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Interactions of Diazepam and Caffeine: Behavioral and Subjective Dose Effects in Humans[1]

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ROACHE, J. D. AND R. R. GRIFFITHS. *Interactions of diazepam and caffeine: Behavioral and subjective dose effects in humans.* PHARMACOL BIOCHEM BEHAV **26**(4) 801–812, 1987.—The effects of diazepam (DZ) (0, 10, and 20 mg) and caffeine (CAF) (0, 200, 400, and 600 mg) alone and in combination were examined in nine healthy male subjects using a within-subject experimental design in which all subjects received all twelve possible dose combinations. Drug effects were assessed using various psychomotor and cognitive performance tasks, staff (observer) ratings of subject behavior, and subject ratings of mood and drug effect. DZ treatment alone impaired performance on all tasks and produced staff and subject ratings indicative of sedative drug effects. CAF treatment alone facilitated performance on two psychomotor tasks requiring rapid reaction speed and increased staff ratings of subject restlessness and subject ratings of tension, alertness, arousal, and CAF symptoms. CAF generally antagonized the DZ-induced ratings of sedation and impairment of psychomotor performance; however, CAF did not consistently antagonize the DZ impairment of immediate recall or delayed recognition memory performance. DZ antagonized the CAF-induced staff-rated restlessness, and subject-ratings of tension, alterness, arousal and CAF symptoms. The results generally support the hypothesis that DZ and CAF produce antagonistic effects through functionally opposing mechanisms, however, the observed effects of drug combinations are dependent on the specific doses being tested and on the measures of drug effect being examined.

Diazepam Caffeine Human studies Behavioral effects Dose effects

WITH the widespread use of benzodiazepines and methylxanthines, there are numerous opportunities for drugs from these two classes of compounds to be administered in combination. Diazepam (DZ), the prototypic 1,4 benzodiazepine, is most frequently prescribed as an anxiolytic although its wide spectrum of activity makes it useful as a muscle-relaxant, sedative-hypnotic, and anticonvulsant as well [30]. The methylxanthine, caffeine (CAF), is extensively consumed in coffee, tea, and soda beverages as well as in a variety of pharmaceutical products [18]. Systematic human experimental studies in non-anxious populations have shown that DZ produces dose-related psychomotor and cognitive performance impairment and sedative-like mood changes [15, 21, 23, 28, 29]. Although human subjects report feeling stimulated or more alert following CAF ingestion, improvements in mental or psychomotor performance are generally not observed [11,17]. High doses of CAF can produce anxiety-like symptoms in normal subjects and anxious patient populations may be hypersensitive to this effect of CAF [6, 18, 44].

Drug interactions between benzodiazepines and methylxanthines seem to be complex. In mice, benzodiazepines have been reported to antagonize CAF-induced seizures [33] and spontaneous motor activity [10], but to facilitate exploratory motor activity [10]. In rats and baboons trained to discriminate lorazepam from placebo, CAF only partly and inconsistently antagonized the lorazepam discriminative cue [2]. In rats trained to discriminate drug from placebo, chlordiazepoxide antagonized the CAF cue while CAF did not antagonize the chlordiazepoxide cue [25]. In humans, methylxanthines have been variably and inconsistently reported to antagonize benzodiazepine-induced sedation and performance impairment [1, 13, 14, 24, 27, 29, 34–36, 38, 45]. Unfortunately, conclusions from many of these human studies are limited by a lack of dose-effect information and/or emphasis on only a narrow range of dependent measures. Finally, there is epidemiological data suggesting clinically significant interactions may occur with the benzodiazepines and methylxanthines. Among patients receiving psychotropic medications, heavy caffeine consumers re-

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TABLE 1

ANOVA F-RATIOS FROM THE TIME-ACTION ANALYSES ON PSYCHOMOTOR PERFORMANCE AND STAFF AND SUBJECT RATINGS

Dependent Measure	CAF† (3,24)	DZ (2,16)	TIME (4,32)	C×D (6,48)	C×T (12,96)	D×T (8,64)	C×D×T (24,192)
Circular Lights	2.57 (0.10)	11.45* (0.001)	7.79* (0.001)	2.31* (0.05)	3.57* (0.001)	10.86* (0.001)	<1.0
Staff-Rated Drug Effect	2.02	7.59* (0.005)	14.34* (0.001)	1.89	1.44	2.73* (0.025)	1.50 (0.10)
Subject-Rated Sluggish-Active	2.41 (0.10)	11.03* (0.001)	2.68* (0.05)	1.28	2.40* (0.01)	3.50* (0.005)	<1.0
Subject-Rated Caffeine Symptoms	4.09* (0.025)	1.84	3.01* (0.05)	1.20	1.84* (0.05)	3.42* (0.005)	1.53 (0.10)

*Asterisks indicate F-ratios which are significant at $p<0.05$; probability levels less than 0.10 are shown in parentheses.

†The ANOVA included the factors CAF (C), DZ (D), and TIME (T) and their interactions. The degrees of freedom (*df*) for the appropriate F-tests are indicated in parentheses. Because the Staff-Rated Drug Effect measure did not include a pre-drug observation, the *df* for the TIME factor and its interactions are as follows: T (*df*=3,24); C × T (*df*=9,72); D×T (*df*=6,48); and C×D×T (*df*=18,144).

ported greater use of benzodiazepines than low to moderate caffeine consumers [19, 20, 41]. These reports suggest that a CAF-induced constellation of anxiety-like symptoms may be mistaken for anxiety or other disorders and that benzodiazepine anxiolytics may, on occasion, be inadvertently prescribed as CAF antagonists.

In the present report, doses of DZ (0, 10, and 20 mg) were given alone and in combination with CAF doses (0, 200, 400, and 600 mg) to healthy human male volunteers. The evaluation of various dose combinations of DZ and CAF was considered important in that one might expect to observe potentiation, antagonism, or no effect depending on the particular dose combination. Several different types of measures (i.e., cognitive and psychomotor tasks and various staff or subject ratings) were examined with the idea that interactions between DZ and CAF may differ qualitatively or quantitatively depending on the type of measure examined.

