± 0.86 (3.30-4.40)
295.8 ± 110.5 (225.6-366.0)	83.5 ± 40.1 (58.1-109.0)	162.4 ± 68.5 (118.9-205.9)	41.2 ± 26.5 (24.4-58.0)
9.2 ± 3.3 (7.1-11.4)	2.5 ± 1.1 (1.8-3.2)	4.9 ± 1.8 (4.9-7.6)	1.5 ± 0.8 (1.0-2.0)
33.5 ± 29.5 (14.8-52.3)	43.6 ± 24.9 (25.8-61.4)	40.6 ± 42.7 (11.9-69.3)	N/A
0.162 ± 0.067 (0.125-0.200)	0.038 ± 0.016 (0.029-0.047)	0.173 ± 0.066 (0.136-0.211)	0.032 ± 0.020 (0.021-0.044)

were still elevated and had scores above those of the other conditions.

Peak ratings of arousal, elation, positive mood, and vigor were significantly higher after 0.25 and 0.5 mg/kg of *d*-methamphetamine and racemic methamphetamine than after placebo ($P < .01$). *d*-Methamphetamine, 0.25 mg/kg, and racemic methamphetamine also produced greater ratings on the friendliness scale compared with placebo ($P < .05$). *l*-Methamphetamine, 0.5 mg/kg, produced greater ratings only on the arousal scale compared with placebo ($P < .05$).

With regard to the State-Trait Anxiety Inventory, Beck Depression Inventory, and Buss Aggression Scale, no significant differences were found between experimental conditions.

DISCUSSION

In this study we show that racemic methamphetamine has effects similar to those of pure *d*-methamphetamine, suggesting that this form of the drug has an abuse potential similar to that for *d*-methamphetamine. In contrast, although *l*-methamphetamine is psychoactive, this isomer alone generally produces less pleasurable effects than doses containing *d*-methamphetamine. Finally, we show that the differing pharmacodynamic profiles of the methamphetamine enantiomers are not a result of differences in biodisposition.

Pharmacokinetics

This is the first experiment to establish the enantiomer-specific pharmacokinetic profile of *d*- and *l*-methamphetamine after racemic methamphetamine. We found that the apparent exposure of the *d*- and *l*-enantiomers was bioequivalent (in terms of AUC in plasma as an exposure marker) after the administration of 0.25 mg/kg and 0.5 mg/kg of *d*- and *l*-methamphetamine; *d*-methamphetamine had a relative exposure close to 90% compared with *l*-methamphetamine. In contrast, after the racemate, *d*-methamphetamine had a relative exposure of 68%, which did not meet the criteria for bioequivalence.

The mechanism by which the AUC for *l*-methamphetamine was greater than that for *d*-methamphetamine after administration of the racemate is not clearly understood. The results of our study suggest that 1 enantiomer is inhibiting or inducing the metabolism of the other. For example, either *d*-methamphetamine or *d*-amphetamine may inhibit the conversion of *l*-methamphetamine to *l*-amphetamine or *l*-methamphetamine or *l*-amphetamine could induce the conversion from *d*-methamphetamine to *d*-amphetamine (or both). As shown in Table I, clearance for the *d*-isomer is similar for both doses and the racemate. For the *l*-isomer, clearance is the same at both doses but is less in the racemate, suggesting inhibition by the *d*-isomer. The AUCs of *d*- and *l*-amphetamine were proportional for all doses of *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. We investigated only one metabolite (amphetamine). Other pathways that account for the observed pharmacokinetic differences after racemic administration may be involved (eg, *p*-hydroxylation). Whether the presence (or absence) of one enantiomer can alter the metabolism of the other needs to be examined further.

