Discriminative Stimulus Effects of Zolpidem in Pentobarbital-Trained Subjects: II. Comparison with Triazolam and Caffeine in Humans

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ABSTRACT

In the present study, four non-drug-abusing humans were trained to discriminate between a hypnotic dose of pentobarbital, 100 mg, and placebo. After acquiring the pentobarbital-placebo discrimination, a range of doses of zolpidem, triazolam, pentobarbital and caffeine were tested to determine whether they shared discriminative stimulus effects with the training dose of pentobarbital. Zolpidem, a rapid-onset, short-duration, quickly eliminated imidazopyridine hypnotic agent, was tested because its discriminative stimulus effects have been shown to differ from those of classic sedative/hypnotic compounds in rodents, but not in nonhuman primates. Triazolam and caffeine were included as positive and negative controls, respectively. The subject-rated and performance-impairing effects of zolpidem, triazolam, pentobarbital and caffeine were assessed concurrently. These four subjects met the discrimination criterion (>80% correct drug identifications on four consecutive sessions) in 4 to 18 (mean = 8.5) sessions, and the pentobarbital-placebo discrimination was well maintained during a test-of-novel-doses and test-of-novel-drugs phase (i.e., placebo and 100 mg pentobarbital occasioned 0–35% [mean = 17%] and 75–100% [mean = 85%] drug-appropriate responding, respectively). Zolpidem, triazolam and pentobarbital generally produced dose-related increases in pentobarbital-appropriate responding and sedative-like, subject-rated drug effects. Caffeine on average produced low levels of pentobarbital-appropriate responding, although some doses of caffeine produced maximal pentobarbital-appropriate responding in some subjects. Caffeine produced some stimulant-like (e.g., jittery, motivated, nervous and stimulated) subject-rated drug effects. Zolpidem and triazolam, and to a much lesser extent pentobarbital, but not caffeine, impaired performance. These results suggest that humans can acquire and maintain a pentobarbital-placebo discrimination, and this discrimination is pharmacologically specific. These results also suggest that despite the somewhat unique biochemical profile of zolpidem, its discriminative stimulus, subject-rated and performance-pairing effects are similar to those of classic sedative/hypnotic compounds like the barbiturates and benzodiazepines. Finally, the results observed in the present study with zolpidem, triazolam and caffeine demonstrate that the discriminative stimulus effects of drugs observed with nonhuman primates can be systematically replicated in humans.

Zolpidem (Ambien®) is a rapid-onset, short-duration, quickly eliminated imidazopyridine hypnotic agent whose actions are mediated at the benzodiazepine recognition site of the GABAA receptor complex (Sauvanet et al., 1988). The receptor-binding profile of zolpidem is somewhat different from that of classic benzodiazepine agonists. Zolpidem selectively binds to the central benzodiazepine1 receptor subtype and shows a different pattern of distribution of binding sites in vitro and in vivo than classic benzodiazepine agonists (Arbilla et al., 1985; Benavides et al., 1988; Biggio et al., 1989; Dennis et al., 1988; Lloyd and Zivkovic, 1988). Other studies with in vivo assays showed that zolpidem does not selectively bind to benzodiazepine1 receptor subtypes, although it does show a unique pattern of dose-effect relationships across different brain regions (Byrnes et al., 1992; Schmid et al., 1995).

Consistent with the biochemical data, preclinical laboratory studies suggest there are meaningful behavioral pharmacological differences between zolpidem and classic anxiolytic/hypnotic compounds (e.g., Cooper and Desa, 1988; Depoortere et al., 1986; Perrault et al., 1990; Sanger and Zivkovic, 1987a, 1988; Yerbury and Cooper, 1989). The discriminative stimulus effects of zolpidem, for example, are distinguishable from the barbiturates and

ABBREVIATIONS: GABA, γ-aminobutyric acid; ARCI, Addiction Research Center Inventory; MBG, morphine-benzedrine group; PCAG, pentobarbital, chlorpromazine, alcohol group; LSD, lysergic acid diethylamide; BG, benzedrine group; A, amphetamine scale; DSST, digit-symbol-substitution test; DEAR, digit-enter and recall; ANOVA, analysis of variance; FI, fixed interval.
benzodiazepines in rodents (Rowlett and Woolverton, 1997; Sanger, 1987; Sanger et al., 1987; Sanger and Zivkovic, 1986, 1987b; Sannerud and Ator, 1995). First, in rats trained to discriminate between zolpidem (2 mg/kg) and vehicle, high doses of triazolam, pentobarbital and chlor diazepoxide (0.3, 20, and 20 mg/kg, respectively) only partially substituted for zolpidem (i.e., each drug occasioned approximately 70% zolpidem-appropriate responding) (Sanger and Zivkovic, 1986). Second, in rats trained to discriminate chlor diazepoxide (5 or 20 mg/kg) from vehicle, a high dose of zolpidem (3 mg/kg) only partially substituted for chlor diazepoxide (i.e., approximately 55–70% drug-appropriate responding) (Sanger et al., 1987). Third, in rats trained to discriminate pentobarbital (8 mg/kg) from vehicle, zolpidem (0.5–4 mg/kg) occasioned less than 50% drug-appropriate responding, whereas triazolam (0.1 and 0.2 mg/kg) occasioned ≥80% drug-appropriate responding (Rowlett and Woolverton, 1997). Fourth, Ro 16–6028 and Ro 17–1812, two mixed agonist-antagonist benzodiazepines, produced drug-appropriate responding in chlor diazepoxide-trained rats, but not in zolpidem-trained rats (Sanger, 1987). Fifth, in rats trained to discriminate between 0.32 and 3.2 mg/kg midazolam from no drug, midazolam (0.032–10 mg/kg), triazolam (0.0032–3.2 mg/kg) and diazepam (0.032–18 mg/kg) produced similar effects: dose-dependent increases first in low-dose (i.e., 0.32 mg/kg midazolam) lever responding and then dose-dependent increases in high-dose (3.2 mg/kg) lever responding (Sannerud and Ator, 1995). Zolpidem (0.032–3.2 mg/kg), by contrast, dose-dependently increased responding only on the low-dose (i.e., 0.32 mg/kg midazolam) lever (Sannerud and Ator, 1995). Finally, CGS 9896, a pyrazoloquinoline, and ZK 91296, a β-carboline, antagonized the discriminative stimulus effects of zolpidem, but not chlor diazepoxide (Sanger and Zivkovic, 1987b).

