Volume 16 Number 1

Journal of

February 1996

Clinical Psychopharmacology

JOURNAL OF
CLINICAL PSYCHOPHARMACOLOGY

VOLUME 16 FEBRUARY 1996 NUMBER 1

CONTENTS

JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY (ISSN 0271-0749) is published bimonthly, in Feb., Apr., June, Aug., Oct., and Dec., by Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201-2436. Subscription rates $114.00 ($149.00 foreign); institutions $174.00 ($209.00 foreign); in-training $57.00 ($92.00 foreign); single copy $24.00 ($26.00 foreign). (Prices subject to change). The GST number for Canadian subscribers is 123394371. Second class postage paid at Baltimore, MD, and at additional mailing offices. POSTMASTER: Send address changes to **JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY,** 351 West Camden Street, Baltimore, MD 21201-2436. Indexed by *Current Contents* (*Clinical Medicine, Life Sciences, Science Citation Index, Research Alert, ISI/BioMed*), *Index Medicus, Excerpta Medica, BIOSIS, PsychInfo* and *Toxicology Abstracts*. Printed in U.S.A.

0271-0749/96/1601-0072$03.00/0
Journal of Clinical Psychopharmacology

Vol. 16, No. 1
Printed in U.S.A.

Acute Tolerance to Subjective but not Cardiovascular Effects of *d*-Amphetamine in Normal, Healthy Men

LISA H. BRAUER, PHD,[1,4] JOHN AMBRE, MD, PHD,[2] AND HARRIET DE WIT, PHD[3]

[1]Postdoctoral Fellow, Department of Psychiatry, University of Chicago, Chicago, Illinois; [2]Director, Department of Toxicology and Drug Abuse, American Medical Association, Chicago, Illinois; [3]Associate Professor, Department of Psychiatry, University of Chicago, Chicago, Illinois; and [4]Research Associate, Department of Psychiatry, Duke University Medical Center, Durham, NC

This is a descriptive report on the relationship between the pharmacokinetics and pharmacodynamics of *d*-amphetamine in healthy, normal volunteers. Six men, aged 22 to 31, attended two experimental sessions during which they received single oral doses of 20 mg of *d*-amphetamine. Plasma levels of drug and measures of drug effect were collected predrug and at regular intervals for 24 hours after drug administration. Plasma drug levels peaked at 4 hours and remained at detectable levels for 24 hours after drug administration. Subjective ratings, including "feel drug" and "feel high" peaked at 1½ to 2 hours and returned to baseline levels by 3 to 4 hours. Evaluation of phase plots (*i.e.*, drug effect vs. drug concentration) indicated that acute tolerance developed to the subjective but not to the cardiopressor effects of *d*-amphetamine. This finding implies that individuals who repeatedly administer the drug to maintain certain levels of subjective effects may increase plasma drug levels and physiologic effects to toxic levels. (J Clin Psychopharmacol 1996;16:72–76)

THE RELATIONSHIP BETWEEN drug concentration in plasma and drug response is important to investigate because understanding pharmacokinetic-pharmacodynamic relationships may improve our knowledge of the basic mechanisms by which drugs produce their effects. For example, these relationships may reveal the extent to which observed drug effects are directly related to receptor occupancy or to the effects of metabolites.[1] The relationship between drug concentration and drug effect is particularly important in the study of drugs that are abused, because it may influence repeated drug administration within an episode of drug-taking. A major factor believed to maintain repeated ingestion of a drug is its mood-altering, or subjective effects.[2] The drug effects that appear to be most desirable to drug abusers are those experienced during the onset of the drug effect (*e.g.*, the "rush").[3,4] After this initial effect, acute tolerance may develop to the mood-altering effects of the drug. That is, after the drug produces its initial effects on mood, these effects may rapidly dissipate, even though plasma levels of the drug are still increasing. However, tolerance to other effects of the drug, such as the cardiovascular effects, may not develop at the same rate. Consequently, as individuals repeatedly self-administer a drug to maintain desired mood effects, they may inadvertently escalate plasma concentrations and cardiovascular effects to toxic levels.

Several investigators have examined the pharmacokinetic and pharmacodynamic profiles of cocaine in cocaine abusers,[5–9] and the observed relationship between drug concentrations in plasma and drug effects has been inconsistent across studies. For example, Javaid and colleagues[5] found that the times to peak for subjective and physiologic effects of single doses of cocaine corresponded well with plasma levels, but that subjective and physiologic effects had returned to baseline values before plasma levels declined. These findings suggest that acute tolerance developed to both subjective and physiologic effects of cocaine. Fischman and colleagues[6] also demonstrated acute tolerance to both subjective and physiologic effects of single doses of cocaine using different procedures and different measures of drug effect. Other studies have shown that acute tolerance to the subjective and certain physiologic effects of cocaine may develop at different rates.[8,9] For example, Foltin and associates[8] examined subjective and physiologic responses to repeated doses of 96 mg of intranasal cocaine. They found that blood pressure increases corresponded closely with increases in plasma levels of cocaine but that heart rate and subjective responses

