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Subjective Responses and Excretion Patterns of Dextroamphetamine After the Administration of Therapeutic Doses

Amphetamine, a potent sympathomimetic amine, is widely misused [*1–5*]. It is also employed therapeutically in the treatment of certain childhood behavioral disorders. Urinary amphetamine concentrations of 2 mg/100 ml or greater which occur after the use of large intravenous doses are readily detected by routine toxicological examination. The estimation of the drug in body fluids following orally administered therapeutic doses can also be important in forensic medicine [*6–8*].

Several investigators have evaluated the excretion of excessive doses of amphetamine and the profound effect of urinary pH on its excretion and metabolic patterns [*9–12*]. Little data have been presented concerning urinary excretion patterns after doses in the therapeutic range. For this reason, the symptoms and excretion of dextroamphetamine in normal volunteers under controlled laboratory conditions were examined.

Methods

Twelve healthy males between the ages of 21 and 30 were selected from those who volunteered. Each subject received a complete history, physical examination, blood chemistry, and complete blood count before entering the study.[3] All subjects were classified as overtly normal. Subjects were asked to refrain from the use of all drugs, alcohol, and beverages containing caffeine for 18 h prior to testing. Prior to each test session, subjects were tested for the presence of blood alcohol; all test results were negative.

Four capsules were prepared for each subject; these contained either 0, 5, 10, or 15 mg dextroamphetamine sulfate.[4] One capsule was administered at each weekly session

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[3] A twelve-test sequential multiple analyzer (SMA 12/60) blood chemistry was performed for each subject. The twelve tests included measurement of uric acid, inorganic phosphate, cholesterol, lactic dehydrogenase, total protein, albumin, urea nitrogen, glucose, calcium, bilirubin, alkaline phosphatase, and serum glutamic oxalacetic transaminase. A complete blood count was also performed for each subject. This test included red blood cell count, white blood cell differential, hemoglobin level, and hemocrit level.

[4] All doses refer to a 70-kg (150-lb) subject. Doses were individualized based on body weight.

in a double-blind, randomized, complete block design. To insure more uniform absorption, all subjects were instructed not to eat for 3½ h prior to each test session.

Following administration of the capsules, subjects were maintained in a hospital setting for more than 2 h under medical supervision. A modified Cornel Medical Index (CMI) was administered to evaluate the symptoms associated with each treatment. The modified CMI is a list of 47 symptoms, each scored for severity on a 0 to 4 basis, and has been valuable in several previous studies for monitoring acute drug effects [*13,14*].

Urine was collected from each subject for 12 h (0 to 6 and 6 to 12 h); pH and volume were recorded but were not controlled because the study was designed to simulate actual use. The pooled 6-h urine specimens were acidified with HCl, and a modified procedure of Lebish et al [*15*] was used for dextroamphetamine extraction.[5] The quantitative determination of dextroamphetamine was made on a Hewlett-Packard 402 Gas Chromatograph, equipped with a flame ionization detector and a 6 ft (1.8-m), ¼-in. (6.4-mm) outside diameter glass column with 10% OV-17 on Chromosorb W, AW/DMCS, 80/100 mesh packing. Operating conditions were as follows: injector port, 325°C; column, 280°C; detector, 290°C; and nitrogen, 60 ml/min. Absolute retention time was 2.5 min for dextroamphetamine and 3 min for methamphetamine (internal standard). For each group of eight samples analyzed, a control urine and four dextroamphetamine standards of 6.25, 12.5, and 50 μg in 10 ml of control urine were also extracted and analyzed. To each sample was added 15 μg methamphetamine prior to the extraction procedure. The peak height ratio of dextroamphetamine standard to internal standard was plotted against concentration to prepare a calibration curve. This curve was established from 20 sample groups, each group containing four different concentrations of dextroamphetamine sulfate in urine, and was linear over urine amphetamine concentrations of 0.6 to 5.0 μg/ml.

Results and Discussion

The subjects' ability to discriminate between dextroamphetamine and placebo plus the scores derived from the CMI are shown in Table 1. The results indicate that at the lowest dose subjects were unable to consistently distinguish active drug from placebo. As the dose was increased to 10 and 15 mg, about 85% of the subjects were able to identify the active drug. Scores from the modified CMI are consistent with this effect. At the 5-mg dose, scores were not different from placebo, while at the higher doses increased total symptom scores were reported. The responses to selected questions of the modified CMI are shown in Table 2.