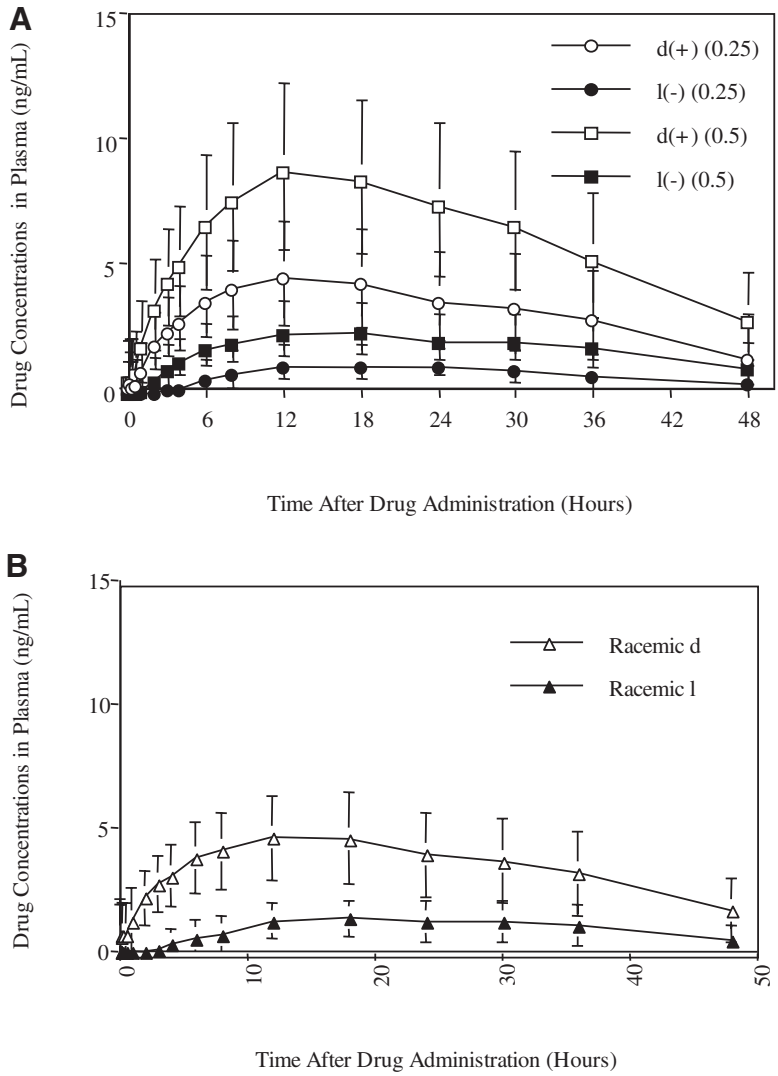

Fig 3. A, Mean plasma concentration–time curves for *d*- and *l*-amphetamine after 0.25 and 0.5 mg/kg of corresponding form of methamphetamine (intravenously). *Open circles*, 0.25 mg/kg of *d*-amphetamine; *solid circles*, 0.25 mg/kg of *l*-amphetamine; *open squares*, 0.5 mg/kg of *d*-amphetamine; *solid squares*, 0.5 mg/kg of *l*-amphetamine. Data are given as mean ± SD (N = 12). **B**, Mean plasma concentration–time curves for *d*- and *l*-amphetamine after 0.5-mg/kg dose of racemic methamphetamine (*d*-methamphetamine/*l*-methamphetamine [1:1]). *Open triangles*, *d*-Amphetamine; *solid triangles*, *l*-amphetamine. Data are given as mean ± SD (N = 12).

The reported half-life of *d*-methamphetamine is approximately 9 to 13 hours[6,24-29] and is similar to our data. Our data show that the $t_{½}$ for *l*-methamphetamine is slightly longer than that for *d*-methamphetamine (approximately 13-15 hours versus 10-11 hours); this is the first comparison of the $t_{½}$ between *d*- and *l*-methamphetamine. The longer half-life (elimination) of *l*-methamphetamine probably accounts for the difference in clearance of the enantiomers after the racemate because the volumes of distribution are similar and clearance was different only when the racemate was given.

Although the AUC and CL for each dose of *d*- and *l*-methamphetamine may be similar, a small difference in elimination could lead to an accumulation of *l*-methamphetamine in the plasma if the racemate were used repeatedly. Drug abusers often take several closely spaced doses of methamphetamine over rela-