Received January 10, 1995, and accepted June 22, 1995.
Address requests for reprints to: Harriet de Wit, PhD, Department of Psychiatry, University of Chicago, MC3077, 5841 South Maryland Ave., Chicago, IL 60637.

reached their peak before plasma levels and declined much more rapidly. This pattern of results suggested that acute tolerance developed to the subjective, but not to the pressor, effects of cocaine. However, a subsequent reanalysis of their data using more quantitative methods showed that tolerance, in fact, developed to the pressor effects of cocaine as well.[10]

Few studies have investigated the relationship between plasma levels of *d*-amphetamine and drug effects in normal, healthy volunteers.[11–13] In general, studies with normal volunteers have found dissociation between plasma levels and drug effects. For example, Angrist and coworkers[13] administered 0.25 mg/kg oral *d*-amphetamine to normal subjects and measured subjective and cardiovascular effects and plasma levels over a 5-hour period. They found that, while plasma levels peaked at 2 to 3 hours after drug administration, cardiovascular and subjective responses peaked at 1 and 2 hours, respectively. Both cardiovascular and subjective effects of *d*-amphetamine had declined by 4 hours after drug administration, while blood levels remained significantly elevated.

Studies with normal volunteers are important to examine tolerance without the possible influence of variables related to repeated drug use, such as conditioned responses and neuroadaptation, which may alter the pharmacodynamic profiles of drugs in drug abusers. Thus, the purpose of this descriptive report is to extend previous findings by examining the relationship between plasma *d*-amphetamine levels and drug effects over a longer period of time (*i.e.*, 24 hours) and on a broader range of dependent measures in normal volunteers. By examining this relationship over a 24-hour period, both ascending and descending limbs of the plasma drug level- and drug effect-time curves can be characterized. Six male subjects attended two sessions during which they received 20 mg of oral *d*-amphetamine. Plasma levels and subjective and physiologic responses were measured predrug and for 24 hours thereafter.

Methods

Subjects

Six healthy men aged 22 to 31 (mean = 27 years) were recruited from the university community with advertisements and posters. To minimize possible pharmacokinetic variability related to gender differences, only men were tested.[14] Interested participants were initially screened over the telephone. Individuals who were within 10% of normal body weight (mean = 74.2 kg, range = 65.4–84.1), reported drinking at least one alcoholic beverage per week (mean = 4.0, range = 1–8), were high school graduates, and were native English speakers were asked to come to the laboratory for an interview. Subjects were screened by a clinical psychologist and a cardiologist to rule out any psychosocial or medical condition that might contraindicate participation in the study. Candidates with past or current serious medical conditions, including cardiac or liver disease, high blood pressure, or abnormal electrocardiograms, or who met criteria for past or current major axis I disorders (excluding nicotine dependence; DSM-III-R) were excluded.

Procedures

Data were collected as part of another study designed to investigate interactions between *d*-amphetamine and the dopamine antagonist pimozide. Because pimozide had no detectable effect on any measure of response to *d*-amphetamine (unpublished data; see below), the results are presented as the mean of the two sessions with *d*-amphetamine. Each subject attended two sessions separated by 1 week. Sessions were conducted in the University of Chicago Clinical Research Center (CRC) and lasted from 6:30 a.m. until 9:45 a.m. the following day. During each session, subjects received a capsule containing 20 mg of *d*-amphetamine. There was no placebo control condition in this study because the variable of interest was plasma *d*-amphetamine levels over time. Subjects were told that the capsules might contain a stimulant/appetite suppressant, sedative/minor tranquilizer, major tranquilizer, or placebo. Subjects gave written informed consent before participation. This study was approved by the University of Chicago Institutional Review Board.

Pairs of subjects were admitted to the CRC at 6:30 a.m. after an overnight fast. Subjects were provided with one glass of clear fruit juice upon arrival, but no other food or drink was available until 1 p.m., when they ate a light lunch. At 7 a.m., a baseline blood sample was obtained from an intravenous catheter placed in the subjects' nondominant arms. Subjects were then allowed to relax and acclimate to the catheter and the surroundings. At 7:20 a.m. they completed baseline mood questionnaires, and physiologic and behavioral measures were obtained (see below). These measures were collected again at 8:30 and at 9:20 a.m. At 9:30 a.m., subjects ingested a capsule containing 20 mg of *d*-amphetamine (Dexedrine; Smith, Kline and French, Philadelphia, PA). This dose of *d*-amphetamine has been shown in previous studies in our laboratory to produce reliable effects on mood without producing adverse physiologic effects.[15] Blood samples (10 ml) were collected before *d*-amphetamine administration (9:25 a.m.) and at 10, 10:30, 11, 11:30, 12 p.m., 12:30, 1, 1:30, 2:30, 3:30, 9:30 p.m. and 9:30 a.m. Subjective and behavioral measures were obtained at the same times as blood samples, whereas physiologic measures were only collected at

hourly intervals until 3:30 p.m. and then at 9:30 p.m. and 9:30 the next morning. When subjects were not completing questionnaires, they relaxed in the testing room. They were allowed to read, watch television, play games, talk, or engage in other leisure activities. After completing the study, subjects attended a debriefing interview and were paid $160.