Studies conducted with nonhuman primates, by contrast, suggest that the discriminative stimulus effects of zolpidem are similar to those of the barbiturates and benzodiazepines. In one study, zolpidem (3.2–10 mg/kg) completely substituted (i.e., >80% drug-appropriate responding) for pentobarbital in baboons trained to discriminate between pentobarbital (10 mg/kg) and vehicle (Griffiths et al., 1992). Similarly, zolpidem (30 mg/kg) completely substituted (i.e., >80% drug-appropriate responding) for pentobarbital in rhesus monkeys trained to discriminate between pentobarbital (10 mg/kg) and vehicle (Rowlett and Woolverton, 1997). Finally, zolpidem (1–10 mg/kg) completely substituted (i.e., >80% drug-appropriate responding) for lorazepam in baboons trained to discriminate between lorazepam (1.8 mg/kg) and vehicle (Griffiths et al., 1992).

To the best of our knowledge, the discriminative stimulus effects of zolpidem have not been examined in humans trained to discriminate between a classic sedative/hypnotic compound (i.e., a barbiturate or benzodiazepine) and placebo. Studies with humans that used subject-rated drug-effect questionnaires, which are thought to be related to the discriminative stimulus effects of drugs in nonhuman laboratory animals (Preston and Bigelow, 1991; Schuster and Johanson, 1988; Schuster et al., 1981), have produced mixed results (Evans et al., 1990; Rush and Griffiths, 1996). In one previous study, for example, zolpidem (15–45 mg) and triazolam (0.25–0.75 mg), a triazolobenzodiazepine hypnotic compound produced a different constellation of subject-rated drug effects in volunteers with histories of drug abuse (Evans et al., 1990). Across the range of doses tested, zolpidem, but not triazolam, increased subject ratings of somatic symptoms like dizziness, anxiousness, queasiness and blurred vision. In addition, the highest dose of triazolam was identified as barbiturate-, benzodiazepine- or alcohol-like nearly twice as often as the highest dose of zolpidem (Evans et al., 1990). To the extent that subject-rated and discriminative stimulus effects of drugs are related, these findings suggest that the discriminative stimulus effects of zolpidem may be distinguishable from those of classic sedative/hypnotic compounds in humans. Other studies, however, have found that zolpidem produces subject-rated drug effects that are qualitatively and quantitatively similar to those of classic sedative/hypnotic compounds in non-drug-abusing humans (Berlin et al., 1993; Rush and Griffiths, 1996).

The purpose of the present experiment was to first determine whether humans could discriminate between a hypnotic dose of pentobarbital, 100 mg, and placebo. Pentobarbital has never been established as a discriminative stimulus in humans even though it has been used as the training drug in experiments with a variety of species including mice (e.g., Balster and Moser, 1987; Rees and Balster, 1988; Rees et al., 1987; Willetts et al., 1991), rats (e.g., Ator and Griffiths, 1989; Bar y and Krimmer, 1979; Nierenberg and Ator, 1990), gerbils (Jarbe, 1976; Jarbe et al., 1975; Johansson and Jarbe, 1975), pigeons (e.g., Evans and Johanson, 1989; Her ling and Winger, 1981; Herling et al., 1980; Jarbe and Ohlin, 1979), rhesus monkeys (e.g., de la Garza and Johanson, 1987; Massey and Woolverton, 1994; Winger and Herling, 1982) and baboons (e.g., Ator and Griffiths, 1983, 1985). After acquiring the pentobarbital-placebo discrimination, a range of doses of zolpidem, triazolam, pentobarbital and caffeine were tested to determine whether they shared discriminative stimulus effects with the training dose of pentobarbital. Zolpidem was tested because, as noted above, its discriminative stimulus effects have been shown to differ from those of classic sedative/hypnotic compounds in rodents (Rowlett and Woolverton, 1997; Sanger, 1987; Sanger et al., 1987; Sanger and Zivkovic, 1986, 1987b), but not in non-human primates (Rowlett and Woolverton, 1997; Griffiths et al., 1992). Triazolam and caffeine were included as positive and negative controls, respectively, because previous drug discrimination experiments conducted with nonhuman primates have shown that triazolam dose-dependently occasions pentobarbital-appropriate responding (Ator and Griffiths, 1989), whereas caffeine does not (Ator and Griffiths, 1985). Finally, to more fully characterize the behavioral effects of zolpidem, triazolam, pentobarbital and caffeine, subject-rated drug-effect questionnaires and performance measures previously shown to be sensitive to the effects of benzodiazepine, barbiturate and nonbenzodiazepine sedative/hypnotic compounds were included (e.g., Kirk et al., 1990; Rush et al., 1993a,b; Rush and Griffiths, 1996).

### Methods

#### Subjects

Four healthy adult volunteers (one male and three females) recruited via newspaper ads, flyers and word-of-mouth completed this experiment. Volunteers were paid $20/session to participate in this experiment and performance-based payment as outlined below.
Three additional volunteers were enrolled in this experiment, but did not complete. Data from these volunteers were not included in the analyses. The four volunteers that completed the experiment ranged in age from 27 to 48 years (mean = 39) and in weight from 62 to 105 kg (mean = 81). These volunteers reported consuming 0 to 237 mg caffeine/day (mean = 89) and had completed 12 to 16 years of education (mean = 14). One subject reported smoking 10 tobacco cigarettes/day. This subject was allowed to smoke ad libitum except while completing the drug-discrimination measures, subject-rated drug-effect questionnaires and performance tasks. Subjects completed questionnaires assessing drug use and medical and psychiatric histories, were interviewed by a psychiatrist, and provided written informed consent before participating. Individuals with current or past histories of serious psychiatric disorder, except nicotine dependence, were excluded. All subjects were in good health with no contraindications to hypnotic medications or caffeine. Drug urine screens conducted during screening were negative for amphetamines, benzodiazepines, barbiturates, cocaine and opioids. In the female subjects, urine pregnancy tests before and periodically during study participation were negative. This study was approved by the Institutional Review Board of the University of Mississippi Medical Center.

**General Procedures**

Subjects participated as outpatients at the Laboratory of Human Behavioral Pharmacology at the University of Mississippi Medical Center Monday through Friday for 52 to 63 (mean = 59) experimental sessions. Subjects were informed that during their participation they would receive various drugs and that these could include placebo, various sedatives, muscle relaxants and anxiolytics, stimulants and weight loss medications, antidepressants and antihistamines. Subjects were told that the purpose of the study was to see if they could tell the difference between various drugs, and how these drugs affected mood and behavior. Other than receiving this general information subjects were blind to the type of drug administered; subjects were given no instructions regarding what they were “supposed” to do or what outcomes might be expected.