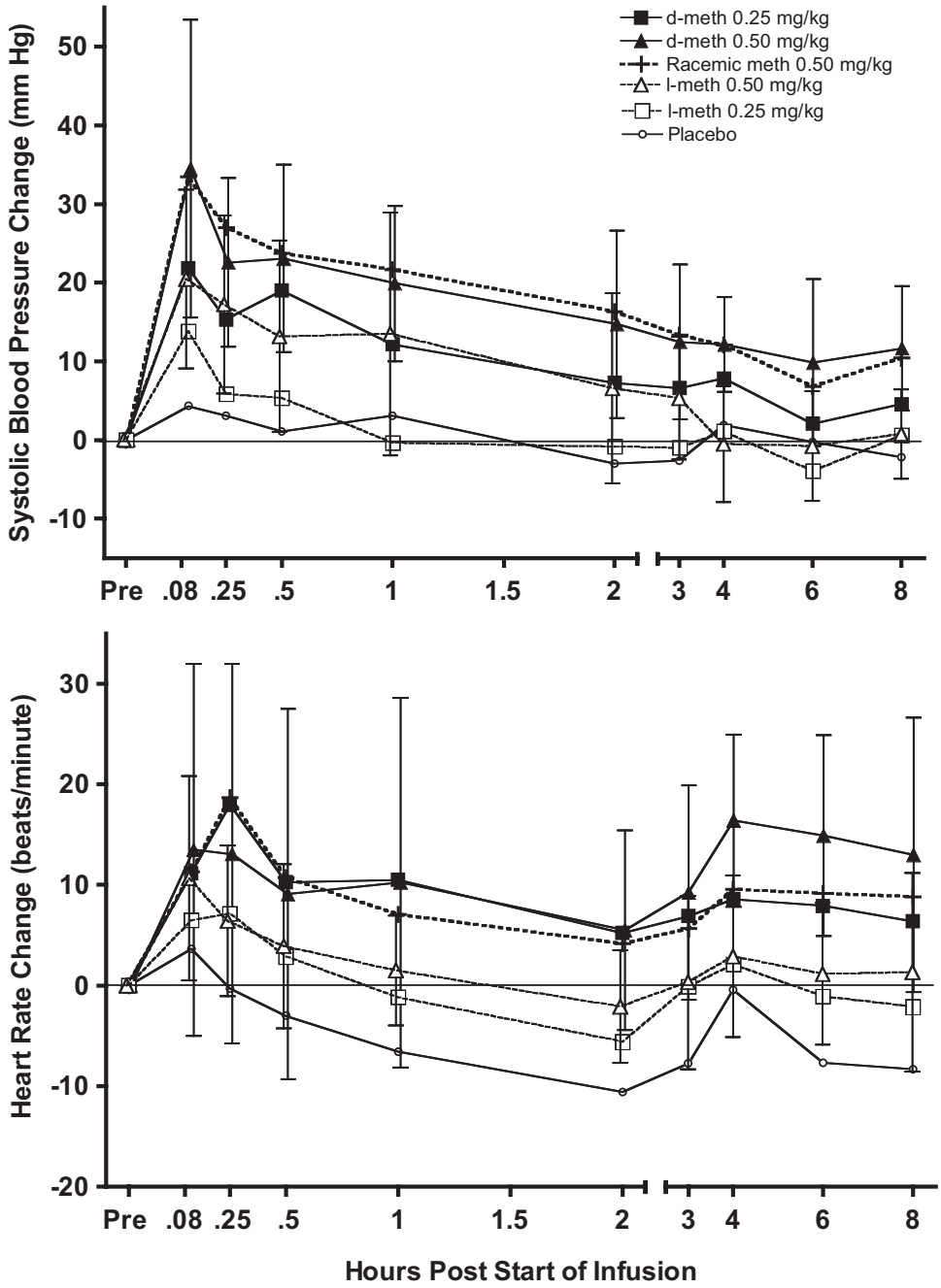

Fig 4. Mean changes in systolic blood pressure and heart rate after *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. *Solid squares*, 0.25 mg/kg of *d*-methamphetamine; *open squares*, 0.25 mg/kg of *l*-methamphetamine; *solid triangles*, 0.5 mg/kg of *d*-methamphetamine; *open triangles*, 0.5 mg/kg of *l*-methamphetamine; *dashed lines*, racemic methamphetamine; *circles*, placebo. Mean data are shown (N = 12), except for 0.5 mg/kg of *d*- and *l*-methamphetamine, for which data are given as mean ± SD. Pre, Predosing.