Dependent measures

Subjective effects were assessed with the Profile of Mood States,[16,17] the 49-item Addiction Research Center Inventory (ARCI[18,19]), a locally developed Drug Effects Questionnaire (DEQ; unpublished), and several Visual Analog Scales. Each of these questionnaires has been shown to be sensitive to the mood effects of a variety of psychoactive drugs, including stimulants.[20] Only data from the MBG (euphoria) and A (stimulant-like effects) scales of the ARCI, and the "feel drug," "like drug," and "feel high" scales of the DEQ will be presented here. Physiologic measures included blood pressure and heart rate and were obtained using a Dynamap Vital Signs Monitor (Critikon, Inc., Palatine, IL). Plasma samples were analyzed for *d*-amphetamine using positive chemical ionization gas chromatography mass spectrometry (Center for Human Toxicology, Salt Lake City, UT) using procedures described elsewhere.[21,22]

Data analyses

Measures obtained immediately before *d*-amphetamine administration (9:25 a.m.) were used as baseline in all analyses. Because analyses of variance revealed that there were no significant differences between the two sessions on any measure, either between the first and second sessions or between sessions when subjects did or did not receive pimozide, the two determinations for each subject were averaged. Data for each variable were plotted, both across time and as phase plots, and inspected to determine whether the pharmacokinetic and pharmacodynamic profiles of *d*-amphetamine covaried (see Figs. 1 and 2).

Results

The time course of plasma levels and several subjective and physiologic effects of *d*-amphetamine are shown in Figure 1. Plasma levels were detectable 1 hour after drug administration and reached a peak level of 40 ng/ml at 4 hours. Plasma levels plateaued and then began to decline 5 hours after drug administration but remained detectable even at 24 hours.

Subjective effects produced a different profile. In general, subjective effects of *d*-amphetamine reached peak levels at 1½ to 2 hours and declined significantly within the first 6 hours of the session. Ratings of "feel drug," "like drug," "feel high," and "euphoria" (ARCI MBG) reached peak levels at 1½ hours, while stimulant-like effects (ARCI A) peaked at 2 hours. Ratings of "feel drug," "like drug," and "feel high" had returned to baseline levels by hour 5, and scores on the A and MBG scales of the ARCI reached baseline levels at 12 hours postdrug (Fig. 1).

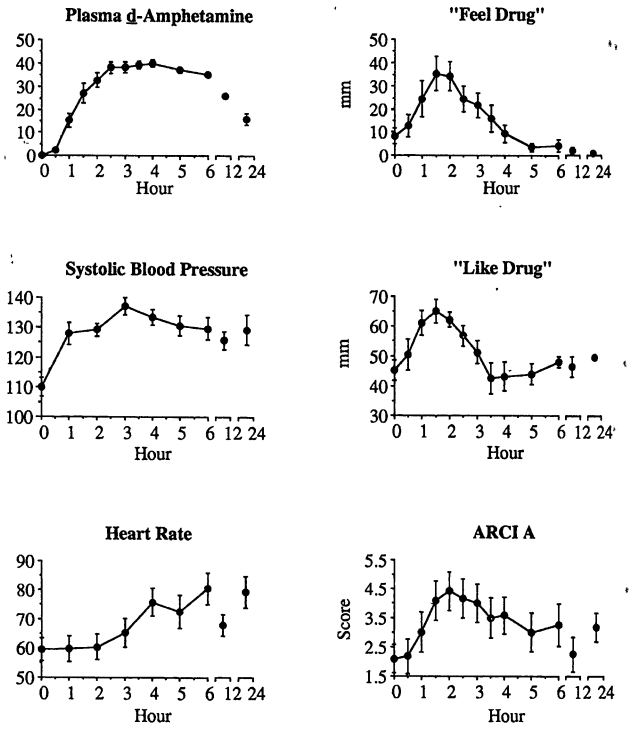

FIG. 1. Mean (SE) plasma levels and drug effects of 20 mg *d*-amphetamine as a function of time. The 0 time point shows values obtained immediately before drug administration (9:25 a.m.), and each subsequent point shows values obtained at various intervals thereafter. "Feel drug" and "like drug" scores range from 0 to 100, and Addiction Research Center Inventory A scale scores range from 0 to 11.

Figure 1 also shows the time course of cardiovascular responses to *d*-amphetamine. In general, changes in systolic blood pressure paralleled changes in plasma drug concentration over time, but blood pressure was still slightly elevated when plasma levels were beginning to decline. In contrast, heart rate remained low while plasma levels were increasing and began to rise 4 hours after drug administration. Heart rate continued to increase for the duration of the session.

Phase plots of plasma drug concentration versus drug effect are shown in Figure 2. This figure illustrates that the subjective effects of *d*-amphetamine show considerable clockwise hysteresis: the relationship between plasma concentration and subjective response changes over the rising and falling phases of the drug concentration curve. This pattern of results suggests the development of acute tolerance. In contrast, the car-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.