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Lack of Preference for Flurazepam in Normal Volunteers

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DE WIT, H., E. H. UHLENHUTH AND C. E. JOHANSON. *Lack of preference for flurazepam in normal volunteers.* PHARMACOL BIOCHEM BEHAV **21**(6) 865–869, 1984.—The reinforcing efficacy of flurazepam (15 and 30 mg) in humans was assessed using an experimental choice procedure. Twelve healthy volunteers were tested in two 3-week choice experiments, in which each dose of the drug was compared to placebo. Subjective effects of the drug (and placebo) were monitored using the Profile of Mood States and a 49-item version of the Addiction Research Center Inventory. The lower dose of flurazepam was chosen equally as often as placebo and produced no significant subjective effects. The higher dose (30 mg) was chosen significantly less often than chance, and produced typical tranquilizer-like effects (e.g., sedation). These results are consistent with previous results using other benzodiazepines such as diazepam and lorazepam, and suggest that the reinforcing efficacy of these drugs in normal volunteers is low.

Flurazepam Drug preference Subjective effects Benzodiazepines Humans

BENZODIAZEPINES have been found to possess minimal reinforcing properties in animal self-administration studies [7]. Only in some animals, and under limited conditions, do these drugs maintain rates of responding that exceed control rates [3, 7, 12]. Despite the relatively low reinforcing potency of benzodiazepines in general, there have been suggestions from animal studies that different drugs within this class may differ in their effectiveness as reinforcers [9,12]. For instance, in a study where rhesus monkeys were trained to self-administer intravenous pentobarbital under a FR 10 schedule, only 2 or 3 out of 5 animals reliably self-administered the benzodiazepines estazolam or lorazepam when these were substituted, whereas 6 out of 6 animals self-administered flurazepam ([12]; Johanson, unpublished observations). Maximal response rates were obtained at intermediate doses (0.01–0.03 mg/kg/injection of flurazepam) and drug intake increased with dose, a pattern that is characteristic of other drugs that are effective reinforcers. In another study where baboons initially were trained to self-administer cocaine under a FR 160 schedule, flurazepam substitution resulted in only modest increases in responding compared to saline [9]. Nevertheless, a typical inverted U-shaped function of dose to response rate was observed, with maximal rates occurring at an intermediate dose.

In humans, variability in the clinical profiles of different benzodiazepines has been reported [2], but there have been only a few studies testing the relative reinforcing efficacy of different benzodiazepines in humans. Studies using human subjects in our laboratory have shown that neither diazepam nor lorazepam serve as effective positive reinforcers in an experimental test of choice [5, 6, 14]. Normal volunteers given a choice between diazepam (5 or 10 mg) or lorazepam (0.5–2.0 mg) and placebo either showed no preference, or, at the higher doses, preferred the placebo. In contrast, when these subjects were allowed to choose between the widely abused stimulant amphetamine and placebo, the large majority of subjects chose to ingest amphetamine [6,13]. Interestingly, other researchers have reported that subjects with a history of sedative abuse do prefer diazepam over placebo in an experimental test of choice [8,11].

In a continuing effort to discover variables that influence the reinforcing properties of benzodiazepines in normal healthy volunteers, the present study was designed to test the effects of another benzodiazepine, flurazepam, in the preference test. Flurazepam was selected because of the suggestion from certain animal studies that this drug may be effective as a reinforcer.

METHOD

Subjects

Twelve healthy volunteers, aged 21 to 35 (5 males, 7 females) participated in this study. They were recruited using advertisements in the local student newspaper, notices posted on the University campus, and word-of-mouth referrals. Prior to acceptance subjects were interviewed to explain the nature of the study and to ascertain their medical, psychiatric and drug use histories. Subjects were accepted if they were considered normal and healthy on the basis of this interview and a subsequent EKG. Most subjects had some experience with psychoactive drugs but none had a history of any type of drug abuse.