Table II. Mean peak changes in physiologic and subjective measures

	Condition					
		l-Methamphetamine			*d-Methamphetamine*	
Measure	*Placebo*	*0.25 mg/kg*	*0.5 mg/kg*	*Racemic methamphetamine*	*0.25 mg/kg*	*0.5 mg/kg*
Physiologic measures (SD)						
Heart rate (beats/min)	3.7 (9.8)	6.5 (8.6)	10.7 (10.2)*	18.7 (23.4)*†	18.0 (11.7)*†	13.5 (18.5)*
Systolic blood pressure (mm Hg)	4.3 (9.9)	13.8 (9.3)	19.5 (11.3)*	33.4 (17.8)*†‡§	21.8 (12.8)*	34.5 (18.9)*†‡§
Diastolic blood pressure (mm Hg)	3.9 (6.5)	6.9 (7.9)	12.8 (6.8)*	15.7 (11.7)*†	13.5 (8.0)*†	20.0 (10.1)*†‡§
Rate-pressure product (heart rate × systolic blood pressure)	911 (2164)	1862 (1387)	3219 (1580)*	4466 (3591)*†	3493 (1874)*†	4438 (2709)*†
Respiration rate (breaths/min)	0.5 (2.3)	−1.1 (3.1)	1.4 (2.3)†	1.8 (4.1)†	4.1 (1.6)*†‡‖	2.9 (2.7)*†
Skin temperature (°C)	−1.9 (2.4)	−3.9 (2.5)*	−4.2 (3.7)*	−4.4 (1.3)*	−5.7 (3.2)*	−5.2 (2.6)*
Subjective measures (SD)						
Intoxication (0-100 verbal rating)	3.1 (4.9)	14.7 (25.3)	40.4 (34.1)*†	39.2 (40.0)*	43.8 (32.3)*†	47.0 (37.8)*†
Monetary value ($)	1.1 (2.4)	4.6 (6.1)	11.3 (8.8)*†	10.7 (9.2)*	11.6 (8.2)*†	14.6 (9.6)*†
Visual analog scales (0-100)						
Intoxication	1.7 (4.7)	14.6 (20.3)	30.3 (24.9)*	24.7 (27.4)*	36.7 (25.6)*†	46.0 (35.3)*†‖
Any drug effect	1.1 (4.0)	15.7 (21.0)	33.0 (27.7)*	29.6 (28.1)*	38.5 (28.6)*†	47.7 (34.1)*†
Drug liking	2.1 (3.9)	14.9 (19.6)	28.6 (24.8)*	33.3 (28.7)*	38.9 (29.1)*†	47.7 (35.1)*†
Good drug effect	0.9 (1.9)	15.3 (20.9)	33.1 (27.4)*	28.8 (29.1)*	37.9 (30.2)*†	48.2 (35.2)*†
High	1.5 (3.7)	13.8 (20.8)	31.0 (25.9)*	25.4 (28.4)*	38.3 (28.8)*†	46.5 (35.0)*†‖
Profile of Mood States						
Arousal (−64 to 68)	−0.2 (4.4)	2.4 (5.3)	4.8 (6.7)*	7.9 (9.1)*†	9.3 (7.8)*†	7.8 (7.4)*†
Elation (0-24)	−1.2 (2.1)	0.3 (3.2)	−0.1 (1.9)	2.5 (5.7)*	3.8 (4.6)*†‡	4.8 (4.7)*†‡
Friendliness (0-28)	−0.9 (2.5)	0.2 (5.2)	1.3 (4.1)	3.9 (6.1)*	4.2 (4.7)*†	2.8 (5.1)
Positive mood (−60 to 24)	−2.2 (3.8)	−1.0 (6.4)	−0.3 (3.7)	2.7 (5.6)*†	2.8 (3.8)*†	4.7 (4.1)*†‡
Vigor (0-32)	−0.8 (3.1)	0.5 (4.5)	1.8 (3.8)	4.2 (5.1)*†	4.9 (5.0)*†‡	4.3 (4.4)*†

*Statistically significantly greater than placebo.
†Statistically significantly greater than *l*-methamphetamine, 0.25 mg/kg.
‡Statistically significantly greater than *l*-methamphetamine, 0.5 mg/kg.
§Statistically significantly greater than *d*-methamphetamine, 0.25 mg/kg.
‖Statistically significantly greater than racemic methamphetamine.

tively short time periods. Enantiomer-specific pharmacokinetic data for repeated methamphetamine dosing are not yet available in humans. There may be a greater stereoselective accumulation of *l*-methamphetamine, and this may increase adverse effects. Because the clearance of the *l*-enantiomer was less after the racemic dose, these effects may be greater for racemic methamphetamine.

The pharmacokinetics of both *d*- and *l*-methamphetamine were dose-proportional in terms of AUC in plasma. Other stimulants have nonlinear pharmacokinetics in humans. For example, we found that 3,4-methylenedioxymethamphetamine (MDMA) (ecstasy) and its metabolite 3,4-methylenedioxyamphetamine (MDA) show stereoselective and nonlinear pharmacokinetics over a range of doses from 0.5 to 1.5 mg/kg.[30] Another stimulant, methylphenidate, also has a chiral structure, and *d*-methylphenidate has a 40-fold higher plasma concentration than *l*-methylphenidate after controlled-release delivery.[31] Thus we initially speculated that methamphetamine might also have stereoselective nonlinear pharmacokinetics. However, our data show that this is not the case for methamphetamine, at least over the dose range studied. At these active and abused doses, methamphetamine follows linear pharmacoki-

netics when the plasma concentration–time profiles (AUC) are being analyzed.

After intravenous dosing, the AUC for *d*-amphetamine is larger than that for *l*-amphetamine. The ratios of AUCs for *d*-amphetamine to *d*-methamphetamine were 0.163 to 0.173. These values are consistent with recent data from our laboratories; plasma AUC ratios for *d*-amphetamine to *d*-methamphetamine were 0.16 to 0.19 after intravenous doses of deuterated or nondeuterated *d*-methamphetamine.[32] However, these AUC ratios for *d*-amphetamine to *d*-methamphetamine after intravenous dosing appeared to be lower than those found after oral dosing of *d*-methamphetamine.[28] The AUC ratios for *d*-amphetamine to *d*-methamphetamine were 0.21 ± 0.25 in plasma and 0.24 ± 0.11 in oral fluid after oral dosing. The difference in the formation of amphetamine between the oral and intravenous routes suggests the existence of some first-pass effects. No published data are available on the pharmacokinetics of amphetamine after *l*-methamphetamine administration. The ratios of AUCs for *l*-amphetamine to *l*-methamphetamine were 0.029 to 0.038, which were markedly lower than those for *d*-amphetamine to *d*-methamphetamine.

