Pharmacology Biochemistry and Behavior, Vol. 58, No. 4, pp. 983–991, 1997
© 1997 Elsevier Science Inc.
Printed in the USA. All rights reserved
0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(97)00329-8

Secobarbital in Humans Discriminating Triazolam Under Two-Response and Novel-Response Procedures

JONATHAN B. KAMIEN, WARREN K. BICKEL, BRANDI J. SMITH, GARY J. BADGER AND JOHN R. HUGHES

Human Behavioral Pharmacology Laboratory, University of Vermont, Burlington, VT 05401

Received 27 August 1996; Revised 28 February 1997; Accepted 4 March 1997

KAMIEN, J. B., W. K. BICKEL, B. J. SMITH, G. J. BADGER AND J. R. HUGHES. *Secobarbital in humans discriminating triazolam under two-response and novel-response procedures.* PHARMACOL BIOCHEM BEHAV **58**(4) 983–991, 1997.—Humans were trained to discriminate the benzodiazepine triazolam (0.32 mg/70 kg) from placebo under a two-response (drug vs. placebo) drug discrimination procedure. Dose–effect curves for several drugs were then determined in a crossover design using the two-response procedure and a 'novel-response procedure' that provided a novel-appropriate response for drugs unlike triazolam or placebo. Three subjects were tested with triazolam (0.1–0.32 mg/70 kg), the barbiturate secobarbital (56–177 mg/70 kg), and caffeine (320 and 560 mg/70 kg). Triazolam dose dependently increased triazolam-appropriate responding under both procedures and generally did not occasion novel-appropriate responding under the novel-response procedure. Secobarbital substituted for triazolam in the two-response procedure and dose-dependently increased novel-appropriate responding as well as occasioned some triazolam-appropriate responding in the novel-response procedure. Caffeine generally occasioned placebo-appropriate responding under the two-response procedure and a mix of novel- and placebo-appropriate responding under the novel-response procedure. Triazolam and secobarbital produced qualitatively similar self-reported drug effects. These results suggest that the novel-response procedure for human drug discrimination may enhance the pharmacological selectivity of triazolam- and placebo-appropriate responding. © 1997 Elsevier Science Inc.

Drug discrimination Novel-response procedure Triazolam Secobarbital Caffeine Subjective drug effects Human subjects

A recently developed novel-response procedure for human drug discrimination may increase the understanding of the relationship between drugs with similar discriminative stimulus effects, such as benzodiazepines and barbiturates. This novel-response procedure uses instructions to provide an alternative response for drugs unlike either placebo or the training drug (i.e., a 'novel response'). Three prior studies of humans discriminating the benzodiazepine triazolam from placebo suggested that use of a novel-response procedure increases pharmacological selectivity of both placebo- and triazolam-appropriate responding (6,21,29). In the first experiment, the psychomotor stimulant *d*-amphetamine occasioned placebo-appropriate responding under a two-response drug discrimination procedure but produced novel-appropriate responding under the novel-response procedure (6). In the second experiment, the opioid agonist hydromorphone occasioned novel-appropriate responding, while the benzodiazepine diazepam substituted completely for triazolam and did not occasion novel-appropriate responding (29). Both of these experiments suggested that the novel-response procedure enhanced the selectivity of placebo-appropriate responding without disrupting generalization among benzodiazepines. Finally, in the third experiment, the benzodiazepine lorazepam dose dependently increased triazolam-appropriate responding while the atypical anxiolytic buspirone occasioned a dose-dependent increase in novel-appropriate responding along with some triazolam-appropriate responding (21). Compared to the cross-substitution of buspirone and diazepam reported for most subjects trained to discriminate diazepam from placebo under a two-key procedure (18,19), the novel-response procedure more clearly differentiated buspirone from a benzodiazepine. Taken together, these results suggested that the novel-response procedure enhances the pharmacological selectivity of both placebo- and triazolam-appropriate responding.

Requests for reprints should be addressed to Jonathan B. Kamien, Ph.D., BioPsych Consulting, 360 Birch St., Denver, CO 80220.

The enhanced selectivity observed with the novel-response procedure is useful for interpreting partial generalization that occurs under two-response procedures (6,21,29). Possible interpretations of partial generalization have included that 1) the test drug shares all the discriminative stimulus effects of a drug but at a lower intensity; 2) the test drug produces stimulus effects that overlap, but are not isomorphic with the effects produced by the training drug; 3) the test drug is completely different than the training drug; and 4) the test drug produced "random" responding or behavior controlled by stimuli or factors unrelated to the discriminative stimulus effects of drug [see (7,42,46) for a summary and discussion of partial generalization). In most cases, data from two-response drug discrimination procedures do not favor one interpretation over another. For example, buspirone occasioned at least partial generalization to benzodiazepines in both humans (18) and nonhumans (11,41,45,48). Determining the similarity of buspirone and benzodiazepine discriminative stimuli based on results from two response procedures is difficult. However, buspirone occasioned both novel- and triazolam-appropriate responding when tested under the novel-response procedure in humans discriminating triazolam (21). This response distribution suggested the second interpretation above, that the discriminative stimulus effects of buspirone overlap with triazolam, but are not isomorphic.

Other response distributions across the placebo-, drug-, and novel-appropriate alternatives are possible and suggest different interpretations. For example, responding that occurred only on the triazolam- and placebo-appropriate alternatives would suggest the test drug shares all the discriminative stimulus effects of a drug but at a lower intensity. This distribution occurred for intermediate doses of triazolam and diazepam (6,29). Responding that occurred only on the novel- and placebo-appropriate alternatives would suggest complete dissimilarity with triazolam as was the case with *d*-amphetamine (6). A distribution of responding across all three alternatives could suggest "random" responding, a disruption of stimulus control, or discriminative stimulus effects in common with the training drug (but at a lower intensity), in addition to having unique discriminative stimulus effects. However, such a distribution has yet to be reported.

The present study investigated whether the novel-response procedure enhances the selectivity of triazolam-appropriate responding so that a closely related sedative/hypnotic could be differentiated from benzodiazepines. Specifically, secobarbital was selected because drug discrimination procedures often do not distinguish benzodiazepine and barbiturate discriminative stimuli [e.g., (8,14,16,26,35)]. Indeed, this reliable cross-substitution of benzodiazepines and barbiturates has led "to the belief that, as a rule, depressant drugs as stimuli represent rather broad stimulus complexes that are not likely to be differentiable without specific drug vs. drug training" [(2), p. 359]. However, at least three types of findings challenge the equivalence of barbiturate and benzodiazepine discriminative stimuli. First, asymmetric or inconsistent substitution results have been observed between benzodiazepines and barbiturates (10,17,30,31,41). Second, selective antagonism of benzodiazepines and barbiturates by the benzodiazepine antagonist flumazenil suggests different mechanisms of actions for their discriminative stimulus effects (1,9,13,37,43,44,47). Third, the successful training of drug vs. drug discriminations with these compounds demonstrated that the discriminative stimulus effects of benzodiazepines and barbiturates are distinct under appropriate conditions (3,4,12,22). Taken together with the known different pharmacological mechanisms of action of these drugs, these findings suggest that the discriminative stimulus effects of benzodiazepines and barbiturates are not identical.