Before initiating medication testing, subjects completed one to three (mean = 2) “practice” sessions. These “practice” sessions were used to train subjects on the behavioral procedures and to familiarize them with the subject-rated drug-effect questionnaires, performance measures and daily laboratory routine. No medications were administered on these days.

Throughout the study, subjects were requested to refrain from using all psychoactive drugs (with the exception of tobacco and caffeinated products), caffeine and solid food for 4 hr before a scheduled experimental session, and alcohol for 12 hr before a scheduled experimental session. On each experimental session day subjects arrived at the laboratory at approximately 8:00 A.M. and were provided with a light breakfast with a decaffeinated beverage between 8:00 and 8:30 A.M.. Subjects provided a urine sample each session before drug administration that they believed would be screened for drug use outside the laboratory, although these samples were not actually assayed. Subjects also provided an expired air specimen which was assayed for the presence of alcohol using an Alco-Sensor hand-held breathalyzer (Intoximeters, Inc., St. Louis, MO). All expired air specimens were negative and indicated that subjects had complied with our requests.

On experimental session days, subjects completed the subject-rated drug-effect questionnaires and performance tasks at approximately 8:30 A.M., ingested drug at approximately 9:00 A.M. and then completed the drug discrimination, subject-rated drug-effect questionnaires and performance tasks at hourly intervals for 4 h. A minimum of 24 hr separated all drug administrations. One to three subjects participated in this experiment simultaneously. When not completing the drug discrimination, subject-rated drug-effect questionnaires and performance tasks, subjects were allowed to engage in recreational activities (e.g., watch television, play cards or read) or socialize with each other. Subjects were instructed not to discuss their drug effects with each other during the experimental session nor outside the laboratory. During the experimental session, a research assistant was situated in close proximity to the subjects at all times and monitored their conversations unobtrusively to ensure that subjects did not discuss the drug effects with each other.

**Drug Discrimination Procedures**

This experiment consisted of four phases. Subjects completed the four phases in fixed order: 1) sampling phase, 2) test-of-acquisition phase, 3) test-of-novel-doses phase and 4) test-of-novel-drugs phase.

**Sampling phase.** All volunteers completed four sampling sessions to acquaint them with the drug effects. Subjects reported to the laboratory and completed the subject-rated drug-effect questionnaires and performance tasks (described below). During the first two sampling sessions, subjects ingested four capsules that contained a total of 100 mg pentobarbital. Pentobarbital was identified by letter code (e.g., drug A), but the volunteers were not explicitly informed of the capsules’ contents. During these sampling sessions subjects were instructed to pay close attention to how drug A made them feel, because in the future they would not be told whether they received drug A, and that in these future sessions they could earn extra money by correctly identifying when they had received drug A. A unique letter code was used for each subject.

During the two remaining sampling sessions subjects did not receive any capsules. During these sampling sessions, subjects were instructed to pay close attention to the absence of the effects of drug A because in the future they would not be told when they had not received drug A, and that in these future sessions they could also earn extra money by correctly identifying when they had not received drug A.

Below are the instructions given to each subject during the sampling phase. These instructions were printed on a piece of paper and subjects were instructed to carefully read them before each sampling session.

**Instructions (sampling sessions 1 and 2).** This is drug A. When you receive drug A, you can earn extra money by responding on the button labeled A. During this session you should pay close attention to how drug A makes you feel, because in the future we will not tell you if you received drug A. Instead, you will have to decide whether or not you received drug A. In these future sessions, if you received drug A you can earn extra money by responding on the button labeled drug A. Whenever you do not receive drug A, you can earn extra money by responding on the button labeled not drug A.

**Instructions (sampling sessions 3 and 4).** The past 2 days you received drug A. Today you will not receive any capsules. You should pay close attention to the absence of the effects of drug A, because in the future we will not tell you if you received drug A. Instead, you will have to decide whether or not you received drug A. In these future sessions, if you received drug A you can earn extra money by responding on the button labeled drug A. If you feel you did not receive drug A, you can earn extra money by responding on the button labeled not drug A.

This instruction set is somewhat different than that used in the majority of previous human drug discrimination experiments (cf. Heishman and Henningfield, 1991; Lamb and Henningfield, 1994). Most previous human drug discrimination studies instructed volunteers that their task was to learn to discriminate between two drugs (e.g., drug A and drug B) (see Kamien et al., 1993 for a review). We chose to use this instruction set because it may be more similar to the discrimination learned by nonhuman laboratory animals (Overton et al., 1983). Because this experiment was designed in part to compare the discriminative stimulus effects of drugs across species, it was important that the human and nonhuman components be as methodologically similar as possible.

**Test-of-acquisition phase.** After the sampling phase, a test-of-acquisition phase was conducted to determine whether subjects could discriminate between 100 mg pentobarbital and placebo. On
test-of-acquisition days, subjects ingested capsules under double-blind conditions, but were not told whether the capsules contained 100 mg pentobarbital (e.g., drug A) or placebo (e.g., not drug A). Subjects were not explicitly instructed that they would be attempting to acquire a drug-placebo discrimination. After capsule administration, subjects completed the drug-discrimination tasks, subject-rated drug-effect questionnaires and performance measures (described below) at hourly intervals for 4 hr. Subjects were instructed that they could change their responses on the drug-discrimination measures between hours 1, 2, 3 and 4 based on what they believed at the time. After completing the drug-discrimination measures, subject-rated drug-effect questionnaires and performance tasks at the 4-hr observation, subjects opened a sealed envelope that informed the subject and the research assistant of the identity of the drug administered (i.e., drug A or not drug A). The criterion for having acquired the discrimination was $\geq 80\%$ correct responding on four consecutive sessions on the FI 1-s schedule of point presentation and the point-distribution tasks (described below). Order of drug administration was random except that each subject received each training condition, 100 mg pentobarbital and placebo, at least twice.

Below are the instructions given to each subject during the test-of-acquisition phase. These instructions were printed on a piece of paper and subjects were told to read them carefully before each experimental session. These instructions were also used during the test-of-novel-doses and test-of-novel-drugs phase described below.

**Instructions (test-of-acquisition phase).** Today we will not tell you whether you received drug A or not drug A. Instead, you will have to decide whether you received drug A or not drug A. If you think you received drug A you can earn extra money by responding on the button labeled drug A. If you do not think you received drug A, you can earn extra money by responding on the button labeled not drug A. You can change your drug identifications throughout today’s session based on what you believe at the time. At the end of today’s session, you will be given an envelope that will tell you if you received drug A or not drug A. The number of points that you accumulated on the correct button will then be converted to money and you will be told how much bonus money you earned during today’s session. At the end of some sessions, we may not be able to tell you whether you received drug A or not drug A. The days that we are unable to tell you whether you received drug A or not drug A will be called “test” days. On these test days, your bonus earnings will be the total amount of money you earned on both the drug A and not drug A buttons.