The lower AUC values for *l*-amphetamine after *l*-methamphetamine administration suggest reduced metabolism of *l*-methamphetamine to *l*-amphetamine, resulting in lower levels. Higher *d*-methamphetamine levels compared with *l*-amphetamine levels have been observed in drug abusers, probably reflecting abuse of racemic methamphetamine.[33] Thus stereoselective differences in amphetamine metabolism must be considered before the toxicology data of amphetamine in drug abusers are interpreted. Nagai et al[33] analyzed urine from 30 Japanese methamphetamine addicts and classified the data into 5 groups: In the first group (n = 16), only *d*-methamphetamine and *d*-amphetamine were found; in the second group (n = 1), only *l*-methamphetamine and *l*-amphetamine were found; in the third group (n = 5), *d*-methamphetamine and *d*-amphetamine were greater than *l*-methamphetamine and *l*-am-

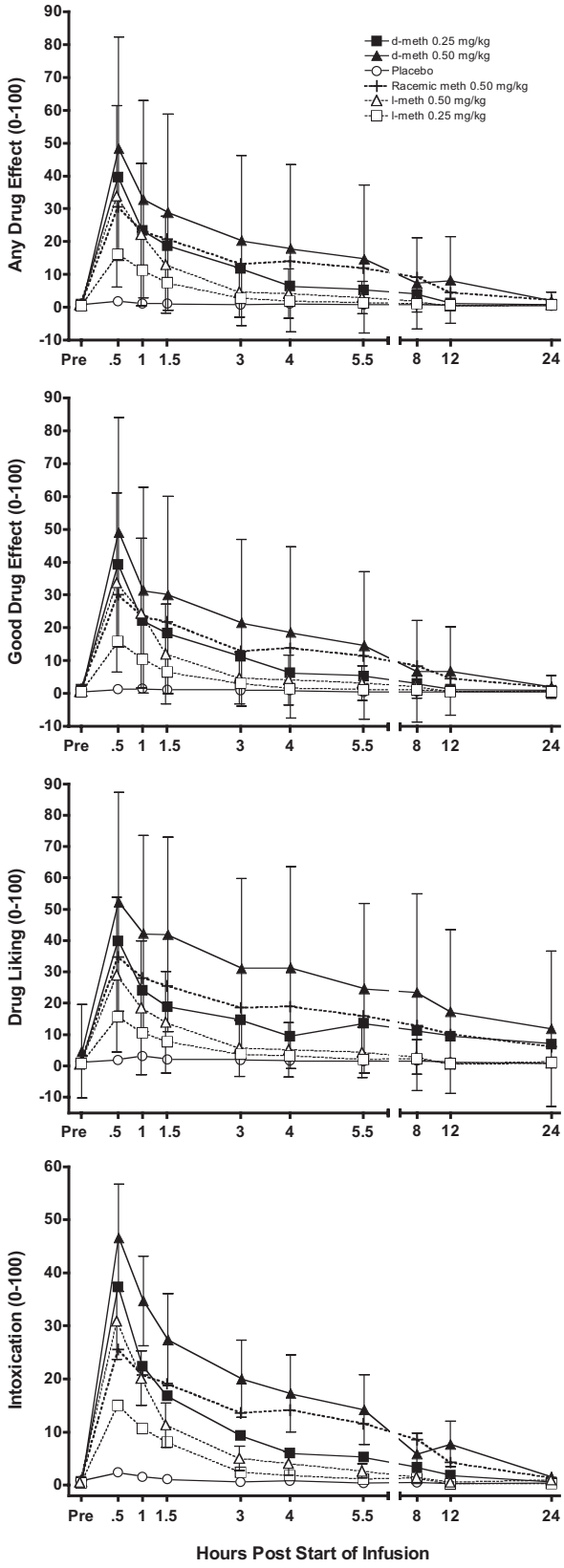

Fig 5. Mean visual analog scale subjective responses after *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. *Solid squares*, 0.25 mg/kg of *d*-methamphetamine; *open squares*, 0.25 mg/kg of *l*-methamphetamine; *solid triangles*, 0.5 mg/kg of *d*-methamphetamine; *open triangles*, 0.5 mg/kg of *l*-methamphetamine; *dashed lines*, racemic methamphetamine; *circles*, placebo. Mean data are shown (N = 12), except for 0.5 mg/kg of *d*- and *l*-methamphetamine, for which data are given as mean ± SD.