METHOD

Subjects

Participants were nine, healthy, paid, male volunteers ranging in age from 18–37 years (mean=28 years) and weighing 49.1–90.9 kg (mean=73.6 kg). Five subjects were Black, three were Caucasian, and one was Oriental. All subjects had completed high school or an equivalency exam. All subjects reported experience with alcohol and marijuana although none reported daily use; only two subjects were cigarette smokers (1 pack/day) and no subject reported regular use of other drugs of abuse. During a given subject's participation (6 weeks), moderate use of caffeine, alcohol, or marijuana was permitted; however, subjects were instructed to abstain from the use of all other drugs and to not drink alcohol or smoke marijuana within 12 hr of an experimental session. Breath samples were tested for alcohol and urine samples were tested for the presence of opioids and barbiturates with an EMIT system analyzer; drug-free breath and urine samples were required before each experimental session. Subjects were instructed not to ingest solid food or caffeine-containing beverages after 0800 hr on the morning of an experimental session and subjects were not permitted to eat food until 2 hr after drug administration. Subjects were included in this study only if they reported minimal usage of caffeine; only two subjects reported regular coffee consumption (1–2 cups/day), three subjects reported regular tea consumption (1–2 glasses/day), and all subjects reported moderate usage of soda beverages.

General Procedure

Before beginning the study, subjects reported to the laboratory for instruction and practice on the tasks and were informed that during their participation, they might receive placebo or various types of sedative and stimulant drugs alone and in combination. Subjects participated in the study on a Monday-Wednesday-Friday schedule for a total of 16 experimental sessions. Each session ran from 0930–1500 hr during which time subjects completed a battery of questionnaires and performance tasks prior to drug administration (T=0) and repeatedly every hour after drug administration for a total of 4 hours (T=1 to T=4). No more than four subjects participated in the experiment at one time and the times of drug administration and test battery completion were staggered so that one subject was tested every 15 minutes. In order to facilitate motivation and performance, subjects were paid additional money ($10–$25) at the completion of the study contingent upon how well they did on all of the performance tasks.

Drug Administration

All drugs were contained in three gelatin capsules and were administered orally (under double-blind conditions) between 1000–1100 hr. Four doses of CAF (caffeine anhydrous) (0, 200, 400, 600 mg) and three doses of DZ (Valium®) (0, 10, 20 mg) were administered alone and in combination such that all 12 possible dose combinations (4 doses CAF × 3 doses DZ) were administered to each subject. Placebo was always administered on the first and third sessions to allow for acclimation to the experimental conditions and 200 mg CAF was administered on the second session to screen for possible CAF hypersensitivity. Beginning with the fourth session, the 12 possible dose combinations were administered over 12 consecutive sessions. The order of these dose combinations was determined for each subject by a balanced

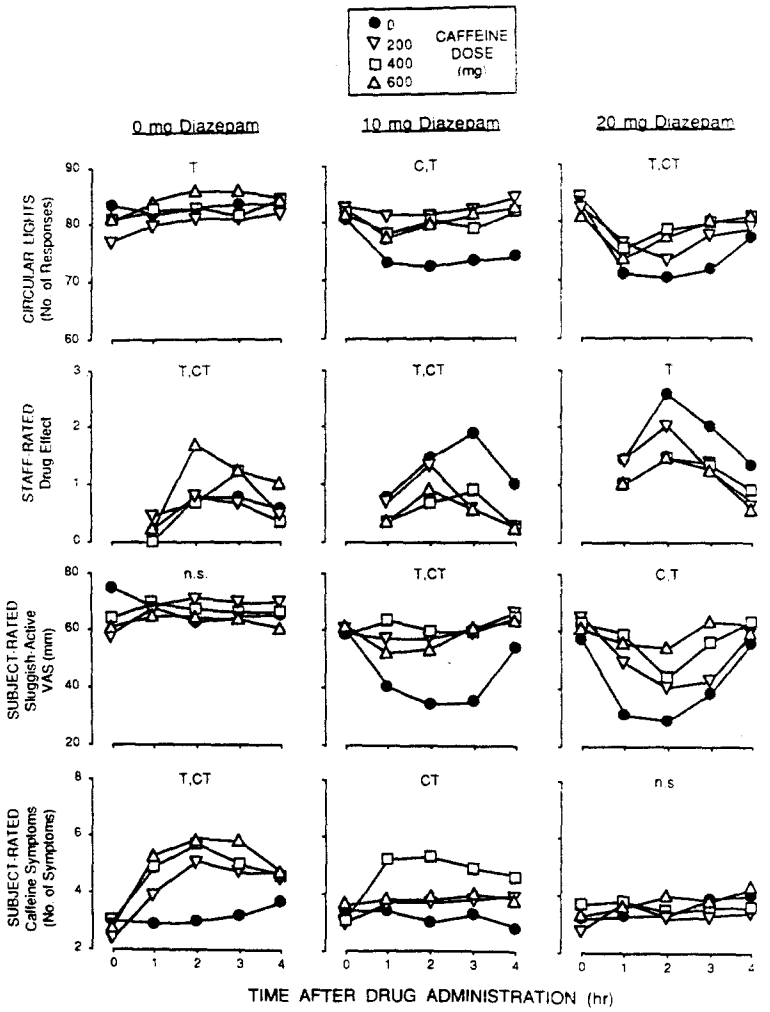

FIG. 1. Time-action functions on psychomotor performance and staff and subject ratings. Each column of panels presents data from one of the DZ dose levels (i.e., 0, 10, and 20 mg); each panel presents data from the four CAF dose levels (i.e., 0, 200, 400 and 600 mg) combined with a particular DZ dose. Y axes: circular lights scores, staff ratings of drug effect magnitude, subject ratings on a "sluggish-active" visual analog scale (VAS), and subject ratings of CAF target symptoms. X axes: time after drug administration in hours (time "0" denotes pre-drug values; there was no pre-drug observation for the staff ratings). Data points show means of nine subjects. Separate two-factor ANOVAs: were performed for each DZ dose level; significant ($p<0.05$) effects of CAF (C), TIME (T), and CAF × TIME (CT) interactions are indicated above each panel (n.s. indicates non-significant effects).

block design which blocked across CAF dose level (i.e., all 4 CAF doses were represented within each of three blocks); DZ doses were systematically varied within each block. Each subject was randomly assigned to a different balanced block dose sequence.

Performance Tasks

Circular lights and digit-symbol-substitution task (DSST). Subjects repeatedly performed the circular lights task and a computerized version of the DSST every hour from T=0 to T=4. Circular lights was a psychomotor task which has been described [21] and used extensively [21, 23, 42] in previous research. The task required subjects to press a series of buttons in response to the randomly sequenced illumination of associated lights; the score was the number of correct button presses during a 1-min session. The DSST was a psychomotor/cognitive task which has been described previously [31]. The task required subjects to use positions on a numeric keypad to reproduce geometric symbol patterns associated with digits displayed on the video screen; the score was the number of patterns correctly reproduced during a 90-sec session.