In the present experiment, all drugs were tested under both a standard two-response and the novel-response drug discrimination procedure using a crossover design. This design enabled within-subject comparison of responding under both procedures. Self-reported effects were also collected to evaluate the relationship between self-reported and discriminative stimulus effects.

METHOD

Subjects

Six females and 16 males, 20–45 years of age, were recruited through newspaper and poster advertisements. Subjects were in good health with no history of drug or alcohol abuse or significant psychiatric illness according to medical histories, physical exams, EKGs and routine laboratory screening. Current abstinence from amphetamine, barbiturates, benzodiazepines, cocaine, opioids, and cannabinoids was confirmed via urinalysis before the study began using the Enzyme Multiplied Immunoassay Technique (EMIT®; Syva Corporation, San Jose, CA). Participants were instructed to refrain from solid food and caffeine for 4 h and to abstain from alcohol for 24 h before every session. Smokers were told to maintain their regular smoking routine; however, no smoking was allowed during the session itself. Subjects received compensation at the rate of $4.00 per hour and could receive up to a $12.00 bonus for discrimination performance each session (see below). Subjects provided informed consent for study participation following a full explanation of the procedures. The study was approved by University of Vermont's Institutional Review Board.

Apparatus

Commodore 64 microcomputers were programmed to present all questionnaires and performance tests in a prearranged and timed sequence (Table 1). Subjects responded on a numeric key pad and on three buttons. A Macintosh Plus microcomputer collected the data through a network from the Commodore 64 microcomputers and saved magnetic and printed copies as each task was completed.

Design

All subjects were trained to discriminate 0.32 mg/70 kg triazolam from placebo (lactose). This training dose was selected based on results from previous studies (6,21,27,29). Subjects initially attended a nondrug session to become acquainted with the computer tasks and the routine of the laboratory sessions. The study then proceeded in six phases with sessions conducted 3–5 days/week.

Crossover Design

Once testing was completed under the first set of instructions (Table 2), subjects repeated the test-of-acquisition and tests of novel doses under the other set of instructions. The order of the two procedures was balanced across subjects.

Training (phase 1). During sessions 1–4, subjects were given instructions for the training procedure (Table 2). The training dose of triazolam (0.32 mg/70 kg) and placebo were administered on alternate days. During these sessions subjects were informed of the letter code appropriate for the drug at the time of drug administration. They were also given a notebook and instructed to attend carefully to any drug effects and

TABLE 1

OUTLINE OF EXPERIMENTAL SESSION AND ORDER OF PRESENTATION OF MEASURES

11:00 A.M.	Sobriety, vital signs, pregnancy, balance, hand coordination, arithmetic, blood pressure, breath alcohol, heart rate
11:20 A.M.	Addiction Research Center Inventory, Adjective checklist, DSST
11:30 P.M.	Drug capsule administration
12:30 P.M.	60-min postdrug assessment cycle Fixed-interval 1-s drug discrimination, Addiction Research Center Inventory, Point distribution drug discrimination, adjective checklist, Discrete choice drug discrimination, visual analog scales, DSST
1:00 P.M.	90-min postdrug assessment Fixed-interval 1-s drug discrimination, Addiction Research Center Inventory, Point distribution drug discrimination, adjective checklist, Discrete choice drug discrimination, visual analog scales, DSST
1:10 P.M.	Envelope A sealed envelope containing the letter code identity of the administered drug, or the information that it was a test day, was opened and shown to the subject.
2:11 P.M.	Subjects go to the recovery area.
3:00 P.M.	Recall task initiated Two three-syllable words were given to the subject to remember.
3:30 P.M.	Recall task completed Subject repeated the two, three-syllable words.
3:40 P.M.	Prerelease sobriety tests and vital signs balance, hand coordination, simple arithmetic, blood pressure, heart rate

record them in the notebook. Bonus money was earned in these sessions by responding appropriately during the three discrimination measures (see below).

Tests-of-acquisition—two-response procedure (phase 2). The triazolam training dose and placebo were administered at least twice in random order and subjects were given instructions for the two-response procedure (Table 2). Subjects performed the drug discrimination tasks and responded according to which drug they received (see Discrimination Measures, below). The correct identity of the letter code associated with the administered drug was not revealed until the end of the experimental session. Responding appropriately to the letter code of the administered drug resulted in additional monetary compensation. Subjects had to meet a discrimination criterion ($\geq$80% of responses on the key appropriate to the training condition) on four consecutive sessions within a total of eight sessions to progress to phase 3. If this criterion was not met, subjects were dismissed from the study. This discrimination criterion was applied only to responding reinforced according to a fixed-interval 1-s schedule of point presentation (see Discrimination Measures, below) to maintain close similarity with procedures commonly used with nonhumans [see (20)].

Tests-of-acquisition—novel-response procedure and two-response procedure (phases 3 and 5). Subjects were assigned to respond under the two-response or the novel-response procedure and the training drugs were again administered. Under the two-response procedure, responding on the third key produced no programmed consequences and no instructions were given about the appropriate response when receiving a drug not exactly like the training drugs (Table 2). Under the novel-response procedure, instructions indicated that only responses on the third key would be reinforced in the presence of a drug not exactly like the training drugs and designated the appropriate response under this condition (Table 2). Responding had to meet the discrimination criterion following the triazolam training dose and placebo on two consecutive sessions within a maximum of four sessions to progress to phase 4 or 6. Subjects not meeting this criterion were dismissed from the study. Bonus money was earned in this phase by responding appropriately on the drug discrimination tasks.

Testing—novel-response or two-response procedures (phases 4 and 6). The order of drug testing and the order of doses for a given drug was mixed. Test-of-acquisition sessions (i.e., sessions preceded by administration of the triazolam training dose or placebo) were interspersed between tests to ensure that subjects maintained accurate discrimination. If at any time during the testing phase a subject's responding did not meet the discrimination criterion on an interspersed test-of-acquisition session, criterion-level responding during two additional test-of-acquisition sessions was required before conducting any more test sessions. After a test session, subjects were informed only that it was a test session and that the correct letter code would not be revealed. The novel-response procedure instructions indicated that if they had received a drug that was not precisely like the training conditions, then only novel-appropriate responding would be reinforced, and the two-response procedure instructions indicated that reinforcement for test sessions would be the average from the preceding four test-of-acquisition sessions. These contingencies were only implied, however. Actual bonus earnings on all test sessions were, in fact, not contingent on test session responding, but were instead equal to the average amount earned on the last four acquisition sessions. Bonus earnings were awarded at the completion of a subject's participation in the study.