**Test-of-novel-doses phase.** After the test-of-acquisition phase, subjects entered a test-of-novel-doses phase to determine whether other doses of pentobarbital shared discriminative stimulus effects with the training dose. The test-of-novel-doses phase consisted of test days interspersed with test-of-acquisition days. Approximately half the days were test days, and the other half were test-of-acquisition days. As noted above, subjects were instructed that there would be days on which they would not be given any feedback concerning the accuracy of their drug-discrimination performance, and that these days would be designated test days. On test days subjects were credited with the total amount of money earned on both response options (i.e., the drug A option and not drug A option). Thus, test days were identical with test-of-acquisition days except that subjects did not receive any feedback concerning their drug-discrimination performance, and they received the total amount of money earned on both response options. Subjects were not told the purpose of test days, nor did they know when the test days were scheduled until after they opened the sealed envelope.

To ensure that subjects continued to maintain the 100 mg pentobarbital-placebo discrimination throughout the test-of-novel-doses phase, test-of-acquisition days were intermixed among the test days. These test-of-acquisition days were identical with those in the test-of-acquisition phase (i.e., subjects received 100 mg pentobarbital or placebo, completed the drug discrimination tasks at hourly intervals for 4 hr after drug administration, were informed whether they had received drug A or not drug A and received bonus money contingent on the accuracy of their drug-discrimination performance). If a subject responded incorrectly on a test-of-acquisition day, additional test-of-acquisition days were scheduled. These additional test-of-acquisition days continued until the subject correctly identified both conditions once (i.e., 100 mg pentobarbital and placebo).

On test days in the test-of-novel-doses phase, subjects received 25, 50 or 150 mg pentobarbital. Each dose was administered one time. The order of drug administration was random during this phase of the experiment except that an active dose of drug was never administered on more than three consecutive sessions.

**Test-of-novel-drugs phase.** After the test-of-novel-doses phase, subjects entered a test-of-novel-drugs phase to determine whether a range of doses of zolpidem, triazolam and caffeine shared discriminative stimulus effects with 100 mg pentobarbital. The procedures used in the test-of-novel-drugs phase were similar to those used in the test-of-novel-doses phase (i.e., approximately half the days were test days and the other half were test-of-acquisition days); subjects were instructed that there would be days on which they would not be given any feedback concerning the accuracy of their drug-discrimination performance and that these days would be designated test days; subjects were credited with the total amount of money earned on both the drug A and not drug A options on test days; subjects were not told the purpose of test days, nor did they not know when the test days were scheduled until after they opened the sealed envelope; and subjects received additional test-of-acquisition days if they responded incorrectly on a test-of-acquisition day.)

On test days in the test-of-novel-drugs phase, subjects received zolpidem (2.5, 5, 10 and 20 mg), triazolam (0.0625, 0.125, 0.25 and 0.5 mg) or caffeine (50, 100, 200 and 400 mg). Each dose of each drug was administered one time. The order of drug administration was random during this phase of the experiment except that an active dose of drug was never administered on more than three consecutive sessions.

**Drug Discrimination Measures**

During each of the phases described above, three procedures used previously to assess drug-discrimination performance were presented in fixed order (e.g., Preston et al., 1987, 1989, 1990; Preston and Bigelow, 1994). The order in which the tasks are described corresponds to the order in which the subject completed them. As described below, in each procedure, responses on the correct option were converted to money. All drug-discrimination measures were completed 1, 2, 3 and 4 hr after oral drug administration. Unless otherwise stated, the drug discrimination tasks were administered on an Apple Macintosh microcomputer (Apple Computer, Inc., Cupertino, CA).

**Operant responding.** In this procedure, volunteers responded under a FI 1-s schedule of point presentation (e.g., Bickel et al., 1989, 1993; Kamien et al., 1994). Volunteers used a computer mouse to point to and click on one of two buttons on the computer video monitor, labeled drug A and not drug A. The first response made after each 1-s interval elapsed increased the total number of points accumulated on that button by one. Volunteers were not explicitly instructed that a FI schedule was in effect, but were able to observe on the computer video monitor the cumulative number of points that they had earned. Volunteers responded on this procedure for 180 s. To minimize superstitious or random responding, switching from one button to the other initiated a 10-s interval during which time responding on either button had no programmed consequences. Points accumulated on the correct button were exchangeable for money at a rate of 0.5 cents/point. Thus, subjects could earn a maximum of $3.60/session on this task. The dependent measure in this procedure was percent pentobarbital-appropriate responding.

**Point distribution.** In this procedure, the subject distributed 50 points between two options (i.e., drug A or not drug A) depending on how certain he/she was of the identity of the administered drug (e.g., Oliveto et al., 1992a,b, 1994, 1995). Points accumulated on the cor-
rect option were exchangeable for money at a rate of $0.01/point. Thus, volunteers were able to earn a maximum of $2.00/session on this task. The dependent measure in this procedure was percent pentobarbital-appropriate responding.

**Discrete-choice procedure.** This paper-and-pencil task required subjects to circle either drug A or not drug A depending on which drug condition he/she thought they received that session. Each correct identification was exchangeable for money at a rate of $0.50/ correct identification. Thus, volunteers were able to earn a maximum of $2.00/session on this task. The dependent measure in this procedure was percent pentobarbital-appropriate responding (e.g. Oliveto et al., 1992a,b, 1994, 1995).

**Subject-Rated Drug-Effect Questionnaires and Performance Measures**

Subject-rated drug-effect questionnaires and performance measures were administered on an Apple Macintosh microcomputer. The subject-rated drug-effect questionnaires and performance tasks were completed in fixed order. The order in which the tasks are described corresponds to the order in which the subject completed them. These questionnaires and performance measures were completed approximately 30 min before drug administration, and 1, 2, 3 and 4 hr after drug administration.

**ARC1.** The short form of the ARCI consisted of 49 true/false questions and contained five major subscales: MBG (a measure of euphoria); PCAG (a measure of sedation); LSD (a measure of dysphoria); and BG and A scales (empirically derived amphetamine-sensitive scales) (Jaziniak, 1977; Martin et al., 1971).

