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

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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[6] 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 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 response

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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 6-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

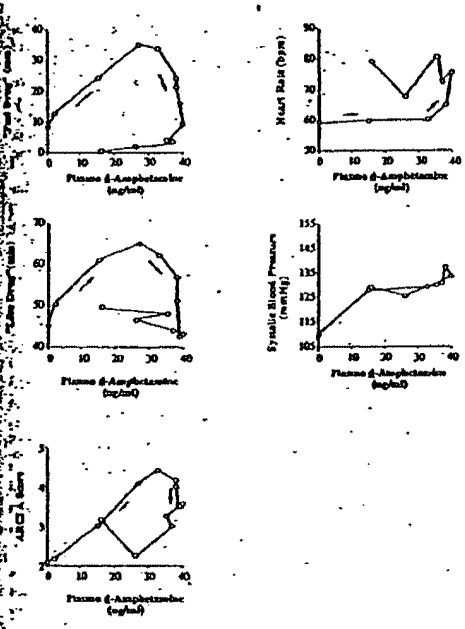


FIG. 2. Phase plots of drug concentration versus drug effect for systolic blood pressure and for representative subjective responses to d-amphetamine. Subjective responses to d-amphetamine (left panel) show marked clockwise hysteresis, suggestive of acute tolerance to these effects. In contrast, the panel on the right shows no evidence of hysteresis, and thus of acute tolerance, to the cardiopressor effects of d-amphetamine. (ARCI, Addiction Research Center Inventory).

diopressor effects of *d*-amphetamine show little or no hysteresis: the maximal effect on blood pressure is produced by plasma *d*-amphetamine concentration of about 15 to 20 ng/ml and is sustained throughout the experimental session. Thus, there is no evidence of acute tolerance development to these effects.

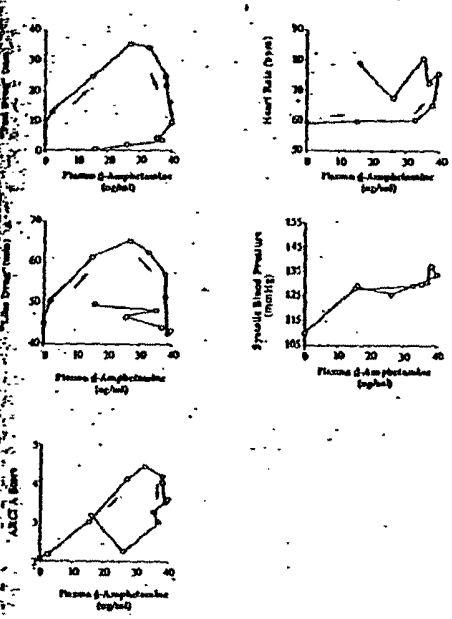
Discussion

The purpose of this report was to describe the relationship between plasma concentrations and subjective and physiologic effects of *d*-amphetamine in six healthy, normal men. The results of the study indicate that the time course of plasma levels and drug effects of *d*-amphetamine are dissociable. For example, although plasma levels peaked 4 hours after drug administration and were still detectable at 24 hours, subjective effects peaked at approximately 2 hours and declined within 6 hours (Fig. 1). Systolic blood pressure rose quickly, and the increase was sustained. The heart rate response was apparently dampened initially and then exhibited a delayed rise. These results suggest tolerance to the subjective effects of *d*-amphetamine but not to the pressor effects. At similar plasma drug concentrations, subjective responses were greater on the ascending compared with the descending limb of the concentration-effect curve. This is evident in the phase plots as marked clockwise hysteresis (Fig. 2). In the absence of evidence for the production of active antagonist metabolites[1] of *d*-amphetamine, the most likely explanation of this finding is the development of acute tolerance. Cocaine exhibits a similar phenomenon (*e.g.*, see ref. 7).

An interesting finding in this study was the time course of the heart rate effects of *d*-amphetamine. Heart rate remained at baseline levels until 5 hours into the session and began to rise steadily thereafter, at a time when plasma levels were beginning to decline (see Fig. 1). A similar pattern of physiologic response to *d*-amphetamine has been reported in a study by Martin and colleagues.[13] They found that although blood pressure rose steadily within the 5 hours after drug administration, heart rate remained low during this time and did not begin to increase until blood pressure was declining. Martin and colleagues[13] attributed this relationship to reflexive slowing of the heart rate in response to increased blood pressure. Our findings also suggest an early physiologic reflex response and a later adjustment to the pressor rise. These cardiovascular responses are consistent with the mechanism of action of *d*-amphetamine (*i.e.*, release of norepinephrine at sympathetic nerve synapses). Norepinephrine infusion causes a pressor response with reflex cardiac slowing. The actual heart rate depends on a balance of chronotropic modifying factors.[13]

Although the results of this study are suggestive of the development of acute tolerance to some of the effects of *d*-amphetamine, the absence of a placebo control condition makes it difficult to rule out other possible interpretations of the data. For example, the time course of the cardiovascular effects of *d*-amphetamine could be related to nonpharmacologic factors such as uncontrolled variations related to circadian rhythms or to environmental events. The time course of the subjective effects could be the result of adaptation to repeated administration of the questionnaires. These issues can only be addressed by subsequent studies including a placebo control condition. Nevertheless, the results are consistent with the development of acute tolerance and are in agreement with the findings of studies with another psychomotor stimulant, cocaine (see above).

The findings of this study have implications for understanding the toxicity sometimes associated with stimulant abuse. It is commonly assumed that individuals self-administer doses based on the subjective effects experienced.[2] Thus, as subjective effects begin to wane,



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The findings of this study have implications for understanding the toxicity sometimes associated with stimulant abuse. It is commonly assumed that individuals self-administer doses based on the subjective effects experienced.[2] Thus, as subjective effects begin to wane,

individuals may take additional doses of the drug. The consequences of such a pattern may be dangerous because subjective effects appear to dissipate at times when plasma levels and physiologic responses are still maximal or rising. Thus, individuals who repeatedly self-administer the drug in an attempt to maintain a certain level of euphoria may be at increased risk for cardiovascular toxicity. These results also suggest that acute tolerance to the subjective effects of *d*-amphetamine may develop in drug-naive, normal volunteers in much the same manner as acute tolerance to cocaine's effects develops in cocaine abusers. Additional studies with *d*-amphetamine should be conducted to characterize more fully the relationship between plasma levels and drug effects.

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