Doses of triazolam (placebo, 0.1, 0.18, 0.24, and 0.32 mg/70 kg), secobarbital (placebo, 56, 100, 133, and 177 mg/70 kg), and caffeine (320 and 560 mg/70 kg) were tested. All doses of a drug were tested before starting the next, except for caffeine in two subjects (KM and TF) where one caffeine dose was tested before testing triazolam and the other dose was tested before testing secobarbital. The ratio of test-of-acquisition sessions to test sessions was about 1:2, and no more than three test sessions occurred consecutively.

Experimental Session

Sessions began at 1100 h, and subjects typically remained at the laboratory for 5 h (see Table 1 for details). Before each session, baseline field sobriety tests (tests of balance, hand coordination, and simple arithmetic) were completed. At the beginning of each session, blood pressure, breath alcohol levels, and heart rate were recorded. Urine samples were obtained before each session and each week one randomly selected sample was screened for illicit drugs via EMIT assay. Pregnancy tests were conducted for all female subjects before each session and all tests were negative. Baseline self-report questionnaires and the Digit Symbol Substitution Task (DSST) were completed on the computer before drug administration. Capsules were then administered. Assessment cycles were completed at 60 and 90 min postdrug administration. Each assessment cycle included drug discrimination tasks, self-report

TABLE 2
INSTRUCTIONAL SETS

Training (Phase 1)
For this part of the experiment, you will be administered one of two drugs, either Drug ____ or Drug ____. You will be immediately told which drug you are receiving. After the drug is administered, you will complete the computer tasks according to the drug you received. At the end of the session you will earn up to $12.00 depending upon your performance during the tasks.

Tests of acquisition (Phase 2)
For this part of the experiment, you will be administered one of two drugs, either Drug ____ or Drug ____ without being informed of which drug you are receiving. You will complete the computer tasks and indicate which drug you think you received. At the end of the session you will be told which drug you received. If you indicated correctly, you will earn up to $12.00.

Two-response instructions (Phases 3, 4, 5, and 6)
For this part of the experiment, you may have a Drug ____ day, a Drug ____ day or a test day on any given session. On a test day, the drug you receive may be precisely Drug ____, precisely Drug ____ or may not be precisely like Drug ____ or Drug ____. You will not be given any information at the beginning of the session to indicate which drug you receive, or if it is a test day. You will proceed with the computer tasks and indicate which drug you received. Use the left key to indicate Drug ____ and the middle key to indicate Drug ____. At the end of the session, you will be told which drug you received, Drug ____ or Drug ____ or if it was a test day. On every day you will earn up to $12.00 if you respond correctly. However, you will not be told how much you earned on each test day until the study is completed.

Novel-response instructions (Phases 3, 4, 5, and 6)
For this part of the experiment, you may have a Drug ____ day, a Drug ____ day, or a test day on any given session. On a test day, the drug you receive may be precisely Drug ____, precisely Drug ____, or may not be precisely like Drug ____ or Drug ____. You will not be given any information at the beginning of the session to indicate which drug you receive, or if it is a test day. You will proceed with the computer tasks and indicate which drug you received. You will have the opportunity to make one of three responses for indicating the drug you received. Use the left key to indicate Drug ____, the middle key to indicate Drug ____, and the right key (N) to indicate that the drug is not precisely like Drug ____ or Drug ____. At the end of the session, you will be told which drug you received, ____ or ____, or whether it was a test day.

BONUS: If you had a test day and the drug was ____ or ____ you will earn the average amount you received on the last four ____ and ____ days only if you responded on either the ____ or ____ keys. If it was a test day and the drug you received was neither ____ nor ____, then you will earn the amount you responded on the N key. On every test day you will not be told whether you received ____, ____, or N until the end of the study. Thus, you will not be told how much you earned on each test day until the study is completed.

The blanks in these instructions were filled in with letters (e.g. "A" and "B") that corresponded to the training stimuli but varied among subjects.

measures, and the DSST. A sealed envelope that contained the letter code identity of the administered drug, or the information that it was a test day, was opened at the end of the session for each subject. Subjects were then released to a recovery area. Blood pressure, heart rate, field sobriety, and a recall task were completed before release.

Dependent Measures

Discrimination measures. Drug discrimination data were collected during each assessment cycle using three procedures (FI 1-s schedule of point presentation, point distribution, and discrete choice) presented in fixed order [see (6) and (32) for a full description of the Discrimination Measures]. In the first procedure, a fixed-interval 1-s schedule of point presentation was arranged on three keys corresponding to the training drug, placebo, and novel-drug effects. Consequences were programmed on this last key only when the novel-response procedure instructions were in effect. Thus, the first response made after each 1-s interval elapsed increased the total number of points accumulated on a given key by one. The number of points accumulated on each key was displayed continuously on the video screen below its corresponding letter. This schedule lasted 3 min, and the number of points earned on each manipulandum and the overall rates of responding were recorded. Each point on the correct letter code was worth $0.013. In the second procedure, subjects distributed 50 points between the two drug codes depending upon how certain they were of the identity of the drug administered. These amounts were displayed under the appropriate letter on the video screen and subjects were given a chance to change their point distributions before "locking them in." Each point on the correct code was worth $0.04. In the third procedure, subjects made a discrete choice response that indicated by letter code (e.g., A or B) the drug they received. An arrow pointing to the letter code chosen was displayed on the video screen and subjects were given a chance to change their choice prior to "locking it in." Each correct identification was worth $2.00. In each procedure only correct responses were reinforced with money. Maximally correct responding in each of the three discrimination tasks was worth $2.00.

Potential earnings from all three drug discrimination procedures were displayed in a composite amount at the end of each session. These amounts were displayed as dollar amounts that would be paid if a given letter code was appropriate for that day's drug administration.

Self-report measures. Three questionnaires were completed: the Addiction Research Center Inventory short form (ARCI), an adjective rating scale and visual analog scales (VAS). The ARCI consisted of 49 true/false questions that were scored as five subscales: morphine-benzedrine group (MBG), a measure of "euphoria"; pentobarbital-chlorpromazine-alcohol group (PCAG), a measure of "sedation"; lysergic acid diethylamide (LSD), a measure of "dysphoria"; and the benzedrine group (BG) and amphetamine group (A) scales, which are sensitive to *d*-amphetamine-like effects (24). The adjective rating scale listed 32 adjectives that were rated on a five-point scale from 0 (no effect) to 4 (maximum effect).