Subjects signed a consent form prior to participation which outlined the study in detail and indicated the common side effects of the drugs they might be given. They were informed that they would not be told what drug they ingested

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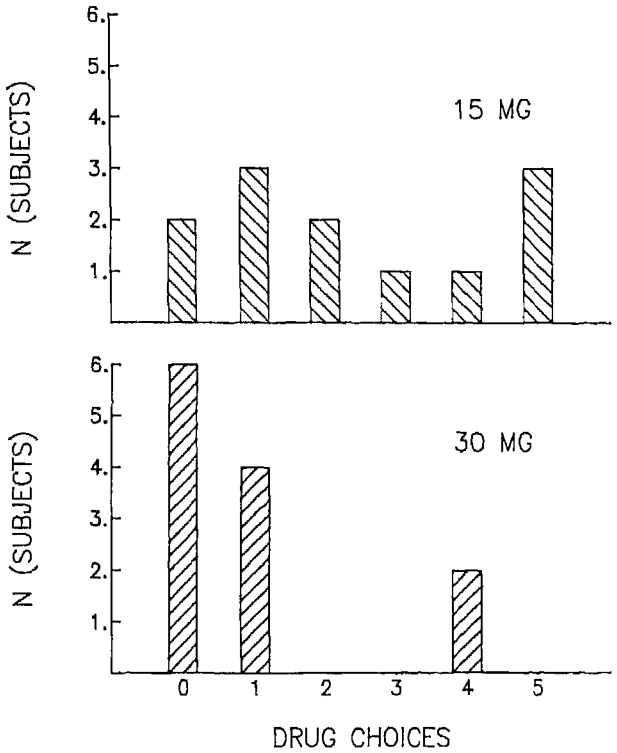

FIG. 1. Number of subjects who chose drug 0, 1, 2, 3, 4 and 5 times on the choice trials. Top panel shows results for 15 mg and bottom panel for 30 mg.

at the time, except that it would be either an anorectic, minor tranquilizer, or a placebo, and that the dose would be within the usual daily therapeutic range. Each subject also agreed not to take other drugs, except their normal amounts of coffee or cigarettes, 12 hours before and 6 hours after taking a capsule. Except for the actual drug ingested, subjects were completely informed of all other procedural details as outlined below.

Procedure

Subjects participated in both experiments, presented in counterbalanced order. The procedure for each experiment was identical except for the drugs available, which were as follows: Experiment 1: flurazepam, 15 mg versus placebo; Experiment 2: flurazepam, 30 mg versus placebo. These doses of flurazepam are within the therapeutic range for the drug's hypnotic effect [1].

Each experiment consisted of three sessions per week over a 3-week period, resulting in a total of nine sessions. During the first four sessions, the subject reported to the experimental room between 9 and 10 a.m. At that time, he/she filled out subjective effects forms (see below) and received a colored capsule for immediate ingestion. Approximately half of the subjects received flurazepam during sessions 1 and 3 and placebo during sessions 2 and 4. The order was reversed for the other half. For each subject, drug and placebo each were dispensed in a capsule of a consistent and distinctive color in order to facilitate identification. Capsule colors were assigned randomly across subjects to avoid the influence of color preference. Each subject was instructed

TABLE 1

RELATIONSHIP OF LIKING RATINGS TO CHOICE

	Liking			
	Placebo > Drug		Drug > Placebo	
	≤2 Drug Choices	≥3 Drug Choices	≤2 Drug Choices	≥3 Drug Choices
Experiment				
15 mg:	4	0	1	1
30 mg:	6	0	2	2
Totals	10	0	3	3

Each cell represents the number of subjects under each condition. Data from subjects whose ratings of drug and placebo were equal are not included in the table.

during the initial four sessions to note the capsule colors, and to try to associate each of the two colors with the effects of the substances contained in them. After ingesting the capsule, subjects were free to leave the experimental room and return to their normal activities. They took three additional sets of subjective effects forms with them which they were to fill out 1, 3 and 6 hr later. In addition, subjects filled out a questionnaire at hour 6, indicating whether they liked the drug (from "disliked a lot" to "liked a lot"), what they thought the capsule contained (stimulant, tranquilizer or placebo), and whether they had experienced any unusual reactions.