The excretory pattern of dextroamphetamine in urine is tabulated in Table 3. Both urinary concentration and dextroamphetamine recovery increased with dose in a linear fashion during the 0 to 6-h and 6 to 12-h collection periods. The results of the urine analyses indicate that under normal conditions approximately 30% of the oral dose of dextroamphetamine is excreted within the first 12 h after administration. This percentage excretion is similar to that reported by other investigators using higher doses [*16,17*].

Clinical studies have demonstrated that the rate of excretion of dextroamphetamine and consequently its duration of action is directly related to urinary pH [*8*]. Davis et al [*9*] reported that for urinary greater than 8.0, less than 5% of the total amphetamine dose is excreted in the urine as unchanged drug. Conversely, when the urine pH was established at values of less than 5.0 by oral administration of ammonium chloride, the

[5] A 10-ml sample of urine was made alkaline with 2 ml of 20% potassium hydroxide solution and extracted with 50 ml of ether. The ether was dried over potassium hydroxide pellets, filtered through sodium sulfate, mixed with six drops of acetic anhydride, and evaporated to a volume of 50 μl of dryness for assay by gas-liquid chromatography.

TABLE 1—*Subjective effects of dextroamphetamine sulfate after oral administration to twelve subjects.*

	Dextroamphetamine Sulfate, mg/70 kg			
	0	5	10	15
Modified CMI scores[a]	5.5	6.3	8.7	10.8
Number believed they had drug	7	6	10	10

[a] Each value represents the mean from twelve subjects.

TABLE 2—*Number of subjects responding positively to selected questions of the modified CMI.*

	Dextroamphetamine Sulfate, mg/70 kg			
Question	0	5	10	15
Increase in appetite	1	2	0	0
Decrease in appetite	2	4	7	6
Feel unsteady	5	3	6	8
Feel internal trembling	2	2	10	8
Weakness	0	1	6	6
Anxious	4	2	7	10

TABLE 3—*Excretion of amphetamine in urine.*[a]

	Dextroamphetamine Sulfate, mg/70 kg			
	0	5	10	15
Volume of urine, ml				
0 to 6 h	369 (147)	382 (153)	512 (283)	435 (195)
6 to 12 h	360 (170)	359 (162)	447 (104)	335 (163)
Amphetamine, mg				
0 to 6 h	0	0.47 (0.25)	1.37 (1.05)	2.03 (1.17)
6 to 12 h	0	1.41 (0.50)	2.88 (0.86)	4.32 (1.27)
Total amphetamine, mg				
Excreted in 12 h	0	1.4 (0.49)	2.9 (0.86)	4.3 (1.27)
Dose excreted, %	...	28	29	28
Confidence interval, mg				
Lower	...	1.05	1.89	3.42
Upper	...	1.76	3.42	5.17

[a] Values listed as means with standard deviations in parentheses.

total excretion of unchanged amphetamine approached 60% of the administered dose. In addition, alkalinization of urine has been reported to intensify amphetamine psychosis [*12,18*], which appears to be related to amphetamine metabolites rather than to amphetamine plasma concentrations [*12*].

This study indicates that under ordinary conditions (in which pH is not artifically controlled), therapeutic doses of dextroamphetamine can be detected in urine for up to 12 h after oral administration. Given either a 0 to 6 or a 6 to 12-h collection, gross estimation of the dose administered is possible. The study also suggests that the effect of oral doses of 5 mg and less in young males may be due more to environment than to actual drug effect.

Summary

Twelve male medical and graduate students received dextroamphetamine sulfate in doses of 0, 5, 10, and 15 mg/70 kg body weight. The study was conducted in a double-blind manner, and treatments were assigned according to randomized, complete block design. The drug was given orally and subjects were instructed not to eat 3½ h prior to administration. After administration, total urine output was collected for 12 h; no attempt was made to control urinary pH to more realistically approach the general clinical usage of amphetamines. The urine was pooled into two 6-h segments and analyzed for amphetamine concentration. Subjective impressions of the treatments were also evaluated by means of the Cornell Medical Index Questionnaire.

Results showed that approximately 30% of the total dose was excreted unchanged within 12 h after administration. The amount excreted agreed very closely with the doses given and paralleled the scores for subjective impressions by the subjects. None of the subjects felt that their driving would be impaired for any of the doses administered. This study indicates that under ordinary conditions (in which pH is not artifically controlled), therapeutic doses of dextroamphetamine can be detected in urine for up to 12 h after oral administration.

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