Choice reaction. Subjects performed a previously reported [22] computerized reaction time task every hour from T=0 to T=4. The task required subjects to press one of two telegraph keys (spaced 15 cm apart) in response to a randomly selected digit (1–8) displayed in the center of the video

TABLE 2
ANCOVA F-RATIOS FROM THE PERFORMANCE TASKS

Task	Measure†	CAF (df=3,24)	DZ (df=2,16)	CAF×DZ (df=6,47)
Circular Lights	AUC	10.03* (0.001)	27.44* (0.001)	1.21
	PK	6.45* (0.005)	40.32* (0.001)	1.31
DSST	AUC	2.87 (0.10)	16.01* (0.001)	<1.0
	PK	2.78 (0.10)	19.62* (0.001)	<1.0
Serial-Subtraction	AUC	2.15	5.50* (0.025)	<1.0
	PK	1.84	4.26* (0.05)	<1.0
Choice Reaction	AUC	3.29* (0.05)	4.36* (0.05)	<1.0
	PK	1.59	5.27* (0.025)	<1.0
Recall: No. Correct	AUC	<1.0	4.68* (0.01)	2.15 (0.10)
	PK	<1.0	10.45* (0.005)	1.77
Recall: Position Errors	AUC	<1.0	6.04* (0.025)	1.09
	PK	<1.0	3.45 (0.10)	1.69

*Asterisks indicate F-ratios which are statistically significant at $p<0.05$; probability levels less than 0.10 are indicated in parentheses.
†AUC and PK refer to area-under-the-curve and peak drug effects, respectively.

screen. Subjects were to press the left or right key dependent on whether the digit was even or odd, respectively. A trial began with the presentation of a digit and was terminated when either key was depressed; the inter-trial interval varied randomly from 0.5–5.0 sec. There were a total of 12 trials but only responses from the latter ten trials were utilized in determining the number of correct responses and the median reaction time (in msec); the number of correct responses was not significantly affected in this study.

Number recall. Subjects completed a computerized number recall task every hour from T=0 to T=4. For this task, subjects used a numeric keypad to reproduce each of ten 8-digit numbers which were displayed on the video screen one at a time. A trial consisted of a 3 sec presentation of a randomly selected 8-digit number; immediately following the termination of the video display, the subject was to reproduce the number on a numeric keypad. The subject's responses were displayed on the video screen following which the subject had an option to re-enter the number to correct typographical errors. Each 8-digit number was randomly selected such that no single digit was repeated within an 8-digit number and the number never began with zero. Subjects were instructed to repeat the number "out loud" since verbal repetition was found to facilitate performance on the task. The scores on this task were the total number of 8-digit numbers which were reproduced correctly (out of ten possible) and the total number of "position errors" which occurred. A position error was defined as the failure to correctly type the correct digit into the correct position of an 8-digit number; since there were ten 8-digit numbers, it was possible to make a total of 80 position errors.

Serial subtraction of numbers. Subjects completed a paper and pencil serial subtraction task every hour from T=0 to T=4. The task involved serial subtractions of 3, 7, or 17 from three different randomly selected 4-digit numbers; each task execution involved 10 subtractions of 3, 10 subtractions of 7, and 10 subtractions of 17. The scores were the number of errors and the number of seconds required to complete the 30 subtractions; the number of errors was not significantly affected in the present study.

Delayed recognition. This recognition task has been described previously [42]. The task involved the memorization of ten pictures of easily recognizable items. At one hour post-drug (T=1), subjects were allowed 1-min to memorize ten pictures presented on a file card. Subjects were not tested for recognition of the memorized pictures until the end of the experimental session (i.e., at T=4, after a 3 hr delay). For the recognition test, subjects were presented with the complete list of 165 pictures which contained each picture labeled by number (No. 1–165) and were to identify the cor-

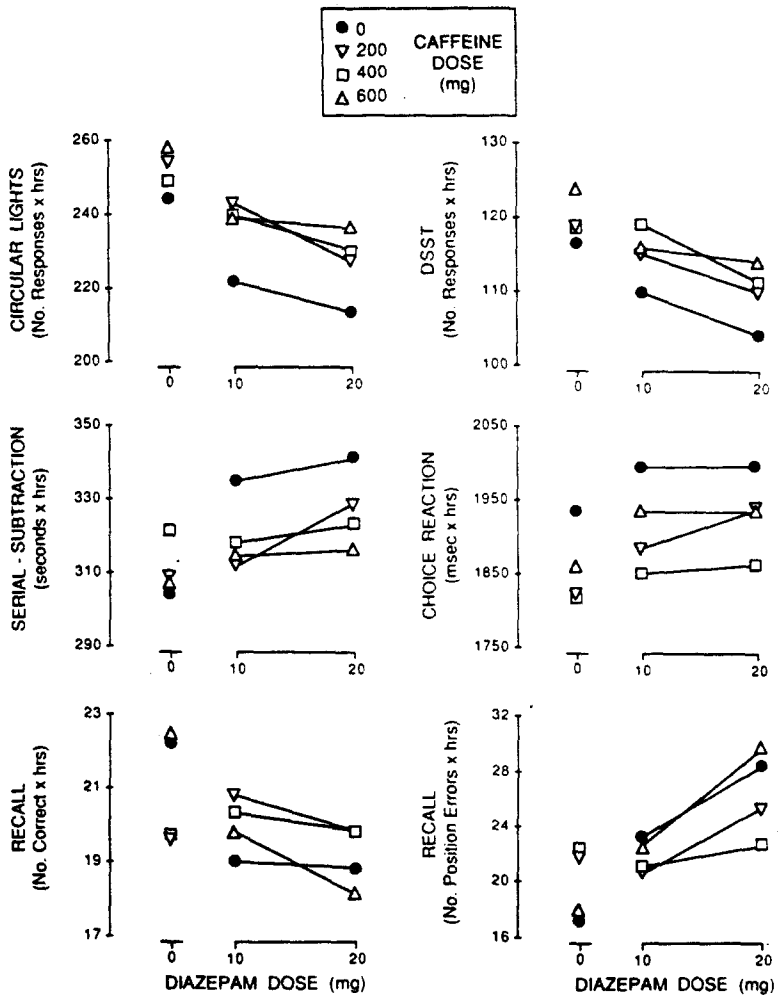

FIG. 2. Dose-response functions for area-under the time-action curve (AUC) measures on several performance tasks. Y axes: post-drug AUC values, adjusted for the pre-drug covariate, on circular lights, DSST, serial-subtraction, choice reaction, and recall (both number correct and position errors) tasks. As indicated on each of the axes, the units of the AUC measures are the task scores × hr. X axes: DZ dose in mg. Data points show adjusted means of nine subjects.

rect 10 pictures they had previously memorized by writing the appropriate numbers onto 10 blank lines; the scores were the number correct out of 10.