During the last five sessions, the procedure was identical in every respect except that the subjects were given a choice of the two colored capsules to ingest. The number of times a drug was chosen was taken as the indicator of its positive reinforcing properties.

Subjective Effects

The scales used to assess subjective effects were an experimental version of the Profile of Mood States (POMS; [15]) and a shortened version of the Addiction Research Center Inventory (ARCI; [10]). This version of the POMS consists of 72 adjectives commonly used to describe momentary mood states. Subjects indicate how they feel at the moment in relation to each of the adjectives on a 5-point scale ranging from "not at all" (0) to "extremely" (4). There are eight clusters of items (subscales) which have been separated empirically using factor analysis (Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, and Elation). The value of each subscale is determined by adding the numbers checked for each adjective in the cluster and dividing the total by the number of adjectives. Two additional subscales, Arousal and Positive Mood, were derived from the other subscales as follows: Arousal = (Anxiety + Vigor) − (Fatigue + Confusion); Positive Mood = Elation − Depression. The ARCI consists of 49 true/false items which have been separated into 5 clusters described as measuring typical drug effects such as stimulant-like (BG and A), euphoria (MBG), sedation (PCAG) and dysphoria (LSD).

The scores on each subscale of both the POMS and ARCI were averaged for drug and placebo at each of the four time periods using data from the first four sessions of each experiment. Sessions 5–9 were not included in these analyses be-

TABLE 2
DRUG AND PLACEBO CAPSULE IDENTIFICATION

	Identification: "Placebo"	"Stimulant"	"Tranquilizer"	Total
Drug Capsule				
15 mg Flurazepam	6	3	3	(12)
30 mg Flurazepam	2	1	9	(12)
Placebo Capsule				
15 mg Experiment	7	2	3	(12)
30 mg Experiment	10	0	0	(10)*

*Two subjects were undecided in their identification of placebo capsules.

cause of the possibility of expectancy effects during choice sessions. A two-way repeated measures analysis of variance was performed separately for each factor. The main factors were Drug (drug or placebo) and Hour (0, 1, 3 and 6). If a significant ($p<0.05$) Drug × Hour interaction was found, further statistical tests were conducted to determine at which hours the drug and placebo scores were significantly different.

RESULTS

Subjects chose 15 mg flurazepam as often as they chose placebo (mean drug choice=2.4, s.e.=0.52), but at the 30 mg dose, they chose drug an average of only one time out of five (s.e.=0.41) (Fig. 1). Only two subjects chose the 30 mg dose more than once (4 times each), and neither of these subjects consistently chose drug in the 15 mg experiment (0 and 2 drug choices).

Table 1 shows the relationship between differences in subjects' drug and placebo liking ratings on the sampling sessions and the number of times they chose drug (dichotomized as 0–2 or 3–5 times). The data in Table 1 were analyzed using a log linear analysis [4], with 3 factors (drug dose, liking, choice), revealing a borderline overall effect of choice ($z=1.86$, $p<0.07$) across the two doses of flurazepam, as well as a marginally significant interaction between liking and choice ($z=1.86$, $p<0.07$). It is apparent from the data in Table 1 that: (1) more subjects chose drug 0–2 times than chose it 3–5 times regardless of their liking scores (i.e., an overall effect of choice), and (2) subjects who liked placebo more than drug were more likely to choose placebo (i.e., an interaction between liking and choice). Liking drug more than placebo was not predictive of choosing drug. These effects were evident at both doses (i.e., the interactions with drug dose were non-significant), although there were more subjects who were indifferent in their relative liking ratings of drug and placebo (i.e., the liking scores were tied) in the 15 mg experiment.