**Visual-analog scales.** This task consisted of 34 100-mm visual-analog scales that were presented on the video screen, one at a time. Subjects were instructed to rate each item on the basis of how they felt at the present time. Each visual-analog scale was anchored at the left-most extreme with “Not at All” and at the right-most extreme with “An Awful Lot.” The items rated were: Do you feel any drug effect?; Do you feel any bad effects?; Do you feel any good effects?; Do you feel high?; Do you like the drug?; Do you feel alert-energetic?; Do you feel drunk?; Do you feel vigorous?; Do you feel elated?; Do you feel friendly?; Do you feel drowsy?; Do you feel stimulated?; Do you feel confused?; Do you feel restless?; Do you feel jittery?; Do you feel nervous?; Do you feel carefree?; Do you feel relaxed?; Do you feel as if you are able to concentrate?; Do you feel fidgety?; Do you feel hungry?; Do you feel dizzy/light-headed?; Do you have itchy skin?; Do you feel tired?; Do you feel excited?; Do you feel motivated?; Do you feel sweary?; Do you feel thirsty?; Do you feel a turning in your stomach?; Do you feel sleepy?; Do you feel happy?; Do you feel as if you are in a good mood? Do you feel a need/desire to talk? And do you feel as if your performance is impaired?.

**Digit-enter and recall (DEAR).** This was a modified version of the number-recall task (Roache and Griffiths, 1987a,b), which has been described previously (e.g., Evans et al., 1990; Mumford et al., 1995a,b). Subjects used a numeric keypad to reproduce randomly selected 8-digit numbers which were displayed on the computer screen one at a time. The task consisted of two components, an enter component in which subjects copied (entered) the 8-digit number after it was displayed on the screen, and a second component in which the subject recalled (reentered) the 8-digit number after it disappeared from the screen. At the beginning of each trial, an 8-digit number appeared on the computer screen. If the subject entered the number incorrectly, the trial was discontinued, and a different 8-digit number was presented. If the number was entered correctly, the trial continued to the second component; the number disappeared from the screen and, either immediately (five trials) or after a 10-s delay (five trials), the subject was required to recall (i.e., reenter the 8-digit number using the numeric keypad) the number. The task continued until the subject had correctly entered 10 8-digit numbers in the first component (i.e., 10 trials were initiated) or 25 incorrect attempts were made. The dependent measure was the total number of 8-digit numbers correctly reproduced in the second (recall) component (i.e., trials correct). The maximum possible score was 10.

**Digit-symbol-substitution test (DSST).** A computerized version of the DSST, which has been described previously, was used in this experiment (McLeod et al., 1982). Subjects used a numeric keypad to enter a geometric pattern associated with 1 of 9 digits displayed on a video screen. Subjects had 90 s to enter as many geometric patterns as possible. The dependent measures were the number of geometric patterns the subject attempted to enter (i.e., trials completed) and the number of patterns the subject entered correctly (i.e., trials correct).

**Drug Administration**

All drug conditions were administered in a double-blind fashion. Zolpidem (Ambien®, Searle and Co., Chicago, IL), triazolam (Halcion®, Upjohn Company, Kalamazoo, MI), pentobarbital (Nembutal®, Abbott Laboratories, Abbott, IL) and caffeine (Vivarin®, Smithkline and Beecham Pharmaceuticals, Philadelphia, PA) doses were prepared by encapsulating commercially available capsules/tablets in a size 00 capsule. Lactose was used to fill the remainder of all the capsules. Placebo capsules contained only lactose.

During each experimental session subjects ingested four capsules. Zolpidem, triazolam, pentobarbital and caffeine doses were varied by administering the appropriate number of active and placebo capsules. Capsules were taken orally with approximately 150 ml of water. Drug administration procedures were designed to ensure that subjects swallowed the capsules and did not open them in their mouths and taste the contents (Mumford et al., 1996). To accomplish this the research assistant: a) watched the subject to ensure that he/she swallowed the capsules and did not remove them from his/her mouth; b) conducted a brief oral examination to ensure that the subject was not hiding the capsules under his/her tongue; and c) spoke with the subject to determine whether they had anything in their mouth.

**Data Analysis**

Statistical analyses of group data were conducted to examine drug effects on the drug-discrimination measures, subject-rated drug-effect questionnaires and performance measures. Drug discrimination data collected during the test-of-acquisition phase were averaged across all exposures to placebo and 100 mg pentobarbital on the four sessions that subjects met the discrimination criteria and analyzed by repeated measures ANOVA with drug (placebo and 100 mg pentobarbital) and Time (1, 2, 3 and 4 hr postdrug) as factors. Subject-rated drug-effect questionnaire and performance data were also averaged across all exposures to placebo and 100 mg pentobarbital on the four sessions that subjects met the discrimination criteria and analyzed by repeated measures ANOVA with drug (placebo and 100 mg pentobarbital) and Time (1, 2, 3 and 4 hr postdrug) as factors. The mean square error term from the drug × time interaction term was used to conduct Dunnett’s post hoc test comparing 100 mg pentobarbital with placebo at each postdrug time point.

Drug discrimination data collected during the test-of-novel-doses and test-of-novel-drugs phases were averaged across the 1-, 2-, 3- and 4-hr observations, because preliminary analyses showed that drug discrimination performance did not vary systematically as a function of time. For the placebo and 100-mg pentobarbital conditions, drug-discrimination data were averaged across all exposures during the test-of-novel-doses and the test-of-novel-drugs phases. Two sets of analyses were then conducted. First, a one-factor repeated measures ANOVA included all 17 dose conditions (placebo and the 16 drug conditions). A second, two-factor, repeated measures ANOVA was then conducted to determine between-drug differences. Factors for this ANOVA were drug (triazolam, zolpidem, pentobarbital and caffeine) and dose (four levels for triazolam, zolpidem, pentobarbital and caffeine). Placebo values were omitted from these analyses. Between-drug differences were inferred if the main effect
of drug or the interaction of drug and dose attained statistical significance.

Subject-rated drug-effect questionnaire and performance data collected during the test-of-novel-doses and test-of-novel-drugs phases were also analyzed statistically. For the placebo and 100-mg pentobarbital conditions, subject-rated drug-effect questionnaire and performance data were averaged across all exposures during the test-of-novel-doses and the test-of-novel-drugs phase. Repeated measures ANOVA with drug (placebo and the 16 drug conditions) and time (predrug, and 1, 2, 3 and 4 hr postdrug) as factors were then used to analyze these data. The mean square error term from the drug × time interaction term was used to conduct Dunnett’s post hoc test comparing placebo with each of the 16 drug conditions at each postdrug time point. For all statistical analyses, effects were considered significant for $P < .05$.