Staff Ratings

The research staff, who were "blind" to the specific drugs administered to subjects, rated subject behavior each hour following drug administration from T=1 to T=4. Staff knew only that subjects might receive a placebo or various sedative and stimulant drugs alone and in combination. The staff rated the subjects' behavior once each hour in regard to " . . . the subject's behavior only during the last hour." Staff rated the following seven dimensions: (1) "The subject has shown a drug effect"; (2) "The subject seems to have been uncomfortable or has complained of discomfort"; (3) "The subject has indicated that he felt really good or liked the drug effect"; (4) "The subject has appeared to be drowsy or sedated"; (5) "The subject has been abnormally clumsy or uncoordinated"; (6) "The subject has been abnormally restless or fidgety"; (7) "The subject has been irritable or disagreeable." Staff rated each dimension with a five-point rating scale (0–4); the five points were labeled as "not at all," "a little," "moderately," 'quite a bit," and "extremely," respectively.

Subject Ratings

Profile of Mood States (POMS) Questionnaire. Subjects completed the POMS Questionnaire before taking drug (T=0) and at 2 hr after drug (T=2). The POMS Questionnaire is a 65-item, five-point adjective rating scale which is considered to be a standardized subjective mood state inventory [32]. From the 65 items, seven standard factor scores were determined and two additional factors were calculated as composites of the other factors. All of these factors are identified in Table 4.

Drug Effect Questionnaire. Subjects completed a Drug Effect Questionnaire at each hour following drug administration (T=1 to T=4). Subjects placed a mark on a 100 mm

line in order to respond to each of two separate questions. Question 1 was "How strong of a drug effect are you feeling?"; the extremes of the 100 mm line were labeled "I feel no drug effect at all (not at all)" and "I feel an extremely strong drug effect (extremely strong)." Question 2 was "Do you like the way the drug makes you feel right now?". The line for this question was bisected at the midpoint. The midpoint was labeled "I feel neutral about it" and the left and right extremes were labeled "I do not like the way it makes me feel at all (strong dislike)," and "I like it extremely well, it really feels good (strong liking)," respectively.

Visual Analog Scale (VAS) Mood Questionnaire. Subjects completed this VAS Mood Questionnaire every hour from T=0 to T=4. The questionnaire contained 14 different 100 mm lines each labeled at the extremes with opposing adjectives. The specific adjectives used to label the left and right extremes of the lines are presented in Table 5. Several of these adjective pairs (items 2, 3, 7, 9, and 12) were taken from scales previously employed in other studies [4, 13, 16, 34].

Caffeine Symptom Checklist. Subjects completed a CAF symptom checklist repeatedly every hour from T=0 to T=4. This checklist contained 25 phrases which described psychic and somatic target symptoms related to known effects of CAF; subjects indicated the presence or absence of a particular symptom "during the last hour." (Copies of the Caffeine Target Symptom Checklist are available from the authors upon request.) The data were the number of symptoms present as rated by the subject.

Statistical Analysis

All data were subjected to a repeated measures analysis of variance (ANOVA) and/or analysis of covariance (ANCOVA). Analyses included the factors of CAF dose level (i.e., CAF at 0, 200, 400 and 600 mg) and DZ dose level (i.e., DZ at 0, 10 and 20 mg); when time course was examined, the third factor of time (i.e., TIME at 0, 1, 2, 3, and 4 hr) was also included. Unless otherwise specified, data were analyzed by ANCOVAs which employed the pre-drug value (i.e., T=0) as a covariate in the analysis of post-drug peak effect and area-under-the-curve (AUC) data taken from T=1 to T=4; with the POMS data, pre-drug values were covaried in the analysis of the post-drug measures taken at T=2 only. ANOVAs were employed in the analysis of all staff ratings and the subject ratings on the Drug Effect Questionnaire since these measures did not have a pre-drug observation. All AUC data were calculated with the use of the trapezoidal rule.

RESULTS

Time Course

Table 1 presents the F-ratios from 3 factor (CAF, DZ and TIME) ANOVAs on selected variables representing the different types of measures obtained in this experiment; Fig. 1 shows the time-response functions for the DZ and CAF dose combinations on these variables. As shown in Table 1, a significant main effect of CAF was only obtained with the subject-rated CAF symptoms; main effects of DZ were obtained with the other three measures. All four measures showed main effects of TIME and TIME interactions with both DZ and/or CAF. To facilitate interpretation of these results, separate ANOVAs were performed for each dose level of DZ on each of these variables; significant effects from these analyses are indicated within each panel of Fig. 1.

TABLE 3

ANOVA F-RATIOS OF AREA-UNDER-THE-CURVE VALUES FROM THE STAFF-RATED DRUG EFFECT QUESTIONNAIRE

Rating Dimension	CAF (df=3,24)	DZ (df=2,16)	CAF×DZ (df=6,48)
Drug Effect Magnitude	2.04	7.51*	2.06
		(0.005)	(0.10)
Subject Discomfort	<1.0	1.43	1.20
Subject Drug Liking	1.31	<1.0	1.01
Drowsy/Sedated	3.30*	7.96*	1.31
	(0.05)	(0.005)	
Clumsy/Uncoordinated	3.64*	8.74*	1.24
	(0.05)	(0.005)	
Subject Restlessness	3.70*	4.05*	<1.0
	(0.05)	(0.05)	
Subject Irritability	<1.0	1.39	<1.0

*Asterisks indicate F-ratios which are statistically significant at $p<0.05$; probability levels less than 0.10 are indicated in parentheses.

As can be seen in Fig. 1, in the absence of CAF, both 10 and 20 mg DZ impaired circular lights performance and increased staff ratings of drug effect and subject ratings of sluggishness (i.e,. a lower score on the bipolar scale of "sluggish-active" indicates more sluggish). These effects generally were apparent by the first hour, reached peak effect by the second hour, and returned towards pre-drug levels at subsequent time-points. In the absence of DZ, all three CAF doses produced increases in the number of subject-rated CAF symptoms which were apparent by the first hour, reached peak effects by the second hour and returned towards pre-drug levels at subsequent time-points. When given alone, 600 mg CAF produced a significant increase in the staff ratings of drug effect. There was also a tendency for 200 and 600 mg CAF to increase circular lights performance relative to pre-drug levels while performance was stable over time with the placebo condition. The results obtained with the combinations of DZ and CAF indicate that CAF generally antagonized the DZ-induced circular lights impairment, the increases in staff ratings of drug effect, and the subject ratings of sluggishness. At the 10 mg DZ dose level, all CAF doses more or less prevented the DZ effects but at the 20 mg DZ dose level, the antagonism was less complete and DZ effects were not completely blocked. There was a dose-relationship to the CAF antagonism of the effects of 20 mg DZ in that 200 mg CAF generally produced a less complete antagonism than did higher doses of CAF. With the subject ratings of CAF symptoms, 20 mg DZ completely prevented the CAF effects but the 10 mg DZ dose produced a less complete antagonism in that 400 mg CAF still produced effects. The staff ratings of drug effect showed a noteworthy effect of the drug combinations. Although, the 600 mg CAF and 10 mg DZ doses each produced increases in staff ratings when given alone, the combination of these two doses did not produce staff ratings greater than placebo levels.