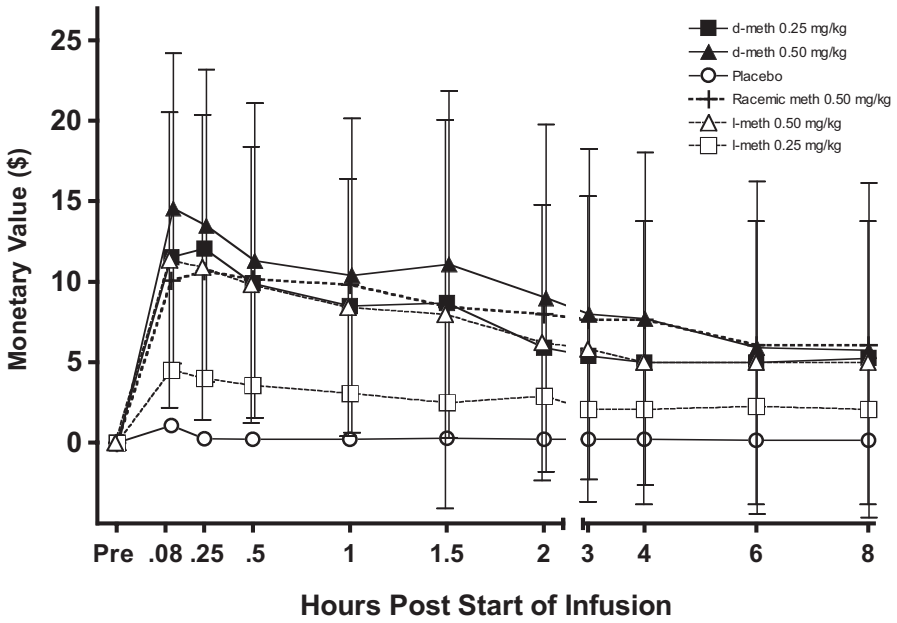

Fig 6. Mean visual analog scale subjective response for monetary value after *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. *Solid squares*, 0.25 mg/kg of *d*-methamphetamine; *open squares*, 0.25 mg/kg of *l*-methamphetamine; *solid triangles*, 0.5 mg/kg of *d*-methamphetamine; *open triangles*, 0.5 mg/kg of *l*-methamphetamine; *dashed lines*, racemic methamphetamine; *circles*, placebo. Mean data are shown (N = 12), except for 0.5 mg/kg of *d*- and *l*-methamphetamine, for which data are given as mean ± SD.

phetamine; in the fourth group (n = 4), *l*-methamphetamine and *l*-amphetamine were greater than *d*-methamphetamine and *d*-amphetamine; and in the fifth group (n = 4), *l*-methamphetamine was greater than *d*-amphetamine and *l*-amphetamine was less than *d*-amphetamine. The metabolic profile found in the fifth group supports our finding that the AUC for amphetamine is much smaller for the *l*-enantiomer compared with the *d*-enantiomer after methamphetamine administration. Although the methamphetamine crystals analyzed by Nagai et al did not contain the racemic form (1:1), these findings show that methamphetamine can be abused as either *d*-methamphetamine or *l*-methamphetamine or as some combination of both enantiomers.

We found that amphetamine pharmacokinetics may depend on the dose of the parent drug, methamphetamine. Within the same enantiomers, the AUC ratios of amphetamine between the 2 doses (0.5 and 0.25 mg/kg) were 1.9 for the *d*-isomer and 2.6 for the *l*-isomer. A dose-proportional increase in the AUC for *d*-amphetamine occurred after *d*-methamphetamine administration. However, our data suggest that a higher dose of *l*-methamphetamine may produce a slight increase in the AUC for *l*-amphetamine that is not dose-proportional. The underlying mechanism for this finding is not clear. It is possible that *d*-methamphetamine inhibits the metabolism of *d*-amphetamine or that the enzyme that mediates the conversion of *d*-methamphetamine to *d*-amphetamine may be limited or saturated.

Pharmacodynamics

Differences in cardiovascular and subjective effects also occurred between enantiomers. In general, *d*-methamphetamine and racemic methamphetamine produced significantly longer-lasting cardiovascular and subjective effects than *l*-methamphetamine. Although the peak effects of 0.5 mg/kg of *l*-methamphetamine were similar to those with the doses containing *d*-methamphetamine, these effects dissipated rapidly (Figs 4 and 5). The 0.5-mg/kg *l*-methamphetamine dose produced significantly fewer subjective effects across time than the comparable dose of *d*-methamphetamine and racemic methamphetamine. The exception was monetary value, which remained similar to all doses containing *d*-methamphetamine across time (Fig 6). For those effects that were increased by the higher *l*-methamphetamine dose, the magnitude was similar to the

0.25-mg/kg *d*-methamphetamine dose. In contrast, the 0.25-mg/kg dose of *l*-methamphetamine produced few physiologic or subjective effects, often no greater than placebo. Both isomers produced a dose-response effect for the majority of subjective measures.