**Results**

**Drug discrimination performance during the test-of-acquisition phase.** The four subjects met the discrimination criterion in 6, 6, 18 and 4 (S01, S02, S03 and S04, respectively) (mean = 8.5) sessions. During the four test-of-acquisition sessions in which subjects met the discrimination criteria, mean percent pentobarbital-appropriate responding on the FI 1-s schedule of point presentation was 0 across the experimental sessions for all subjects when placebo was administered, and 100, 100, 100 and 99% (S01, S02, S03 and S04, respectively) (mean = 99.8%) pentobarbital-appropriate responding when 100 mg pentobarbital was administered. Statistical analyses of the group data revealed that the placebo and the 100-mg pentobarbital condition differed significantly at each of the four observations (Dunnett’s = 1.3) (data not shown). Performance under the point-distribution and discrete-choice procedure was similar to that observed under the FI 1-s schedule of point presentation (data not shown).

**Subject-rated and performance effects during the test-of-acquisition phase.** Figure 1 shows the 15 visual-analog scales that were significantly affected by 100 mg pentobarbital during the test-of-acquisition phase (Dunnett’s = 1.6–30.0). This figure shows that pentobarbital’s effects typically differed significantly from placebo 1 hr after drug administration, peaked 2 to 3 hr after drug administration, but no longer differed significantly from placebo by 4 hr after drug administration. The remaining visual-analog scales were not significantly affected by the administration of 100 mg pentobarbital.

Figure 2 shows 4 ARCI subscales, along with 2 DSST measures described below, that were also significantly affected by 100 mg pentobarbital during the test-of-acquisition phase (Dunnett’s = 1.2–2.5). This figure shows that relative to placebo 100 mg pentobarbital significantly increased PCAG and LSD scores, and decreased BG and A scores. The pentobarbital time-course function on the ARCI scales was generally similar to that observed on the visual-analog scales described above. The remaining ARCI scales were not significantly affected by the administration of 100 mg pentobarbital (data not shown).

Figure 2 also shows that 100 mg pentobarbital significantly impaired DSST performance 1 to 3 hr after drug administration (Dunnett’s = 3.0–6.0). DEAR performance was not significantly affected by the administration of 100 mg pentobarbital (data not shown).

**Drug discrimination performance during the test-of-novel-doses and test-of-novel-drugs phase.** Accurate discrimination performance was maintained on the test-of-acquisition sessions that were interspersed among the test sessions in the test-of-novel-doses and test-of-novel-drugs phase. Specifically, on these test-of-acquisition sessions, placebo occasioned 0, 13, 19 and 35% (S01, S02, S03 and S04, respectively) (mean = 17%) pentobarbital-appropriate responding on the FI 1-s schedule of point presentation (fig. 3, filled symbol above PL). By contrast, on these test-of-acquisition sessions, 100 mg pentobarbital occasioned 85, 78, 100 and 75% (S01, S02, S03 and S04, respectively) (mean = 85%) pentobarbital-appropriate responding (fig. 3, filled symbol above PTB 100). Performance under the point-distribution and discrete-choice procedure was similar to that observed under the FI 1-s schedule of point presentation (data not shown).

Triazolam, zolpidem and pentobarbital generally increased pentobarbital-appropriate responding as a function of dose (fig. 3). Triazolam (0.063, 0.125, 0.25 and 0.5 mg) on average occasioned 25, 75, 75 and 88% pentobarbital-appropriate responding on the FI 1-s schedule of point presentation, respectively (fig. 3, upper left panel). The doses of triazolam that were identified as pentobarbital-like varied across the individual subjects (fig. 3, lower panels). All doses of triazolam tested occasioned at least 75% pentobarbital-appropriate responding in one subject (S04), whereas the three higher doses of triazolam occasioned at least 75% pentobarbital-appropriate responding in two subjects (S01 and S03) (fig. 3). Only the highest dose of triazolam occasioned at least 75% pentobarbital-appropriate responding in the final subject (S02) (fig. 3). Performance under the point-distribution and discrete-choice procedure was similar to that observed under the FI 1-s schedule of point presentation (data not shown).

Zolpidem (2.5, 5, 10 and 20 mg) on average occasioned 38, 94, 94 and 77% pentobarbital-appropriate responding on the FI 1-s schedule of point presentation, respectively (fig. 3, upper left panel). The doses of zolpidem that were identified as pentobarbital-like also varied across the individual subjects (fig. 3, lower panels). All doses of zolpidem occasioned at least 75% pentobarbital-appropriate responding in two other subjects (S01 and S04). Intermediate doses of zolpidem occasioned at least 75% pentobarbital-appropriate responding in the final subject (S02), whereas the lowest and highest dose occasioned less than 10% pentobarbital-appropriate responding. Performance under the point-distribution and discrete-choice procedure was similar to that observed under the FI 1-s schedule of point presentation (data not shown).

Pentobarbital (25, 50, 100 and 150 mg) on average occasioned 50, 19, 85 and 94% pentobarbital-appropriate responding on the FI 1-s schedule of point presentation, respectively (fig. 3, upper left panel). The doses of pentobarbital that were identified as like the training dose of pentobarbital also varied across the individual subjects (fig. 3, lower panels). All doses of pentobarbital occasioned at least 75% pentobarbital-appropriate responding in one subject (S04), whereas only the two highest doses of pentobarbital occasioned at least 75% pentobarbital-appropriate responding in two other subjects (S01 and S02). Finally, 25, 100 and 150 mg
Fig. 1. Time-course functions for 100 mg pentobarbital and placebo for the 15 visual-analog scales that were significantly affected during the test-of-acquisition phase. x-axes, time after drug administration in hours; Pre, predrug. Data points show means of four subjects for the last four sessions that subjects met the discrimination criteria. Filled symbols indicate those values which are significantly different from the corresponding placebo value at the same time point (Dunnett’s post hoc tests, $P \leq .05$). Standard error bars are omitted for clarity.
pentobarbital, but not 50 mg pentobarbital, occasioned at least 75% pentobarbital-appropriate responding in one subject (S03). Performance under the point-distribution and discrete-choice procedure was similar to that observed under the FI 1-s schedule of point presentation (data not shown).

Caffeine (50, 100, 200 and 400 mg) on average occasioned 38, 0, 25 and 25% pentobarbital-appropriate responding on the FI 1-s schedule of point presentation, respectively (fig. 3, upper left panel). Some of the doses of caffeine tested occasioned high levels of pentobarbital-appropriate responding in two subjects, although this effect was not dose dependent (fig. 3, lower panels). The 200-mg dose of caffeine occasioned 100% pentobarbital-appropriate responding in one subject (S02), whereas the 50- and 400-mg doses of caffeine occasioned 100% pentobarbital-appropriate responding in another subject (S03). All of the doses of caffeine tested occasioned 50% or less pentobarbital-appropriate responding in the two remaining subjects (S01 and S04). Performance under the point-distribution and discrete-choice procedure was similar to that observed under the FI 1-s schedule of point presentation (data not shown).