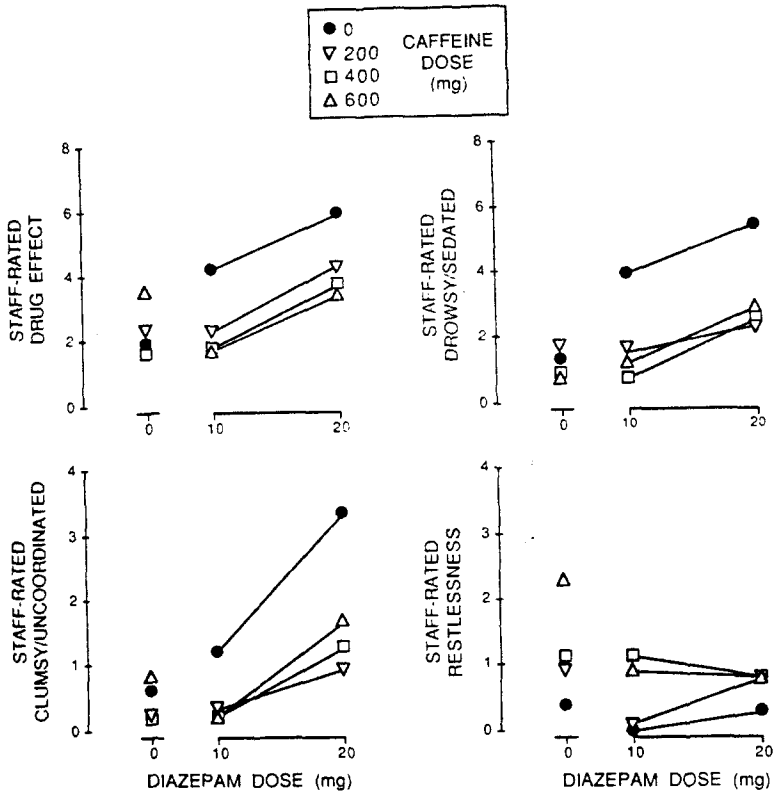

FIG. 3. Dose-response functions for area-under the time-action curve (AUC) values from staff-rated measures. Y axes: post-drug AUC values from staff ratings of drug effect, drowsy/sedated, clumsy/uncoordinated, or restlessness. The units of the AUC measures are rating scores × hr. X axes: DZ dose in mg. Data points show means of nine subjects.

Performance Measures

Table 2 presents the ANCOVA F-ratios from the performance tasks for two indices of post-drug performance (i.e., peak magnitude of effect and area under the time-action curve). Analyses of both the peak and AUC measures generally yielded comparable results; since the AUC measure may be considered as most representative of the overall drug effect, only this measure was considered in subsequent analyses. As can be seen in the table, significant main effects of DZ were obtained with all tasks, a CAF main effect was observed only with the circular lights and the choice reaction tasks and CAF × DZ interactions were not observed on any task.

Figure 2 presents the AUC measures of performance plotted as DZ dose-response functions for all six of the tasks identified in Table 2. DZ significantly impaired performance on all of the tasks. The significant main effect of CAF on the choice reaction task reflects a general facilitation of performance. CAF alone (i.e., 0 mg DZ) decreased reaction time in a manner such that the 400 mg dose produced the greatest facilitation and 600 mg produced less facilitation of performance than the lower doses. This non-monotonic dose-response pattern of CAF effects was still apparent in combination with DZ doses; at the 10 and 20 mg DZ dose levels, 400 mg CAF produced the greatest facilitation while the 200 and 600 mg doses produced less or no facilitation. If these data were plotted as a CAF dose-response, the curves would be "U-shaped" with DZ producing an "upward shift" in the CAF dose-response curve. The significant main effect of CAF on circular lights reflects the tendency for CAF to facilitate performance when given alone (as noted for Fig. 1) and to antagonize the DZ-induced impairment when given in combination. Although the ANCOVAs did not detect significant effects of CAF on the other tasks, certain effects are clear. CAF generally attenuated the magnitude of DZ-induced impairment on the DSST and serial-subtraction tasks. With the recall task, the 200 and 400 mg doses of CAF tended to impair recall performance (i.e., decreased number correct and increased position errors) when given alone but tended to attenuate the DZ-induced impairment when given in combination with DZ; 600 mg CAF did not produce any effect either alone or in combination with DZ.

Results from the delayed recognition task (data not shown) were generally comparable to those observed with the recall task. The number of pictures correctly recognized was significantly reduced by DZ, $F(2,16)=6.42$, $p<0.01$; CAF alone tended to reduce performance and CAF combined with DZ failed to antagonize the impairment observed with either drug alone.

Staff Ratings

Table 3 presents the ANOVA F-ratios from the staff

TABLE 4

ANCOVA F-RATIOS OF 2 HR POST-DRUG SCORES FROM THE SUBJECT-RATED PROFILE OF MOOD STATES (POMS) QUESTIONNAIRE

POMS Factor	CAF (df=3,24)	DZ (df=2,16)	CAF×DZ (df=6,47)
Anger/Hostility (AH)	3.77* (0.025)	<1.0	1.32
Confusion/Bewilderment (CB)	<1.0	1.74	<1.0
Depression/Dejection (DD)	<1.0	3.40 (0.10)	1.25
Fatigue (FAT)	3.76* (0.025)	9.59* (0.005)	1.28
Friendly (FRD)	5.05* (0.01)	4.84* (0.025)	<1.0
Tension/Anxiety (TA)	2.76 (0.10)	3.99* (0.05)	1.30
Vigor (VIG)	3.76* (0.025)	10.13* (0.005)	<1.0
Arousal (ARL)	4.17* (0.025)	10.45* (0.005)	<1.0
Total Mood Disturbance (TMD)	2.39 (0.10)	5.49* (0.025)	<1.0

*Asterisks indicate F-ratios which are statistically significant at $p<0.05$; all probability levels less than 0.10 are indicated in parentheses.