Table 2 shows the accuracy of drug and placebo identification. The 30 mg dose was correctly identified as a tranquilizer by the majority of subjects, but the 15 mg dose was identified as "placebo" by most. Most subjects correctly identified placebo in both experiments.

There were no significant drug or drug-by-hour effects on the POMS or ARCI scales at the 15 mg dose of flurazepam. The 30 mg dose affected scores on the Vigor, Fatigue, and Arousal subscales of the POMS and the PCAG and BG scales of the ARCI. Significant Drug-by-Hour interactions were obtained on the Fatigue, $F(3,33)=3.16$, $p<0.05$, and Arousal, $F(3,33)=3.07$, $p<0.05$, subscales of the POMS as well as the PCAG Scale of the ARCI, $F(3,33)=3.48$, $p<0.03$. Post-hoc tests (Fishers LSD) indicated that the interactions were due to differences between drug and placebo scores at hours 1 and 3 for Fatigue and Arousal at hours 1, 3 and 6 for PCAG (Fig. 2). A significant main effect of Drug was also obtained on the Vigor subscale of the POMS, $F(1,11)=6.06$, $p<0.05$, and the BG Scale of the ARCI, $F(1,11)=6.37$, $p<0.03$. Scores were overall lower on drug sessions than on placebo sessions on these subscales.

DISCUSSION

Consistent with previous studies of benzodiazepine preference in subjects without a history of drug abuse, subjects in this study chose the lower dose of flurazepam as often as they chose placebo, but avoided the drug at the higher dose. Liking scores, drug identification and subjective effects scores indicated that the 15 mg dose was too low to be differentiable from placebo in the majority of subjects. The 30 mg dose, on the other hand, produced clear sedative-like effects on mood, and the majority of subjects correctly identified it as a tranquilizer.

Data from the two subjects who most consistently chose 30 mg flurazepam were closely examined for other distinctive characteristics that might be associated with strong preference for the drug. However, it was found that the two subjects who chose 30 mg flurazepam on 4 occasions were not exceptional in their normal daily consumption of cigarettes, alcohol, coffee or marijuana, relative to the rest of the group. One subject identified the 30 mg dose of flurazepam as a stimulant (and claimed during debriefing that she had strongly expected to receive a stimulant). The other subject identified it as a tranquilizer. The latter subject also rated his liking of flurazepam as less than neutral (i.e., dislike), but stated that he had had an especially unpleasant reaction on one of the placebo sessions. There was no indication from these results that flurazepam would be a robust reinforcer in non-laboratory situations, even in these subjects who chose it most often.

Because of the lack of experimental control over the subjects' activities outside the laboratory, the possibility exists that the subjects overcame minor sedative effects (e.g., at the 15 mg dose of flurazepam) by increasing their caffeine consumption on drug sessions. While this may have oc-