The items in the list were grouped into two subscales: 1) a sedative scale, consisting of adjectives describing sedative effects [e.g., (28)], and 2) a stimulant scale, consisting of adjectives describing stimulant effects [e.g., (15)]. The VAS consist of nine 100-point horizontal lines anchored with "not at all" on one end and "extremely" on the other. On these scales subjects moved an arrow pointing to the line that represented the extent to which they experienced the strength of the drug effect, effects similar to each training condition (identified by letter code), similarity to novel stimulus effects, drug-liking, "good" drug effects, "bad" drug effects, drug-induced "high," and "anxious" effects produced by the drug.

DSST. A computerized version of the Digit Symbol Substitution Test was used (25). Briefly, randomly selected digits appeared on the center of the video screen. Subjects responded on a numeric keypad to reproduce a geometric pattern associated with a digit according to the code presented continuously at the top of the screen. Subjects were instructed to complete as many patterns as possible while maintaining accuracy during the 90-s presentation of the task. Data collected were the number of correctly completed trials and the number of trials completed.

Drugs

Triazolam, triazolam-placebo, secobarbital, and caffeine were administered via two blue opaque capsules (size 0). Capsules were prepared by the Medical Center Hospital of Vermont pharmacy from lactose mixed with triazolam (The Upjohn Company, Kalamazoo, MI), secobarbital (Sigma Chemical Co., St. Louis, MO), or caffeine (Sigma Chemical Co., St. Louis, MO). All capsules were administered 60 min before the first postdrug assessment cycle. Similar secobarbital doses using this pretreatment time have produced behavioral effects previously in a human drug discrimination experiment (5).

Data Analysis

Discrimination data within each session were averaged across the 60- and 90-min assessment cycles. Statistical analysis of discrimination responding was limited to the data from the FI 1-s task to maintain consistency with previous published reports. The results of the ARCI scales and the adjective rating scales were analyzed as the mean change from predrug scores. The results from the VAS and the DSST were analyzed as the mean of the scores from the 60- and 90-min assessment cycles. Data for each drug were analyzed separately.

Statistical analyses were conducted using data from those subjects who received the same test drug doses. The results were analyzed in a repeated-measures ANOVA with two within-subject factors: procedure (two-response and novel-response procedures) and dose (placebo, 0.10, 0.18, 0.24, and 0.32 mg/70 kg triazolam; placebo, 56, 100, 133, and 177 mg/70 kg secobarbital or 320 and 560 mg/70 kg caffeine). Greenhouse-Geisser corrections for violation of sphericity were employed where appropriate. The focus of the analysis was 1) to evaluate triazolam, secobarbital, and caffeine dose effects on discrimination, self-reports, and performance; and 2) to determine if potential dose effects were altered by the novel-response procedure. In addition to reporting the significance of the overall *F*-test for equality of means across all doses including placebo, the significance of the linear trend across the active doses is presented when significant. The significance associated with the linear trend provides a more specific test of the hypothesis of an increasing (or decreasing) dose effect across the active doses. Analyses were performed using BMDP statistical software (University of California, Berkeley, CA). Significance was determined at $\alpha = 0.05$.

RESULTS

Participation

Only the results for the three subjects who completed dose–effect curves under both of the conditions (two-response and novel-response; see below) are presented. These subjects required 56, 48, and 58 sessions to complete the study. Of the 19 subjects who did not complete the study, eight quit the study before completing all sessions under both of the conditions, and the rest were dismissed for failing to learn the discrimination ($n = 3$) or unreliable attendance ($n = 8$).

Discrimination Measure

Because responding across the three discrimination measures was identical, only results from the FI 1-s component are presented. Individual data from the three subjects who were tested under both procedures are presented in Fig. 1. Triazolam generally occasioned only dose-dependent increases in triazolam-appropriate responding under both the two-response and novel-response procedures. The only novel-appropriate responding occasioned by triazolam under the novel-response procedure occurred following a single dose of triazolam (0.18 mg/70 kg) in a single subject (KM) .

Secobarbital completely substituted for triazolam in all subjects under the two-response procedure (Fig. 1). Under the novel-response procedure, secobarbital occasioned 100% novel-appropriate responding following at least two doses in all three subjects. In addition, secobarbital occasioned 100%

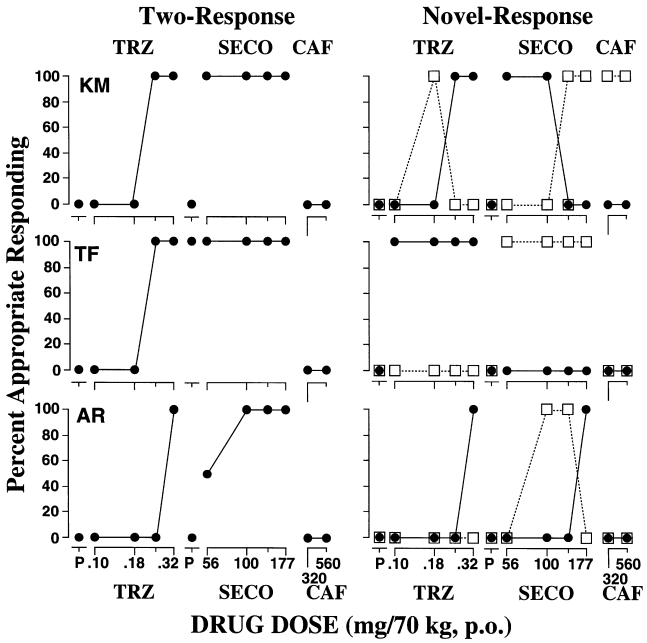

FIG. 1. Each panel depicts results from an individual subject responding under the two-response procedure (left panels) or the novel-response procedure (right panels). TRZ, SECO, and CAF label dose–effect functions for triazolam, secobarbital, and caffeine, respectively. Each point represents the mean percentage of triazolam-(circles) or novel-(squares) appropriate responding from the 60- and 90-min measurements.

triazolam-appropriate responding following at least one dose in two of the three subjects.

Under the two-response procedure, caffeine (320 and 560 mg/70 kg) occasioned exclusively placebo-appropriate responding in all three subjects. Under the novel-response procedure, caffeine occasioned novel-appropriate responding in one subject and placebo-appropriate responding in the other two subjects (Fig. 1).

ANOVA was conducted on the averaged data from these three subjects. Under both the two-response and novel-response procedures, triazolam increased triazolam-appropriate responding as a linear effect of dose, $F(1, 2) = 82.9$, $p < 0.05$. The triazolam dose–effect curves did not differ significantly between the two procedures, $F(1, 2) = 1.0$, NS. Following secobarbital, the differences in responding across the two procedures were statistically significant [interaction between procedure and active doses of secobarbital; $F(1, 2) = 22.2$, $p < 0.05$]. In addition, the increase in novel-appropriate responding occasioned by secobarbital approached significance [linear effect of secobarbital dose, $F(1, 2) = 15.4$, $p < 0.07$]. Caffeine did not produce a significant dose effect under either procedure, nor did responding differ significantly between procedures.