One-factor repeated measures ANOVA revealed a significant effect because of dose for percent pentobarbital-appropriate responding on the FI 1-s schedule of point presentation ($F_{16,48} = 3.5$). Two-factor repeated measures ANOVA revealed a significant effect of drug ($F_{3,9} = 7.0$), whereas the interaction of drug and dose approached, but did not achieve, statistical significance ($F_{9,27} = 2.1$, $P = .07$). Inspection of figure 3 (upper left panel) suggests that these effects resulted because pentobarbital-appropriate responding was generally an increasing function of dose for triazolam, zolpidem and pentobarbital, but not caffeine.

Subject-rated and performance effects during the test-of-novel-doses and test-of-novel-drugs phase. Table 1 shows the 21 visual-analog scales, 3 ARCI subscales (i.e., A, BG, PCAG) and 3 performance measures (i.e., trials completed and trials correct on the DSST, and trials correct on the DEAR) were significantly affected by at least one of the dose conditions during the test-of-novel-doses and test-of-novel-drugs phase. Figure 4 shows dose-response and time-course functions of triazolam, zolpidem, pentobarbital and caffeine for two visual-analog scales (drug effect and sleepy) and PCAG scores on the ARCI. This figure shows that triazolam, zolpidem and pentobarbital generally increased ratings of drug effect and sleepy, and PCAG scores on the ARCI as a function of dose and time, although significant drug effects were generally observed only with the two higher doses of each drug. Figure 4 shows that the time-course functions of triazolam, zolpidem and pentobarbital were generally similar. Drug effects were generally evident 1 hr after drug administration, peaked 2 to 3 hr after oral drug administration and were no longer significantly different from placebo by 4 hr after drug administration.

Caffeine, by contrast, did not significantly increase subject ratings of drug effect and sleepy across the range of doses tested, nor did it increase PCAG scores on the ARCI (fig. 4; table 1). Instead, caffeine significantly increased subject ratings of bad effects, itchy skin, jittery, motivated, nervous and stimulated above levels observed with placebo (table 1). The effects of caffeine were observed 1 to 3 hr after oral drug administration (table 1). Zolpidem, triazolam and pentobarbital generally did not affect these subject-rated items to a statistically significant degree (table 1).

Figure 5 shows the dose-response and time-course functions for triazolam, zolpidem, pentobarbital and caffeine for the three performance measures (i.e., trials completed and trials correct on the DSST and trials correct on the DEAR). This figure and table 1 show that triazolam and zolpidem impaired DSST and DEAR performance as an orderly function of dose and time. The time-action functions of triazolam and zolpidem on these performance measures differed somewhat from those observed on the subject-rated drug-effect questionnaires described above. Most notably, figure 5 shows that the performance-impairing effects of triazolam and zolpidem persisted throughout the 4-hr experimental session.

Pentobarbital produced only transient performance impairment (i.e., 150 mg pentobarbital significantly decreased trials correct on the DSST 2 hr after oral drug administration) (fig. 5, table 1). Finally, caffeine did not significantly impair DSST or DEAR performance (fig. 5, table 1).

Discussion

The present experiment demonstrated that human research subjects can acquire and maintain a discrimination between a hypnotic dose of pentobarbital, 100 mg, and placebo. Zolpidem, triazolam and pentobarbital generally produced dose-related increases in pentobarbital-appropriate responding. On average, caffeine produced low to moderate levels of pentobarbital-appropriate responding and this effect.
Fig. 3. Dose effects for triazolam (TRZ), zolpidem (ZLP), pentobarbital (PTB) and caffeine (CAF) on the FI 1-s schedule of point presentation. X-axes, dose in milligrams; data points above “PL” designate placebo values. Data points in the upper left panel show means of four subjects; brackets show 1 S.E.M. The remaining four panels show data from the individual subjects. In the individual-subject panels, data points are averaged across the 4-hr experimental session. Filled symbols indicate the training conditions. Numbers in parentheses indicate the number of sessions each training condition was administered; brackets show 1 S.E.M.
was independent of dose. These findings suggest that the pentobarbital-placebo discrimination is pharmacologically specific, because other sedative compounds dose-dependently increased pentobarbital appropriate responding, whereas a methylxanthine stimulant, caffeine, did not. Zolpidem, triazolam and pentobarbital produced sedative-like, subject-rated drug effects, whereas caffeine produced some stimulant-like (e.g., increased ratings of jittery, motived, nervous and stimulated) subject-rated drug effects. These findings suggest that the discriminative stimulus and subject-rated effects of drugs covary in humans. Zolpidem and triazolam, and to a lesser extent pentobarbital, but not caffeine, impaired performance. Thus, despite the somewhat unique benzodiazepine-receptor-binding profile of zolpidem in some species, in humans its discriminative stimulus, subject-rated and performance-impairing effects are similar to those of classic sedative/hypnotic/anxiolytic compounds like the barbiturates and benzodiazepines.

The present study is, to the best of our knowledge, the first to demonstrate that humans can acquire and maintain a pentobarbital-placebo discrimination. The present findings that pentobarbital can function as a discriminative stimulus are concordant with preclinical laboratory experiments that trained mice, rats, pigeons and nonhuman primates to discriminate between a dose of pentobarbital and vehicle (e.g., Ator and Griffiths, 1985, 1989; Evans and Johanson, 1989; Massey and Woolverton, 1994; Willetts et al., 1991). The present findings extend previous human drug discrimination experiments that established other sedative/hypnotic/anxiolytic compounds (i.e., diazepam, triazolam and buspirone) as discriminative stimuli (e.g., Altman et al., 1977; Johanson, 1991a,b; Kamien et al., 1994; Rush et al., 1995b).

Although pentobarbital has never been explicitly established as a discriminative stimulus in humans, previous experiments that used subject-rated drug-effect questionnaires have found that across a range of doses pentobarbital can be differentiated from placebo (e.g., de Wit et al., 1989, 1992; Griffiths et al., 1983; Kirk et al., 1990; Roache and Griffiths, 1985). Worth noting is that in some of these previous studies 100 mg pentobarbital did not produce subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990). In the present study, by contrast, 100 mg pentobarbital produced subject-rated drug effects that were significantly different from those observed with placebo in non-drug-abusing volunteers (Kirk et al., 1990).
correct drug identifications systematically influenced the subject-rated effects of diazepam and buspirone (Rush et al., 1995b).