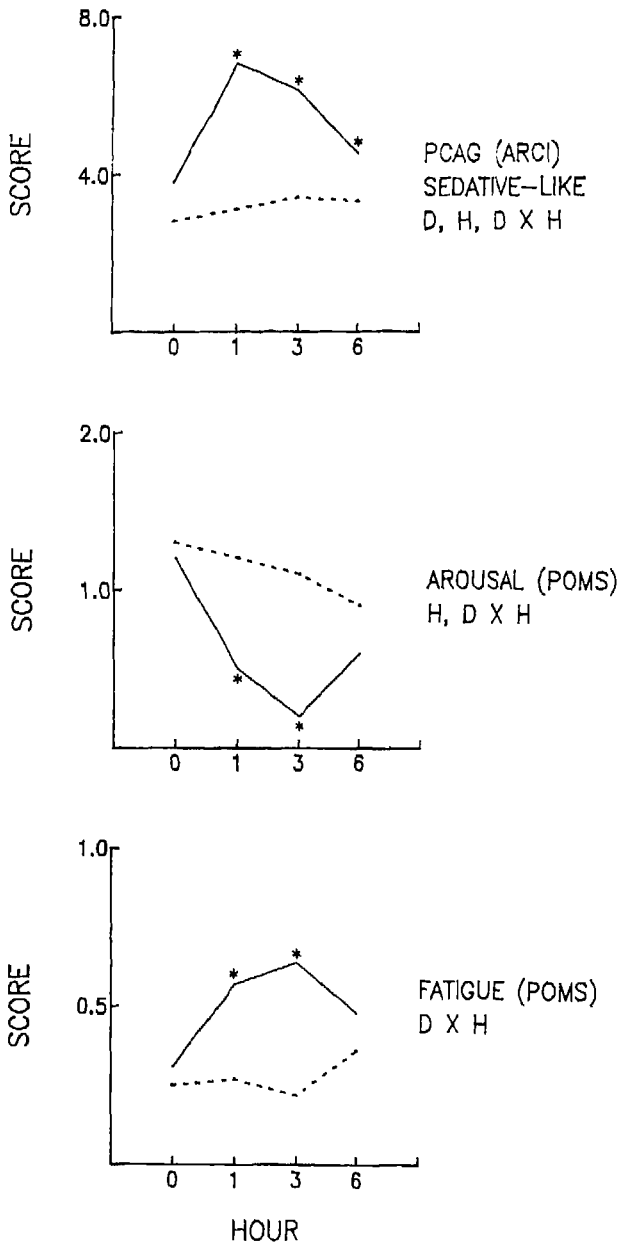

FIG. 2. Scores on POMS and ARCI subscales after 30 mg flurazepam (solid lines) and placebo (broken lines), averaged across sampling sessions for 12 subjects. Hour refers to questionnaires filled out pre-drug (hour 0) and 1, 3 and 6 hours after capsule ingestion. Asterisks indicate hours at which drug and placebo scores are significantly different ($p<0.05$, Fishers LSD post-hoc test). D, H and D×H refer to significant ($p<0.05$) main effects (D—Drug, H—Hour), and interactions (ANOVA).

curred in isolated cases, it seems unlikely that such compensatory increases in drug intake completely masked the sedative effects of 15 mg flurazepam and yet had no effect on the 30 mg dose. A more likely explanation is that 15 mg of drug was simply at the threshold of discriminability.

The subjective effects of 30 mg flurazepam can be contrasted to the effects of doses of lorazepam (2 mg) and diazepam (10 mg) that yielded comparable levels of choice in previous experiments [5, 6, 14]. All three drugs produced significant decreases in Vigor, Arousal and BG, and increases in PCAG. Lorazepam and diazepam decreased scores on the Anxiety subscale of the POMS and increased Confusion. In contrast, flurazepam produced neither of these effects. Lorazepam differed from both diazepam and flurazepam in that it increased LSD scores but failed to increase Fatigue. Thus, while all three drugs showed typical sedative-like effects, there were differences in other subjective effects. These differences may simply be due to variability between experiments, since different subjective effects have been obtained even in experiments testing the same drug. For example, diazepam (10 mg) sometimes does [6] and sometimes does not [14] decrease Anxiety scores. In addition to the qualitative differences in the drugs' subjective effects, there were also differences in time course. Peak subjective effects occurred slightly later with flurazepam (hour 3 for some subscales) than with diazepam (hour 1) in previous studies (e.g., [14]) and the effects were not as long-lasting as those of lorazepam.

The present results showing avoidance of the drug were not expected in view of Johanson's [12] finding of reliable flurazepam self-administration in rhesus monkeys. However, it should be noted that the animals in her study had been pre-selected for their history of pentobarbital self-administration. Not all monkeys reliably self-administer pentobarbital under a FR 10 schedule (Johanson, unpublished observation); the selective use of animals that do respond reliably for pentobarbital may inflate the proportion of animals responding positively for other sedative-like drugs [3].