TABLE 5

ANCOVA F-RATIOS OF AREA-UNDER-THE-CURVE VALUES FROM SUBJECT RATINGS ON THE VISUAL ANALOG SCALE (VAS) MOOD QUESTIONNAIRE

VAS Question (left-right)†	CAF (df=3,24)	DZ (df=2,16)	CAF×DZ (df=6,47)
"sluggish-active"	4.52* (0.025)	9.52* (0.005)	1.26
"calm-excited"	2.30	3.23 (0.10)	<1.0
"drowsy-alert"	6.76* (0.005)	5.36* (0.025)	<1.0
"pleased-unsatisfied"	<1.0	2.04	<1.0
"restless-pacified"	<1.0	<1.0	1.06
"lively-weary"	5.78* (0.005)	8.64* (0.005)	<1.0
"clumsy-well coordinated"	1.43	2.97 (0.10)	1.30
"mentally sharp-mentally dull"	1.10	3.78* (0.05)	1.02
"tense-relaxed"	2.39 (0.10)	3.67* (0.05)	2.27 (0.10)
"energetic-lazy"	5.20* (0.01)	4.28* (0.05)	<1.0
"uneasy-mellow"	2.37 (0.10)	<1.0	1.44
"strong-feeble"	1.71	6.20* (0.025)	1.68
"irritable-peaceful"	<1.0	<1.0	1.89
"tranquil-nervous"	1.18	2.49	1.83

*Asterisks indicate F-ratios which are statistically significant at $p<0.05$; probability levels less than 0.10 are indicated in parentheses.

†Each of the 14 VAS 100 mm lines were labeled at the left- and right-hand extremes with the indicated adjectives.

ratings. Staff ratings of drug effect magnitude showed only a main effect of DZ and ratings of drowsy/sedated, clumsy/uncoordinated, and restless showed main effects of both CAF and DZ; no CAF × DZ interactions were observed with any of these measures. The data from these measures are presented in Fig. 3. DZ increased the staff ratings of sedative-like effects (i.e., drowsy/sedated and clumsy/uncoordinated) and CAF antagonized the DZ-induced increases. With the drug effect magnitude ratings, 10 and 20 mg DZ increased ratings as did 600 mg CAF; CAF combinations with DZ completely antagonized the effects of 10 mg and attenuated the effects of 20 mg DZ. Although 10 mg DZ and 600 mg CAF each increased staff ratings when given alone (as noted for Fig. 1), the combination of these doses was not different than placebo. With staff-rated restlessness, 600 mg CAF alone produced increases which were antagonized by DZ.

Subject Ratings

Table 4 presents the ANCOVA F-ratios from the subject ratings on the POMS Questionnaire. Significant main effects were observed on all but two factors (CB and DD); CAF × DZ interactions were not observed with any POMS factor. The main effects of DZ were due to increases in the FAT and TMD factor scores and decreases in the FRD, TA, VIG, and ARL factor scores. The effects of CAF were due to modest increases in the AH, FRD, VIG, and ARL factor scores and decreased FAT factor scores. Table 5 presents the ANCOVA F-ratios from the subject ratings on the VAS Mood Questionnaire. Only seven of these VAS items (Nos. 1, 3, 6, 8, 9, 10 and 12) showed significant main effects of CAF and/or DZ treatment. The DZ effects were in the direction of increasing ratings of sluggish, drowsy, weary, mentally dull, relaxed, lazy, and feeble. The CAF effects were in the direction of increasing ratings of active, alert, lively, and energetic. Significant CAF × DZ interactions were not observed with any of these items although the F-ratio for the "tense-relaxed" item (No. 9) just failed significance ($p<0.06$). Additional subject ratings which were not included in Tables 4 or 5 were the CAF symptom checklist and ratings of drug effect and drug liking. The ANCOVA on the CAF symptom checklist detected main effects of CAF, $F(3,24)=4.45$, $p<0.025$, and DZ, $F(2,16)=4.67$, $p<0.05$, and a CAF × DZ interaction, $F(6,47)=2.54$, $p<0.05$. The ANOVAs did not detect any significant subject ratings of drug liking and the drug effect ratings showed only a main effect of DZ, $F(2,16)=15.31$, $p<0.001$.

Figure 4 presents selected examples of subject ratings from the Drug Effect, VAS, and the POMS Questionnaires. With the ratings of drug effect, DZ produced increases which were partly although not completely antagonized by CAF. With the VAS items, CAF by itself increased ratings of "alert" or "active" and DZ by itself produced ratings indicating feelings of "drowsy" and "sluggish"; with the DZ-CAF dose combinations, CAF combined with 10 mg DZ produced placebo-like ratings and CAF combined with 20 mg DZ showed a graded, dose-related antagonism of the DZ effect. With the POMS factors, DZ alone produced ratings of fatigue, decreased arousal, and an increase in the total mood disturbance (TMD); CAF showed a tendency to increase