Our findings illustrate that the small enantiomer-specific differences in pharmacokinetics do not explain the differences between isomers with regard to the cardiovascular and subjective effects. The pharmacodynamic differences between isomers could be explained by the metabolite of *d*-methamphetamine, *d*-amphetamine (Fig 3). Although the AUC for the metabolite amphetamine was considerably smaller than that for the parent, methamphetamine, amphetamine by itself is a potent CNS stimulant. The distribution of *d*-amphetamine in the striatum is rapid after *d*-methamphetamine administration.[34] Therefore the enantiomer-specific difference in amphetamine disposition may increase brain levels of *d*-amphetamine, producing significant CNS effects.

Methamphetamine is thought to exert its behavioral effects by increasing midbrain synaptic concentrations of dopamine and norepinephrine by a combination of enhanced release and uptake inhibition.[35-37] However, dopamine release in the nucleus accumbens appears to be most involved in mediating the rewarding effects.[38] The amphetamines interact with several components of the monoamine synapse including the neuronal transporter (uptake transporter), vesicular storage system, and monoamine oxidase.[39,40] Reports indicate that these actions on the synapse are stereoselective, with the *d*-enantiomer being more potent than the *l*-enantiomer.[12,13]

The stereoisomers of methamphetamine produce markedly different dopamine, norepinephrine, and serotonin responses in various brain regions in rats.[41,42] *d*-Methamphetamine (2 mg/kg) is more potent in releasing caudate dopamine than *l*-methamphetamine (12 and 18 mg/kg). By use of in vitro uptake and release assays, *d*-methamphetamine (50% effective concentration [EC_{50}], 24.5 ± 2.1 nmol/L) was 17 times more potent in releasing dopamine than *l*-methamphetamine (EC_{50}, 416 ± 20 nmol/L) and significantly more potent in blocking dopamine uptake (inhibition constant [K_i], 114 ± 11 nm versus 4840 ± 178 nm).[12,13]

These differences in dopamine release could explain the significantly greater subjective effects produced by *d*-methamphetamine (racemic and 0.5 mg/kg) compared with *l*-methamphetamine (0.5 mg/kg) on several measures (ie, "intoxication," "any drug effect," and "drug liking"). The effects of 0.5 mg/kg of *l*-methamphetamine were less than even a lower dose of *d*-methamphetamine (0.25 mg/kg) for "drug liking." Furthermore, the subjective effects for *l*-methamphetamine dissipated relatively quickly, reaching baseline values at 3 hours after dosing compared with approximately 6 hours for *d*-methamphetamine. Peak ratings for arousal, elation, positive mood, and vigor were significantly higher for doses containing *d*-methamphetamine than for placebo and continued to increase over time, whereas *l*-methamphetamine (0.5 mg/kg) produced greater ratings only on arousal, which also dissipated rapidly (trough at 1.5 hours).

The report of Morgan[11] that the cardiovascular system is more affected by the *l*-isomer of amphetamine might lead us to expect a similar or greater cardiovascular response after *l*-methamphetamine. In contrast, all doses containing *d*-methamphetamine significantly increased systolic and diastolic blood pressure, heart rate, and rate-pressure product, whereas *l*-methamphetamine had significantly fewer cardiovascular effects. *d*-Methamphetamine may also activate α-adrenergic receptors by releasing norepinephrine from peripheral sympathetic terminals via monoamine transport mechanisms. In vitro, *d*-methamphetamine's potency for norepinephrine release is twice that of *l*-methamphetamine, which may account for the greater cardiovascular effects that we observed in response to *d*-methamphetamine.[13] Previous reports in humans found that after *d*-methamphetamine administration, systolic blood pressure and diastolic blood pressure increase significantly.[5] We found that heart rate increases but only slightly and that rate-pressure product increases markedly as a result of the increased systolic blood pressure.[5,6,43]

In studies of a related stimulant-like drug, MDMA (ecstasy),[44] the ability of serotonergic antagonists to attenuate MDMA cardiovascular effects suggests that serotonin may play a role in this physiologic response.[45,46] The similar caudate serotonin levels for *d*-methamphetamine (2 mg/kg) and *l*-methamphetamine (12 mg/kg) found in rats could predict the relatively lower cardiovascular effect from *l*-methamphetamine found in our study.[41] In addition, increases in both behavioral and neurotransmitter response to *l*-methamphetamine are not dose-proportional,[41] so the relative effects of the *d*- and *l*-isomer may vary considerably with the doses administered.