A parallel interaction between drug history and preference for benzodiazepines appears to exist in human experiments. The subjects who participated in the present study reported only low to moderate use of common psychoactive drugs: The average weekly consumption of alcohol was 2.8 drinks alcohol per week (range 0–10 drinks week), and average caffeine intake 12 drinks per week (range 0–26 caffeine-containing drinks/week). Twenty-five percent of the subjects were cigarette smokers. In contrast, the only subjects who show a reliable preference for benzodiazepines in experimental tests are those who have a history of sedative abuse [8,11]. It is not clear whether individual differences exist which predispose certain people to abuse particular drugs (and to prefer them in the experimental tests), or whether a history of exposure to these drugs influences drug choice in the subsequent experimental test.

REFERENCES

1. Amrein, R., F. Bovey, J. P. Cano, M. Eckert, W. H. Ziegler, Ph. Coassolo, E. Schalch and J. Burckhardt. Investigation of the relative efficacy of flurazepam, desalkylflurazepam and placebo under steady-state conditions. *Drugs Exp Clin Res* **9:** 85–99, 1983.
2. Ansseau, M., A. Doumont and St. Diricq. Methodology required to show clinical differences between benzodiazepines. *Curr Med Res Opin* **8:** 108–114, 1984.
3. Bergman, J. and C. E. Johanson. The reinforcing properties of diazepam under several conditions in the rhesus monkey. Unpublished manuscript.
4. Bock, R. D. *Multivariate Analysis of Qualitative Data.* Chicago: National Educational Resources, in press.
5. de Wit, H., C. E. Johanson and E. H. Uhlenhuth. Reinforcing properties of lorazepam in normal volunteers. *Drug Alcohol Depend,* in press.
6. de Wit, H., C. E. Johanson, E. H. Uhlenhuth and S. McCracken. The effects of two non-pharmacological variables on drug preference in humans. In: *Problems of Drug Dependence, 1982,* edited by L. S. Harris. NIDA Research Monograph Series No. 43. Washington, DC: U.S. Government Printing Office, 1983, pp. 251–257.
7. Griffiths, R. R. and N. A. Ator. Benzodiazepine self-administration in animals and humans: A comprehensive literature review. In: *Benzodiazepines,* edited by S. I. Szara and J. Ludford. NIDA Research Monograph Series No. 33. Washington, DC: U.S. Government Printing Office, 1980, pp. 22–36.
8. Griffiths, R. R., G. E. Bigelow, I. Liebson and J. E. Kaliszak. Drug preference in humans: Double-blind choice comparison of pentobarbital, diazepam and placebo. *J Pharmacol Exp Ther* **215:** 649–661, 1980.
9. Griffiths, R. R., S. E. Lukas, L. D. Bradford, J. V. Brady and J. D. Snell. Self-injection of barbiturates and benzodiazepines in baboons. *Psychopharmacology (Berlin)* **75:** 101–109, 1981.
10. Haertzen, C. E. Development of scales based on patterns of drug effects using the Addiction Research Center Inventory (ARCI). *Psychol Rep* **18:** 163–194, 1966.
11. Healey, M. L. and R. W. Pickens. Diazepam dose preference in humans. *Pharmacol Biochem Behav* **18:** 449–456, 1983.
12. Johanson, C. E. Reinforcing properties of lorazepam and flurazepam in rhesus monkeys. *Fed Proc* **42:** 345, 1983.
13. Johanson, C. E. and E. H. Uhlenhuth. Drug preference and mood in humans: *d*-Amphetamine. *Psychopharmacology (Berlin)* **71:** 275–279, 1980.
14. Johanson, C. E. and E. H. Uhlenhuth. Drug preference and mood in humans: Diazepam. *Psychopharmacology (Berlin)* **71:** 269–273, 1980.
15. McNair, D. M., M. Lorr and L. F. Droppleman. *Profile of Mood States (Manual).* San Diego: Educational and Industrial Testing Service, 1971.