Self-Reported Drug Effects

Directions of significant self-reported and performance effects of triazolam, secobarbital, and caffeine are shown in Table 3. Self-reported and performance effects did not differ significantly between procedures.

ARCI. Both triazolam [linear effect of dose, $F(1, 2) = 62.2$, $p < 0.01$] and secobarbital [main effect of dose, $F(4, 8) = 6.6$, $p < 0.05$] significantly increased scores on the PCAG subscale of the ARCI, while caffeine produced no significant effects on the ARCI (Table 3). Both triazolam [main effect of dose, $F(4, 8) = 4.1$, $p < 0.05$] and secobarbital [main effect of dose, $F(4, 8) = 5.0$, $p < 0.05$] also significantly decreased scores on the BG subscale of the ARCI (Table 3). The other ARCI subscales were not significantly affected by any drug.

TABLE 3

SIGNIFICANT SELF-REPORTED AND PERFORMANCE EFFECTS*

	TRZ	SECO	CAF
ARCI			
PCAG	↑	↑	
BG	↓	↓	
MBG			
LSD			
AMPH			
Adjectives			
Stimulant		↑	
Sedative			
VAS			
Drug Effect	↑	↑	
Liking			
Good			
Bad			
Anxious			
High	↑	↑	
DSST			
# Correct	↓	↓	
# Complete	↓	↓	

*Table shows directions of significant effects of drug dose. Where no symbol appears, the effect was not significant.

Adjective rating scale. Scores on the adjective rating scale were not significantly affected by triazolam or caffeine. Secobarbital significantly increased scores on the Stimulant scale [linear effect of dose, $F(1, 2) = 19.4$, $p < 0.05$] but did not have a significant effect on the Sedative subscale (Table 3).

VAS. Triazolam and secobarbital, but not caffeine, significantly increased ratings of strength of the drug effect [main effect of dose, $F(4, 8) = 4.85$, $p = 0.05$, and main effect of dose, $F(4, 8) = 11.95$, $p < 0.01$, respectively] and ratings of drug-induced high [main effect of dose, $F(4, 8) = 5.1$, $p < 0.05$, and main effect of dose, $F(4, 8) = 9.0$, $p < 0.01$, respectively; Table 3]. The other VAS scores were not significantly affected by any drug.

Performance measure: DSST. Both triazolam and secobarbital significantly decreased the number of correct patterns completed [linear effect of dose, $F(1, 2) = 97.2$, $p < 0.05$, and main effect of dose, $F(4,8) = 4.9$, $p < 0.05$, respectively; Table 3]. Following triazolam administration, fewer correct patterns were completed under the novel-response procedure than under the two-response procedure, $F(1, 2) = 124.0$, $p < 0.01$ (Table 3). Both triazolam and secobarbital also significantly decreased the number of patterns completed on the DSST [linear effect of dose, $F(1, 2) = 90.5$, $p < 0.001$, and $F(1, 2) = 325.9$, $p = 0.01$, respectively; Table 3].

DISCUSSION

The major finding of this study is that a novel-response procedure for human drug discrimination differentiated the discriminative stimulus effects of secobarbital from triazolam in humans discriminating triazolam. Triazolam and secobarbital each occasioned 100% triazolam-appropriate responding under the two-response drug discrimination procedure, replicating results from studies of nonhuman benzodiazepine discrimination [e.g. (8,30,35). However, when tested under the novel-response procedure, secobarbital was distinguished from triazolam. Dose–effect curves for secobarbital were significantly different between the two procedures, with substantial novel-appropriate responding as well as triazolam-appropriate responding under the novel-response procedure. Triazolam, on the other hand, did not produce substantial novel-appropriate responding, and triazolam dose–effect curves did not differ significantly between the two procedures. Thus, the distribution of responses during testing under the novel-response procedure differentiated the discriminative stimulus effects of secobarbital from triazolam. Such differentiation did not occur when these drugs were tested under a two-response drug discrimination procedure.

Two doses of caffeine were tested under both the two-response and novel-response procedures to provide data with a drug clearly distinct from triazolam. Under the two-response procedure, caffeine occasioned primarily placebo-appropriate responding following both doses, replicating results with squirrel monkeys trained to discriminate midazolam, another benzodiazepine, from saline (41). Under the novel-response procedure, caffeine occasioned either novel- or placebo-appropriate responding, but unlike secobarbital, caffeine did not occasion any triazolam-appropriate responding. Of course, because the doses of caffeine tested also did not produce marked self-reported effects, testing higher doses of caffeine is warranted and might have produced more substantial novel-appropriate responding. Taken together, the results from testing secobarbital and caffeine in the current study suggest that the novel-response procedure is useful for increasing the selectivity of both drug- and placebo-appropriate responding in human drug discrimination.

The novel-response procedure also helped interpret partial generalization results from testing secobarbital under two-response procedures because the distribution of responses across the three alternatives of the novel-response procedure suggests which interpretation of partial generalization is appropriate for a given instance. That is, the distribution of responding in the current study to the novel- as well as the triazolam-appropriate alternatives favors the interpretation that these drugs produce discriminative stimulus effects that overlap, but are not isomorphic with those produced by triazolam. This represents an advance over previous drug discrimination studies, where testing pentobarbital in benzodiazepine-trained subjects has sometimes resulted in partial generalization (10,31,41), which can be interpreted in several ways [e.g., (42)].

Expanding the response alternatives from two responses to include a novel-response alternative had effects similar to increasing response alternatives through other means in previous drug discrimination research. Adding additional response alternatives, whether by training three-choice drug vs. drug vs. placebo discriminations [e.g. (33,34)] or by training discrimination among two doses of the same drug and saline [e.g. (36)], increased the selectivity of responding appropriate to each alternative. Using instructions to designate a response alternative appropriate for when a drug is not similar to either training condition appears to similarly increase the resolution of the drug discrimination procedure.

The way in which the novel-response procedure increased the resolution of triazolam discrimination is best illustrated by placing the current results in the context of the results from all of the drugs that have been tested in humans trained to discriminate triazolam under a two-response and the novel-response procedure to date. Figure 2 shows the maximum average percentages of triazolam-appropriate responding occasioned by four drugs under a two-response procedure (top panel) and triazolam- and novel-appropriate responding occasioned by eight drugs under the novel-response procedure (bottom panels). These data are summarized from the current study (triazolam, secobarbital, and caffeine) and three previously published studies [*d*-amphetamine: (6), hydromorphone and diazepam: (29), buspirone and lorazepam: (21)]. Triazolam was tested in each of the studies; data presented here are averages ± SEM from all four of the studies. The maximum average percentages represent the greatest average percentage of triazolam or novel-appropriate responding across all subjects tested at any dose under a given procedure. [For example, averaging across the three secobarbital group subjects who completed testing in the current study, the maximum average percentrage of triazolam-appropriate responding following secobarbital is 33% (one of three subjects responded 100% on the triazolam-appropriate key following 100 mg/70 kg secobarbital). The maximum percentage of novel-appropriate responding following secobarbital is 100% (all three subjects in the secobarbital group responded 100% on the novel-appropriate key following 133 mg/70 kg secobarbital).]