Zolpidem generally increased pentobarbital-appropriate responding as a function of dose in the present study. These findings are consistent with previous studies that found that zolpidem substitutes for pentobarbital in nonhuman primates trained to discriminate between pentobarbital and vehicle (Griffiths et al., 1992; Rowlett and Woolverton, 1997). Triazolam, a triazolobenzodiazepine hypnotic agent, also dose-dependently increased pentobarbital-appropriate responding in the present study, which is concordant with previous studies that found that benzodiazepines, including triazolam, substitute for pentobarbital in pentobarbital-trained rodents and nonhuman primates (Ator and Griffiths, 1989; Rowlett and Woolverton, 1997). Thus, despite the somewhat unique benzodiazepine-receptor-binding profile of zolpidem, its discriminative stimulus effects are similar to those of classic sedative/hypnotic compounds like the barbiturates and benzodiazepines in nonhuman and human primates.

Caffeine on average occasioned low to moderate levels of pentobarbital-appropriate responding in the present study. The finding that caffeine, a methylxanthine stimulant, did not dose-dependently occasion pentobarbital-appropriate responding in the present study suggests that the pentobarbital-placebo discrimination is pharmacologically specific in humans. However, worth noting is that some doses of caffeine tested in the present experiment occasioned 100% pentobarbital-appropriate responding in some subjects (see S02 and S03 in fig. 3). By contrast, caffeine doses equivalent to those tested in the present study do not occasion drug-appropriate responding above levels observed with vehicle in any baboon trained to discriminate between pentobarbital and vehicle (Ator and Griffiths, 1985). The reason for this apparent discrepancy between baboons and humans is unknown. Interestingly, the two subjects that identified at least one dose of caffeine as pentobarbital-like (i.e., occasioned at least

Fig. 4. Time-course functions and dose effects for triazolam (left column), zolpidem (second from left column), pentobarbital (third from left column) and caffeine (right column) for subject-rated drug effect and sleepy, and PCAG scores on the ARCI during the test-of-novel-doses and test-of-novel-drugs phase. x-axes, time after drug administration in hours; Pre, predrug. Data points show means of four subjects. Filled symbols indicate those values which are significantly different from the corresponding placebo value at the same time point (Dunnett’s post hoc tests, P ≤ .05). Standard error bars are omitted for clarity.
75% drug-appropriate responding) in the present study reported consuming low levels of caffeine (0 and 15 mg/day), whereas the other two subjects reported consuming more moderate levels of caffeine (102 and 237 mg/day). Whether self-reported caffeine use influences a subject's ability to discriminate some doses of caffeine from sedative drugs is unknown.

Zolpidem, triazolam and pentobarbital produced sedative-like, subject-rated effects, although significant effects were generally observed only with the two higher doses of drug. This finding is concordant with several previous studies that assessed the subject-rated effects of zolpidem, triazolam and pentobarbital (e.g., Evans et al., 1990; Kirk et al., 1990; Roache and Griffiths, 1985; Rush and Griffiths, 1996). The absolute magnitude of the sedative-like, subject-rated effects was generally similar for the highest dose of zolpidem, triazolam and pentobarbital. These findings indicate that the doses of zolpidem, triazolam and pentobarbital tested in the present study were equivalent on some behavioral dimension, which is important when other between-drug differences are observed (e.g., differential performance impairment).

Zolpidem and triazolam dose-dependently impaired performance on the DSST and DEAR, which is consistent with previous studies (e.g., Rush and Griffiths, 1996; Rush et al., 1993a,b, 1994a, 1996). Significant impairment was observed throughout most of the experimental session with the two higher doses of zolpidem and triazolam tested. Only the highest dose of pentobarbital tested (150 mg) significantly impaired performance, and this effect was limited to a single postdrug observation and dependent measure (i.e., decreased trials correct on the DSST 2 hr after drug). These findings suggest that across a range of doses that produce similar subject-rated drug effects, pentobarbital produces less performance impairment than zolpidem or triazolam. These findings are generally concordant with a previous study that compared the acute behavioral effects of triazolam and pentobarbital (Kirk et al., 1990). In this study, a range of doses of pentobarbital produced significantly greater subject-rated drug effects than a range of doses of triazolam (Kirk et al.,...
1990). However, across the range of doses tested, pentobarbital and triazolam produced comparable performance impairment (Kirk et al., 1990).

Caffeine did not increase subject ratings of sedation, but instead produced stimulant-like, subject-rated drug effects (e.g., increased ratings of jittery, motivated, nervous and stimulated). These findings are concordant with several previous studies that measured the subject-rated effects of caffeine (e.g., Evans and Griffiths, 1991; Griffiths and Mumford, 1995; Oliveto et al., 1992b; Rush et al., 1995a). Worth noting is the relationship between drug-discrimination performance and the subject-rated effects of the drugs. Drugs that produced sedative-like drug effects (i.e., zolpidem and triazolam) were identified as pentobarbital, whereas drugs that did not produce sedative-like, subject-rated effects (i.e., caffeine) generally were not identified as pentobarbital. These findings are consistent with several previously published human drug discrimination experiments that found that the discriminative stimulus and subject-rated effects of drugs covary (for reviews see Preston and Bigelow, 1991; Schuster and Johanson, 1988; Schuster et al., 1981). Finally, caffeine neither impaired nor improved performance at the doses tested, which is concordant with several previously published studies (e.g., Rush et al., 1994a,b,c, 1995a).

In summary, the present study demonstrated that humans can acquire and maintain a discrimination between 100 mg pentobarbital and placebo. The pentobarbital-placebo discrimination is pharmacologically specific because other sedative compounds (i.e., zolpidem and triazolam), but not caffeine, generally increased pentobarbital-appropriate responding as a function of dose. Similarly, zolpidem, triazolam and pentobarbital, but not caffeine, produced sedative-like, subject-rated drug effects, which further supports the notion that the discriminative stimulus and subject-rated effects of drugs in humans are related (Preston and Bigelow, 1991; Schuster and Johanson, 1988; Schuster et al., 1981). Thus, despite the somewhat unique benzodiazepine-receptor-binding profile of zolpidem, its discriminative stimulus, subject-rated and performance-imparing effects in humans are similar to those of classic sedative/hypnotic compounds like the barbiturates and benzodiazepines. Finally, the drug discrimination results observed in the present study with zolpidem, triazolam and caffeine demonstrate that the discriminative stimulus effects of drugs observed with nonhuman primates can be systematically replicated in humans.

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