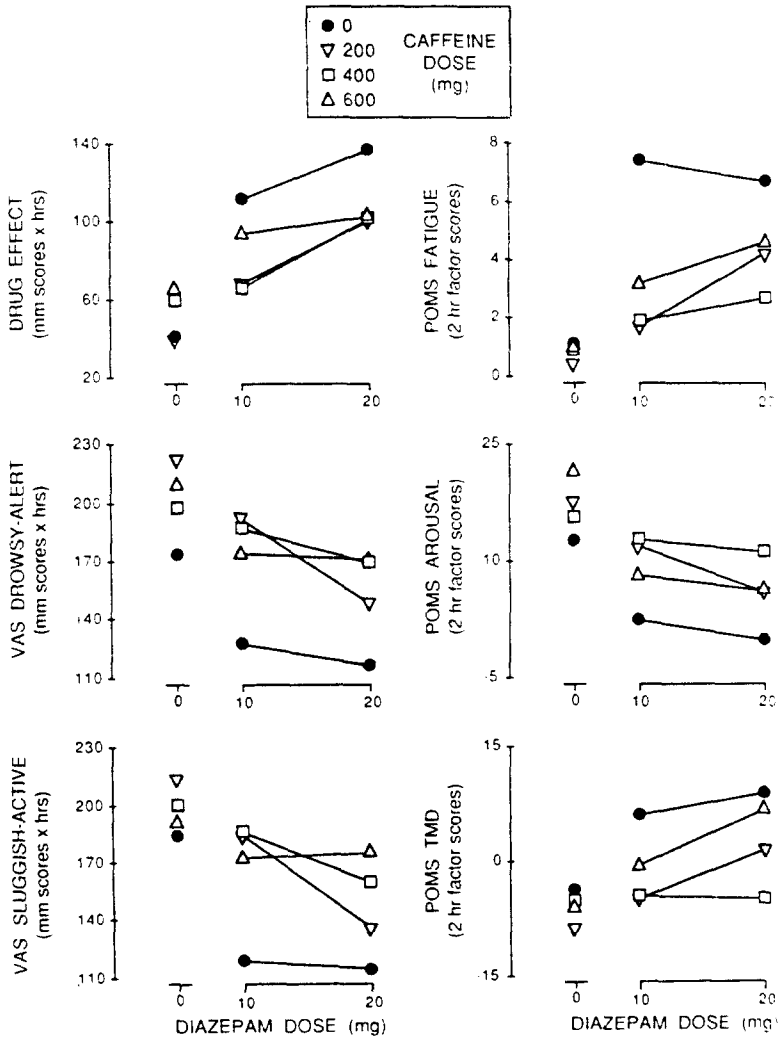

FIG. 4. Dose-response functions from several subject-rated measures. Y axes: ratings of drug effect; the bipolar VAS scales, drowsy-alert and sluggish-active; and the POMS factors, fatigue, arousal, and total mood disturbance (TMD). Drug effect and VAS scale data are post-drug area-under the time-action curve (AUC) values; the units are mm × hr. The POMS factor scores are from observations collected at 2 hr post drug. The data points for all except the drug effect ratings are values adjusted for the pre-drug covariate; drug effect ratings are unadjusted since these ratings were not collected before drug ingestion. X axes: DZ dose in mg. Data points show means of nine subjects.

arousal when given alone, but mostly produced effects to reduce the magnitude of the DZ-induced ratings.

Figure 5 illustrates the effects observed on two additional subject ratings which were more appropriate for presentation as CAF dose-response functions. On the CAF symptom checklist, CAF by itself increased the number of symptoms; whereas 10 mg DZ inconsistently blocked this effect of CAF, 20 mg DZ completely antagonized the CAF effect. With the VAS "tense-relaxed" item, CAF by itself produced increases in ratings of tension (i.e., decreased scores indicate increased tension) which were maximal with the 600 mg dose; both DZ doses completely antagonized the CAF-induced increases in tension. That these data were appropriate for consideration as CAF dose-response functions was verified with ANCOVAs which examined the effect of CAF by itself (i.e., the 0 mg DZ dose); significant CAF dose-effects were obtained with both the CAF symptoms, $F(3,23)=3.58$, $p<0.03$, and the "tense-relaxed" item, $F(3,23)=3.08$, $p<0.05$.

DISCUSSION

The present study employed a wide range of dependent measures in a within-subject experimental design in order to examine the effects of a more complete range of dose combinations of DZ and CAF than have been examined in previous drug interaction studies in human populations. The main conclusions from this study are that DZ and CAF generally produced opposing and/or mutually antagonistic effects and that the observed interactions between DZ and CAF depend

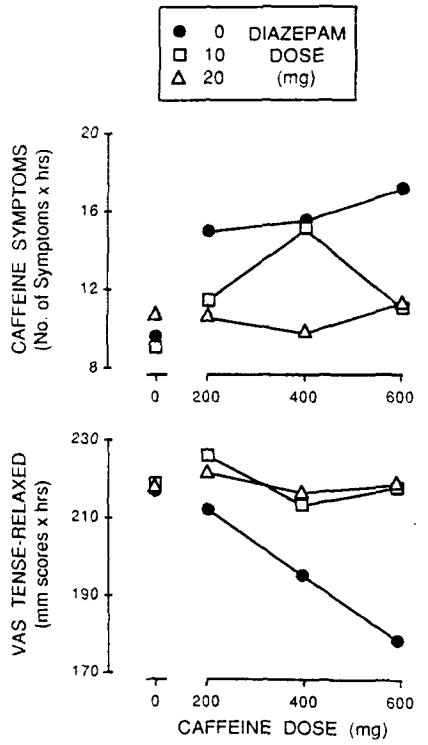

FIG. 5. Two subject-rated measures plotted as CAF dose-response functions. Y axes: post-drug area-under the curve (AUC) values from the CAF symptom checklist and the VAS tense-relaxed scale. All data points are values adjusted for the pre-drug covariate and the units on the AUC measures are scores × hr. X axes: CAF dose in mg. Data points show means of nine subjects.

upon the doses examined and the tasks or rating scales employed as indices of drug effect.

When administered alone, DZ produced a dose-related performance impairment on a variety of tasks, increased staff and subject ratings of drug effect magnitude, increased staff ratings of subject clumsiness and sedation, and increased subject ratings indicating mental and physical sedative-like effects; subject ratings indicating "tranquilizing" effects of DZ alone were not detected in the present study. These results are consistent with numerous reports that DZ impairs psychomotor and cognitive task performance [13, 15, 16, 21, 23, 29, 34–36] and produces sedative-like subjective effects [15, 16, 24, 29, 34]. Some studies have used the "tense-relaxed" VAS scale used in the present study to assess a "tranquilizing" effect of benzodiazepines when given alone [4, 13, 34, 35]; however, other studies have failed to detect benzodiazepine effects on this scale [15,16] and have suggested that healthy subjects may not feel tranquilizing effects of benzodiazepines [16].

When administered alone, CAF increased staff ratings of drug effect magnitude and subject restlessness; increased subject ratings of CAF "target" symptoms; produced subject ratings indicating physical and mental arousal; and increased subject ratings of tension or anxiety. These results are consistent with reports that CAF produces subjective effects of arousal [8, 9, 17] and at high doses produces anxiety-like symptoms in normal research subjects [6, 8, 18, 29, 44] as well as in individuals who regularly consume high doses (i.e., >500 mg/day) through dietary sources [6, 20, 41]. In the present study, CAF by itself facilitated choice reaction speed and somewhat enhanced circular lights performance but had no effect on other tasks or tended to impair recall and recognition performance. While CAF has been reported to facilitate reaction speed [9], most studies have failed to detect CAF-induced improvements in performance except under conditions where performance is deficient or degraded such as may occur following sleep-deprivation or fatigue [11,17]. The effects of CAF on the recall and recognition tasks are consistent with reports that CAF impaired word recall performance [12] or concentration ability [26].