Inspection of Fig. 2 reveals how the distribution of responding under the novel-response procedure allows finer distinctions among similar drugs than are generally possible when drugs are tested under a two-response (drug vs. placebo) procedure. For example, under a two-response procedure, triazolam and secobarbital both substituted for triazolam and occasioned 100% triazolam-appropriate responding following at least one dose (Fig. 2, top panel). Results from humans and nonhumans discriminating benzodiazepines from placebo or saline under two-response procedures suggest that diazepam and lorazepam would similarly substitute for triazolam (20). Thus, response distribution under a two-response procedure did not differentiate among these four drugs. However, expanding the response alternatives to include a novel-response allows comparison of these drugs across two

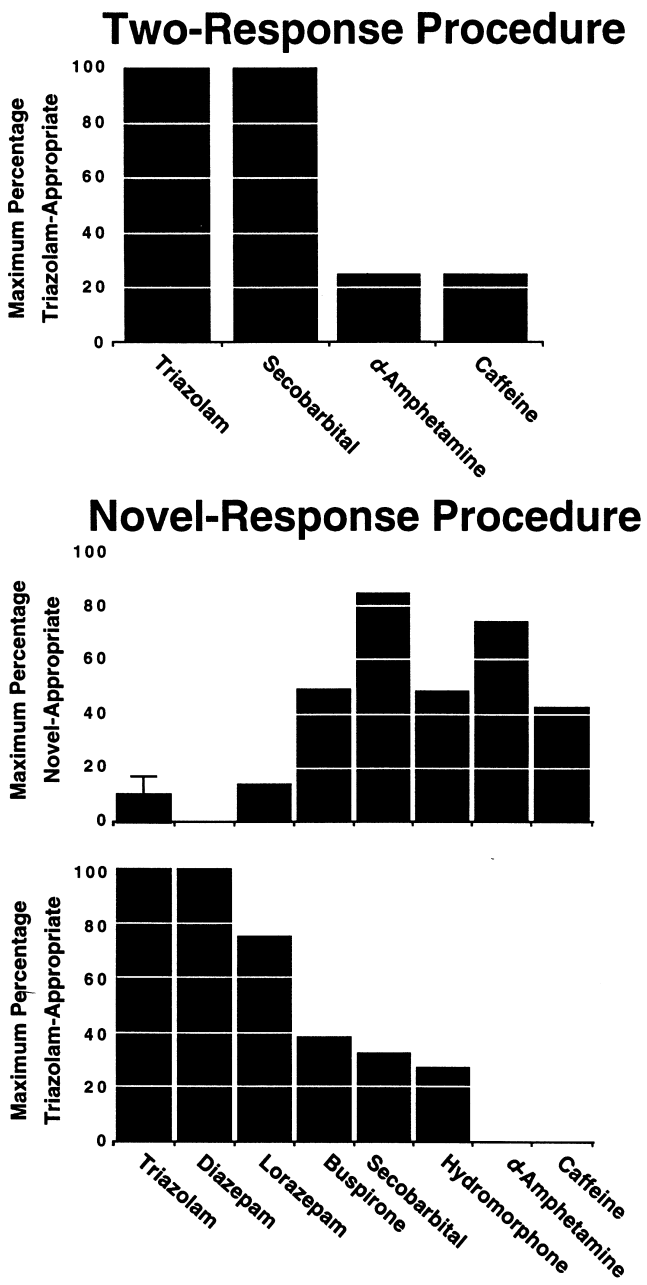

FIG. 2. The maximum average percentages represent the greatest average percentage of triazolam or novel-appropriate responding across all subjects tested at any dose under the two-response procedure (top panel) or under the novel-response procedure (bottom two panels). Diazepam, lorazepam, buspirone, and hydromorphone were tested only under the novel-response procedure; thus data under the two-response procedure are not available. The data are summarized from the current study (triazolam, secobarbital, caffeine) and three previously published studies [triazolam and *d*-amphetamine: (6); triazolam, hydromorphone and diazepam: (29); triazolam, buspirone, and lorazepam: (21)].

dimensions (triazolam-like and novel-like), rather than just the triazolam-like dimension. Consideration of the maximum percentage of novel-appropriate responding (Fig. 2; middle panel) suggests grouping of these drugs into two distinct categories. One category is made up of triazolam, diazepam, and lorazepam, drugs that did not occasion greater than 20% novel-appropriate responding. Secobarbital falls into a 'novel' category made up of drugs that occasioned greater than 20% novel-appropriate responding and also includes buspirone, hydromorphone, *d*-amphetamine, and caffeine.

Consideration of the amount of triazolam-appropriate responding that occurred when a novel-response alternative was present may provide even finer distinctions (Fig. 2, bottom panel). The order in which the drugs are presented in Fig. 2 is a rank ordering based on the maximum percentage of triazolam-appropriate responding that occurred when the novel-response alternative was available. This rank order groups drugs into three categories, each with decreasing similarity to the triazolam training drug. One category could be termed "benzodiazepine anxiolytics" and consist of drugs occasioning at least 75% triazolam-appropriate responding under the novel-response procedure. Of the drugs tested so far, triazolam, diazepam, and lorazepam fall into this category. Another category might be "sedative drugs" and consist of drugs occasioning between 20 and 75% triazolam-appropriate responding. These drugs are buspirone, secobarbital, and hydromorphone. Finally, Fig. 2 suggests a third category that might be characterized as "drugs with no similarity to triazolam" and consist of drugs occasioning less than 20% triazolam-appropriate responding. These drugs are *d*-amphetamine and caffeine. Whether these categories continue to make useful distinctions awaits testing of additional drugs under the novel-response procedure as well as expansion of the novel-response procedure to additional classes of training drugs.

In addition to the discrimination measures, several self-report measurements and a measure of performance were collected. Triazolam and secobarbital produced qualitatively similar self-reports and performance effects that were comparable to those reported in previous studies [e.g. (21,38)]. The two doses of caffeine did not produce measurable self-reported changes or affect performance on the DSST. Because results from discrimination testing under the novel-response procedure clearly differentiated triazolam from secobarbital, the present results suggest that the subjective effects scales used in the present study may be less useful for making fine distinctions among the behavioral effects of similar drugs than testing the discriminative stimulus effects of drugs with the novel-response procedure. The suggestion that self-reported effects need not covary with a drug's discriminative stimulus (39) or reinforcing effects (23) has been made previously and underscores that what people say and what they do often differ.