Of interest, racemic methamphetamine had effects similar to those of the highest dose of *d*-methamphetamine. Because of the greater cardiovascular and subjective effects of the *d*-isomer, we would expect the racemic mixture (50:50) of *d*-methamphetamine/*l*-methamphetamine to be less rewarding as a psychostimu-

lant, yet our findings do not support this. There is no simple explanation of why racemic methamphetamine is often as potent as an equal quantity of *d*-methamphetamine. The AUC of *d*-methamphetamine or *l*-methamphetamine given as 0.25 mg/kg alone and the AUC of the same isomer when administered as 0.25 mg/kg in the racemic mixture were equivalent, suggesting similar pharmacologic effects between doses. However, racemic methamphetamine has more than an additive effect compared with the equivalent doses of *d*-methamphetamine/*l*-methamphetamine in the racemic mixture. One possible explanation is that differences may be a result of the metabolite *d*-amphetamine. Both subjective and cardiac effects of racemic methamphetamine were often similar to those of the dose containing more *d*-methamphetamine. In contrast, our lower dose of *d*-methamphetamine (0.25 mg/kg) was often similar to the high dose of *l*-methamphetamine (0.5 mg/kg) (Figs 4 and 5). This suggests that behavioral and cardiac activation by *l*-methamphetamine may be a result of differences in receptor dynamics or may be acting through different pathways or mechanisms than *d*-methamphetamine.

Precursor regulation

Propelled by the methamphetamine epidemic, 20 states are considering legislation that would extend precursor regulation to pseudoephedrine, a drug used in many common OTC cold medicines. Although no one really knows exactly where illicit methamphetamine is produced, media reports suggest that most (80%) of the nation's methamphetamine is smuggled from Mexico or produced in large-scale laboratories. The rest is produced in small, often home-based laboratories that these new laws target.[2,47] Because large laboratories that probably do not rely on OTC cold medicines produce the majority of illicit methamphetamine, the proposed legislation may do little to reduce methamphetamine availability. For example, although seizures of small clandestine laboratories have decreased by 81% in Oklahoma, there are no reports indicating that the rate of illicit supply or abuse has fallen.[2,47] Furthermore, there are indications that pseudoephedrine is now being smuggled from Southeast Asia into the United States.[48] Before further attempts in precursor regulation are promulgated, we believe it is critical to understand the expected consequences of likely changes in precursors on methamphetamine pharmacologic and toxicologic characteristics. Most authorities believe that, in addition to decreasing supply through precursor regulation, treatment and prevention programs will be needed to reduce demand for methamphetamine.[49]

Study limitations

There are limitations to our study. We investigated only the intravenous route of methamphetamine administration. Administration orally, nasally, or via smoking might result in other pharmacologic differences between the 2 enantiomers. We examined only 2 doses of *d*- and *l*-methamphetamine over a limited dose range; however, we achieved subjective and cardiovascular responses that were 25% to 50% of the maximum considered safe, and our low dose of *l*-methamphetamine had effects similar to those of placebo. Higher doses could be toxic and difficult to study safely, even under controlled laboratory conditions, and lower doses probably have minimal effects in partially tolerant abusers. We only investigated single intravenous doses. Because drug addicts often binge, the pharmacologic characteristics of repeated-dosing experiments may provide further insights. Finally, our primary interests were in methamphetamine and its active metabolite, amphetamine, in plasma. Other metabolic pathways such as *p*-hydroxylation and urinary excretion are also important but were not examined in this study.

Conclusions

d-Methamphetamine, alone or as a racemate, produces more subjective and cardiovascular effects than equivalent doses of *l*-methamphetamine. Although a relatively large dose of *l*-methamphetamine produced similar peak subjective and cardiovascular effects, they dissipated more rapidly. The enantiomer-specific difference in *d*-amphetamine disposition and the greater dopamine and serotonin responses in animals with *d*-methamphetamine suggest pharmacologic mechanisms for the differences in response observed with the isomers.[12,13,41] On the basis of our data, we predict that racemic methamphetamine will have an abuse potential similar to that for *d*-methamphetamine. Fortunately, we would not predict a significant increase in behavioral or cardiovascular toxicity with abuse of racemic mixtures; *l*-methamphetamine does not appear to increase the toxic effects of *d*-methamphetamine. However, toxic effects may increase, especially under repeated-dosing conditions, because the stereoselective differences in the pharmacokinetics of *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine may lead to an accumulation of *l*-methamphetamine. The health risks (if any) associated with this remain to be identified. With the assumption that illicit producers will switch precursors (as they have in the past) and racemic methamphetamine will become widely available, it is unlikely that this different form of the drug will increase the rates of abuse or toxic effects. Accordingly,

the potential benefits of precursor control need to be weighed against the burdens of regulation.

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The authors report no conflict of interest.

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