With all three major types of dependent variables, (i.e., performance tasks and staff and subject ratings), the two drugs in combination generally showed mutually antagonistic effects. Examples of DZ effects which were antagonized by CAF were: (1) CAF completely antagonized the impairment produced by 10 mg DZ and produced a dose-related partial antagonism of the impairment produced by 20 mg DZ on most of the performance tasks except for the recall and recognition tasks which did not show consistent CAF effects; (2) CAF antagonized DZ-induced staff ratings of clumsiness, sedation, and drug effect magnitude in a manner such that the effects of 10 mg DZ were completely and the effects of 20 mg DZ were partly antagonized; and (3) CAF completely antagonized the effects of 10 mg DZ on subject ratings of sedation and showed a partial and sometimes dose-related antagonism of the effects of 20 mg DZ on these same measures. Examples of CAF effects which were antagonized by DZ were: (1) DZ produced an upwards shift of the "U-shaped" CAF dose-response function on the choice reaction performance task; (2) DZ completely antagonized the CAF-induced staff ratings of restlessness and drug effect; and (3) DZ completely antagonized the CAF-induced subject ratings of alertness, activity, arousal, tension, and CAF symptoms. Thus many measures showed unidirectional effects in which DZ effects were antagonized by CAF and CAF effects were antagonized by DZ. Several measures showed bidirectional effects (e.g., the choice reaction task and subject ratings on the bipolar drowsy-alert scale) in which DZ and CAF combinations were mutually antagonistic. Finally, with the staff ratings of drug effect, both 10 mg DZ and 600 mg CAF produced effects in the same direction (both increased ratings) but the two drugs in combination produced placebo-like ratings.

A number of previous studies have examined methylxanthine and benzodiazepine interactions in humans. The administration of aminophylline (IV) has been reported to reverse benzodiazepine-induced sedation in patients following surgical anesthesia [1, 38, 45]. In more controlled experimental procedures with healthy volunteer subjects, some studies have involved the administration of single intravenous doses of methylxanthines [24,36] following pretreatment with a single dose of diazepam and in one study [14], subjects received single oral doses of DZ, CAF, or the two drugs in combination. These studies generally showed that methylxanthines partially reversed the effects of DZ on some but not all subject ratings or performance measures; unfortunately, conclusions regarding the efficacy of methylxanthines as benzodiazepine antagonists in these studies are generally limited by a lack of dose-effect information or placebo controls. Only a few studies [13, 29, 34, 35] have examined benzodiazepine-CAF interactions in placebo-controlled study designs. In one such report [35], subjects received either placebo, 10 mg DZ, or 10 mg DZ plus CAF

(250 or 500 mg in coffee); a second study by the same authors [34] repeated the experiment using a 20 mg dose of DZ. These two studies reported that CAF antagonized some but not all of the subject ratings and performance impairment produced by DZ. Only two studies [13,29] have examined CAF-benzodiazepine interactions in a complete factorial design permitting an examination of the effects of either drug alone as well as in combination. In one study [13], placebo or 2.5 mg lorazepam was administered alone or in combination with placebo or a CAF dose (doses of 125, 250, or 500 mg were administered to different groups) in subjects with low or high state anxiety. No differences between the CAF doses were observed and data were collapsed across the different CAF doses. In that study, CAF antagonized the lorazepam impairment of digit-symbol substitution and symbol copying performance and counteracted the lorazepam-induced subject-rated relaxation but did not affect ratings of sedation or impairments on other performance tasks. The second and most complete study [29] involved the administration of one of nine treatments consisting of the factorial combinations of CAF (0, 3, or 6 mg/kg) and DZ (0, 0.15, or 0.30 mg/kg) to different groups of healthy subjects. In that study, CAF only antagonized the DZ impairment of symbol cancellation performance but not the effects of DZ on other tasks or subject sedative ratings.

The results of the present study which showed opposing and mutually antagonistic effects of CAF and DZ are generally consistent with previous reports of antagonistic effects of methylxanthines on a variety of diazepam-induced mood changes and impairments of task performance [24, 34–36]. However, three studies have reported only modest antagonistic effects of CAF on only a few selected measures of benzodiazepine effects [13, 14, 29]. We believe the discrepancies between those three studies and the present one may partly be due to the range of doses tested and the type of study design. The present study was conducted with the statistical power of a within-subject design and involved the administration of a wide range and high doses of CAF (600 mg of the CAF base is the highest dose yet reported in drug interaction studies) to well-practiced subject volunteers. The results showed a clear dose dependence in the antagonistic effects of CAF; CAF more often completely antagonized the effects of 10 mg DZ but only produced a dose-related reduction or partial antagonism of the effects of 20 mg DZ. In contrast, the three studies which did not show robust antagonistic effects of CAF employed a between-groups design and used lower CAF doses; the highest CAF doses were 500 mg of CAF citrate [13] and 6.0 mg/kg of CAF (=420 mg/70 kg man) [14,29].

Another methodological difference between the present study and previous reports, involves the repeated administration of DZ. DZ was used in the present study because this drug is the most frequently prescribed and the most thoroughly studied benzodiazepine. Since the present study was conducted as a within-subject design in which subjects participated three days per week, plasma levels of DZ and its slowly-eliminated, active metabolite, N-desmethyldiazepam (cf. [7]) would have frequently carried over into sessions subsequent to those in which DZ was administered. However, it is not clear what impact this may have had on the results of this study. It is possible that the presence of DZ and its active metabolite would produce tolerance and attenuate the effects of additional acute DZ doses [43]; alternatively, such a carryover might enhance the effect of the acute DZ dose or might provide a background level of sedation which could enhance or attenuate the effects of acute CAF doses. While possible carryover effects of DZ and its metabolites are a confound in the present study and may help to explain quantitative discrepancies between this and other studies, we do not believe it changed the qualitative conclusions regarding DZ and its interactions with CAF. In the present study, there was no evidence of a cumulative sedative effect of DZ across repeated sessions of the experiment; in any case, the DZ dose sequences were balanced across subjects and consistent DZ dose effects were observed. In addition, the results of the present study confirm and extend previous reports of opposing and antagonistic effects of DZ and CAF.

The mechanism(s) of mutually antagonistic effects of DZ and CAF are not known. Studies which have examined pharmacokinetic interactions have generally been negative [14,24] although a recent report [14] suggested that caffeine may physiochemically reduce diazepam plasma levels. Whereas benzodiazepines have been shown to act through a benzodiazepine receptor [37] and CAF is thought to act as an antagonist of the adenosine receptor [5], many reports have suggested that benzodiazepines and methylxanthines interact on a receptor level or at least that the GABA-benzodiazepine system may interact with the adenosine system [5, 33, 39, 40, 46]; however, at lower doses, the interactions are probably not due to competitive-type receptor antagonism [3, 5, 39, 46]. The present results did not show evidence of a competitive type of antagonism; higher doses of either drug would have been necessary to test whether the antagonism was surmountable. We believe that the lack of uniform antagonism across different measures at a particular dose combination suggests that the observed antagonism may involve functionally-opposing effects rather than pharmacological antagonism.

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