Overall, the results from this study support the utility of the novel-response procedure for enhancing the pharmacological selectivity of both drug- and placebo-appropriate responding in human drug discrimination studies. The discriminative stimulus effects of secobarbital were different from triazolam's under the novel-response procedure but were not different under the two-response procedure. As with other "multichoice" drug discrimination procedures, the addition of another response alternative enhanced the resolution of the drug discrimination procedure. This enhanced resolution can be useful for interpreting relationships between drugs that may be unclear from results under two-response procedures. However, other "multichoice" drug discrimination procedures require actual training of responses in the presence of specific stimuli, a process that can be time consuming and costly. A particular strength of the novel-response procedure is that this enhanced resolution results from instructions rather than from exposing subjects to additional training drugs. Further, the novel-response procedure can be made even more cost effective by dosing cumulatively, enabling up to four doses to be tested in a single session (40). Cumulative dosing should also increase subject retention through a four-fold decrease in the number of sessions required to generate a test drug's dose–response curve. Finally, abandoning testing under the two-response procedure for comparison purposes will substantially reduce the very large number of sessions and accompanying high dropout rate that result from crossover designs like the one used in the present study. Clearly, the human novel-response procedure for drug discrimination holds promise for elucidating the relationships between the discriminative stimulus effects of a variety of pharmacologically similar and distinct drug classes and for use in additional procedures such as antagonism studies.

ACKNOWLEDGEMENTS

The authors thank Aaron Richards for technical assistance and Betsy Bahrenburg for medical supervision. Denise Tomkins and especially Leslie Amass and Stephen Higgins provided very helpful comments on earlier versions of this manuscript. Preliminary reports of portions of these data were presented at the Annual Meeting of the College on Problems of Drug Dependence, Toronto, Ontario, Canada, June 1993. This study was supported by USPHS Grants DA-06205 (W. K. B.) and Research Scientist Development Award KO2-DA-00109/11-15 (J. R. H.).

REFERENCES

1. Ator, N. A.; Griffiths, R. R.: Lorazepam and pentobarbital drug discrimination in baboons: Cross-drug generalization and interaction with Ro 15-1788. J. Pharmacol. Exp. Ther. 226:776–782; 1983.
2. Ator, N. A.; Griffiths, R. R.: Asymmetrical cross-generalization with lorazepam and pentobarbital training conditions. Drug Dev. Res. 16:355–364; 1989.
3. Barry, H., III; Krimmer, E. C.: Differential stimulus attributes of chlordiazepoxide and phenobarbital. Neuropharmacology 18:991–998; 1979.
4. Barry, H., III; McGuire, M. S.; Krimmer, E. C.: Alcohol and meprobamate resemble pentobarbital rather than chlordiazepoxide. In: Colpaert, F. C.; Slangen, J. L., eds. Drug discrimination: Applications in CNS pharmacology. Amsterdam: Elsevier; 1982: 219–233.
5. Bickel, W. K.; Bigelow, G. E.; Preston, K. L.; Liebson, I. A.: Opioid drug discrimination in humans: stability, specificity and relation to self-reported drug effect. J. Pharmacol. Exp. Ther. 251: 1053–1063; 1989.
6. Bickel, W. K.; Oliveto, A. H.; Kamien, J. B.; Higgins, S. T.; Hughes, J. R.: A novel-response procedure enhances the selectivity and sensitivity of a triazolam discrimination in humans. J. Pharmacol. Exp. Ther. 264:360–367; 1993.
7. Colpaert, F. C.: The discriminative response: An elementary particle of behavior. Behav. Pharmacol. 2:283–286; 1991.
8. Colpaert, F. C.; Desmedt, L. K. C.; Janssen, P. A. J.: Discriminative stimulus properties of benzodiazepines, barbiturates and pharmacologically related drugs; Relation to some intrinsic and anticonvulsant effects. Eur. J. Pharmacol. 37:113–123; 1976.

9. De Vry, J.; Slangen, J. L.: Differential interactions between chlordiazepoxide, pentobarbital and benzodiazepines antagonists Ro 15-1788 and CGS 8216 in a drug discrimination procedure. Pharmacol. Biochem. Behav. 24:999–1005; 1986.
10. Evans, S. M.; Johanson, C. E.: Discriminative stimulus properties of midazolam in the pigeon. J. Pharmacol. Exp. Ther. 248:29–38; 1989.
11. Hendry, J. S.; Balster, R. L.; Rosecrans, J. A.: Discriminative stimulus properties of buspirone compared to central nervous system depressants in rats. Pharmacol. Biochem. Behav. 19:97–101; 1983.
12. Henteleff, H. B.; Barry, H., III.: Discrimination between oral amobarbital and diazepam effects in rats. Drug Dev. Res. 16:407–416; 1989.
13. Herling, S.; Shannon, H. E.: Ro 15–1788 antagonizes the discriminative stimulus effects of diazepam in rats but not similar effects of pentobarbital. Life Sci. 31:2105–2112; 1982.
14. Herling, S.; Valentino, R. J.; Winger, G. D.: Discriminative stimulus effects of pentobarbital in pigeons. Psychopharmacology (Berlin) 71:21–28; 1980.
15. Hughes, J. R.; Higgins, S. T.; Bickel, W. K.; Hunt, W. K.; Fenwick, J. W.; Gulliver, S. B.; Mireault, G. C.: Caffeine self-administration, withdrawal, and adverse effects among coffee drinkers. Arch. Gen. Psychiatry 48:611–617; 1991.
16. Jarbe, T. U. C.: Characteristics of pentobarbital discrimination in the gerbil: transfer and antagonism. Psychopharmacology (Berlin) 49:33–40; 1976.
17. Johanson, C. E.: Discriminative stimulus effects of diazepam in humans. J. Pharmacol. Exp. Ther. 257:634–643; 1991.
18. Johanson, C. E.: Further studies on the discriminative stimulus effects of diazepam in humans. Behav. Pharmacol. 2:357–367; 1991.
19. Johanson, C. E.: Discriminative stimulus effects of buspirone in humans. Exp. Clin. Psychol. 1:173–187; 1993.
20. Kamien, J. B.; Bickel, W. K.; Hughes, J. R.; Higgins, S. T.; Smith, B. J.: Drug discrimination by humans compared to nonhumans: Current status and future directions. Psychopharmacology (Berlin) 111:259–270; 1993.
21. Kamien, J. B.; Bickel, W. K.; Oliveto, A. H.; Smith, B. J.; Higgins, S. T.; Hughes, J. R.; Badger, G. J.: Triazolam discrimination by humans under a novel response procedure: Effects of buspirone and lorazepam. Behav. Pharmacol. 5:315–325; 1994.
22. Krimmer, E. C.; Barry, H., III.: Pentobarbital and chlordiazepoxide differentiated from each other and from nondrug. Commun. Psychopharmacol. 3:93–99; 1979.
23. Lamb, R. J.; Preston, K. L.; Schindler, C. W.; Meisch, R. A.; Davis, F.; Katz, J. L.; Henningfield, J. E.; Goldberg, S. R.: The reinforcing and subjective effects of morphine in postaddicts—A dose–response study. J. Pharmacol. Exp. Ther. 259:1165–1173; 1991.
24. Martin, W. R.; Sloan, J. W.; Sapira, J. D.; Jasinski, D. R.: Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine and methylphenidate in man. Clin. Pharmacol. Ther. 12:245–258; 1971.
25. McLeod, D. R.; Griffiths, R. R.; Bigelow, G. E.; Yingling, J.: An automated version of the digit-symbol substitution test (DSST). Behav. Res. Meth. Instrum. 14:463–466; 1982.
26. Nierenberg, J.; Ator, N. A.: Drug discrimination in rats successively trained to discriminate diazepam and pentobarbital. Pharmacol. Biochem. Behav. 35:405–412; 1990.
27. Oliveto, A. H.; Bickel, W. K.; Hughes, J. R.; Higgins, S. T.; Fenwick, J. W.: Triazolam as a discriminative stimulus in humans. Drug Alcohol Depend. 30:133–142; 1992.
28. Oliveto, A. H.; Bickel, W. K.; Hughes, J. R.; Shea, P. J.; Higgins, S. T.; Fenwick, J. W.: Caffeine drug discrimination in humans: Acquisition, specificity and correlation with self-reports. J. Pharmacol. Exp. Ther. 261:885–894; 1992.
29. Oliveto, A. H.; Bickel, W. K.; Kamien, J. B.; Hughes, J. R.; Higgins, S. T.: Effects of diazepam and hydromorphone in triazolam-trained humans under a novel-response drug discrimination procedure. Psychopharmacology (Berlin) 114:417–423; 1994.
30. Overton, D. A.: State-dependent learning produced by depressant and atropine-like drugs. Psychopharmacology (Berlin) 10:6–31; 1966.
31. Overton, D. A.: Discriminable effects of benzodiazepines. Psychopharmacol. Commun. 2:339–343; 1976.
32. Preston, K. L.; Bigelow, G. E.; Bickel, W.; Liebson, I. A.: Three-choice drug discrimination in opioid-dependent humans: Hydromorphone, naloxone and saline. J. Pharmacol. Exp. Ther. 243: 1002–1009; 1987.
33. Preston, K. L.; Bigelow, G. E.; Bickel, W. K.; Liebson, I. A.: Drug discrimination in human postaddicts: agonist-antagonist opioids. J. Pharmacol. Exp. Ther. 250:184–196; 1989.
34. Preston, K. L.; Liebson, I. A.; Bigelow, G. E.: Discrimination of agonist-antagonist opioids in humans trained on a two-choice saline-hydromorphone discrimination. J. Pharmacol. Exp. Ther. 261:62–71; 1992.
35. Sanger, D. J.; Joly, D.; Zivkovic, B.: Behavioral effects of non-benzodiazepine anxiolytic drugs: A comparison of CGS 9896 and zopiclone with chlordiazepoxide. J. Pharmacol. Exp. Ther. 232: 831–837; 1985.
36. Sannerud, C. A.; Ator, N. A.: Drug discrimination analysis of midazolam under a three-lever procedure. 1. Dose-dependent differences in generalization and antagonism. J. Pharmacol. Exp. Ther. 272:100–111; 1995.
37. Schechter, M. D.: Specific antagonism of the behavioral effects of chlordiazepoxide and pentobarbital in the rat. Prog. Neuropsychopharmacol. Biol. Psychiatry 8:359–364; 1984.
38. Sellers, E. M.; Schneiderman, J. F.; Romach, M. K.; Kaplan, H. L.; Somer, G. R.: Comparative drug effects and abuse liability of lorazepam, buspirone, and secobarbital in nondependent subjects. J. Clin. Psychopharmacol. 12:79–85; 1992.
39. Smith, B. J.; Bickel, W. K.; Kamien, J. B.: Dissociation of self-reports and discriminative performance. In: Harris, L. S., ed. Problems of drug dependence 1995: Proceedings of the 57th annual scientific meeting. Rockville, MD: U.S. Department of Health and Human Services, NIH Publication No. 96-4116; 1996:250.
40. Smith, B. J.; Bickel, W. K.; Higgins, S. T.; Hughes, J. R.; Kamien, J. B.: Cumulative dosing for human triazolam discrimination using a novel response procedure. In: Harris, L. S., ed. Problems of drug dependence 1994: Proceedings of the 56th annual scientific meeting. Rockville, MD: U.S. Department of Health and Human Services, NIH Publication No. 95-3883; 1995:241.
41. Spealman, R. D.: Discriminative-stimulus effects of midazolam in squirrel monkeys: Comparison with other drugs and antagonism by RO 15-1788. J. Pharmacol. Exp. Ther. 235:456–462; 1985.
42. Stolerman, I. P.: Measures of stimulus generalization in drug discrimination experiments. Behav. Pharmacol. 2:265–282; 1991.
43. Stolerman, I. P.; Garcha, H. S.; Rose I. C.: Midazolam cue in rats: Effects of Ro 15-1788 and pricrotoxin. Psychopharmacology (Berlin) 89:183–188; 1986.
44. Tang, A. H.; Franklin, S. R.: The discriminative stimulus effects of diazepam in rats at two training doses. J. Pharmacol. Exp. Ther. 258:926–931; 1991.
45. Woudenberg, F.; Slangen, J. L.: Discriminative stimulus properties of midazolam: Comparison with other benzodiazepines. Psychopharmacology (Berlin) 97:466–470; 1989.
46. Young, A. M.: The time is ripe for an experimental analysis of measurement issues. Behav. Pharmacol. 2:287–291; 1991.
47. Young, R.; Dewey, W. L.: Differentiation of the behavioral responses produced by barbiturates and benzodiazepines by the benzodiazepine antagonist RO 15-1788. In: Colpaert, F. C.; Slangen, J. L., eds. Drug discrimination: Applications in CNS pharmacology. Amsterdam: Elsevier; 1982:235–240.
48. Young, R.; Urbancic, A.; Emery, T. A.; Hall, P. C.; Metcalf, G.: Behavioral effects of several new anxiolytics and putative anxiolytics. Eur. J. Pharmacol. 143:361–371; 1987.