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Behavioral Effects of CGS 8216 Alone, and in Combination With Diazepam and Pentobarbital in Dogs

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RISNER, M E. AND H E. SHANNON *Behavioral effects of CGS 8216 alone, and in combination with diazepam and pentobarbital in dogs* PHARMACOL BIOCHEM BEHAV 24(4) 1071–1076, 1986 —Beagle dogs (N=3) responded under a multiple fixed-interval (FI) 300 sec, fixed-ratio (FR) 30 schedule of food presentation The pyrazoloquinoline derivative CGS 8216, given either intravenously (0.01–3 0 mg/kg) or orally (0 1–30.0 mg/kg) had little effect on either the rate or temporal pattern of responding during either component Both diazepam (0.3 to 17 5 mg/kg, PO) and pentobarbital (0.1–17.5 mg/kg, PO) produced qualitatively similar effects on behavior Rates of responding during the FI components first increased, then decreased with increasing doses; both drugs produced only dose-related decreases in the rate of responding during the FR components CGS 8216 antagonized some of the behavioral effects of diazepam, FI and FR response rates returned to baseline, however the effects of diazepam on quarter-life values were not appreciably altered by CGS 8216. The effects of pentobarbital on schedule-controlled responding were not antagonized by CGS 8216 These results indicate CGS 8216 is a selective benzodiazepine antagonist that does not produce benzodiazepine-like behavioral effects.

CGS 8216 Diazepam Pentobarbital Multiple FI FR Dogs

CGS 8216 is a benzodiazepine antagonist which potently inhibits [^{3}H]diazepam and [^{3}H]flunitrazepam binding to rat brain membranes [6,24]. However, whether CGS 8216 is a selective benzodiazepine antagonist is controversial CGS 8216 reversed the effects of diazepam on punished behavior in rats both when lever-pressing was suppressed by shock presentation [2] and when drinking was suppressed by shock presentation [17]. In the former study, CGS 8216 also reversed the effects of meprobamate and phenobarbital whereas in the latter study, CGS 8216 reversed only the effects of benzodiazepine receptor ligands. In a related study, CGS 8216 reversed the effects of pentobarbital on water licking suppressed by shock in rats [15]. In addition, CGS 8216 antagonized the discriminative effects of diazepam, but not pentobarbital, in rats [20]

Although CGS 8216 is apparently devoid of typical benzodiazepine-like actions, it does produce pharmacologic effects of its own which in many respects appear to be opposite those of benzodiazepines Bernard *et al* [2] reported that CGS 8216 reduced punished responding in rats when administered alone. In studies using suppression of water licking by shock as a behavioral baseline, CGS 8216 has been reported to either enhance [15] or not affect [5,17] shock-induced suppression of licking. CGS 8216, at a relatively high dose, also reduced social interactions in rats whereas chlordiazepoxide increased social interactions [10]. In addition, CGS 8216 potentiated the convulsant effects of pentylenetetrazole and picrotoxin in mice, although CGS 8216 alone did not produce convulsions [9] The pharmacologic actions of CGS 8216 suggest that it can alter the effects of other drugs either through receptor-mediated interactions or through physiologic interactions. For example, in the studies by Bernard *et al* [2] and Mendelson *et al.* [15], CGS 8216 may have reversed the effects of diazepam on punished behavior by competition at benzodiazepine receptors, but reversed the effects of meprobamate, phenobarbital and pentobarbital because of opposing behavioral actions

The purpose of the present study was to examine the effects of CGS 8216 alone and also its interactions with diazepam and pentobarbital on schedule controlled behavior in dogs. Diazepam was chosen because CGS 8216 inhibits [^{3}H]diazepam binding [6]. Pentobarbital was chosen because its effects on schedule-controlled behavior are very similar to those of diazepam [13,14], but it does not inhibit [^{3}H]diazepam binding [16]. Pedal-pressing behavior was maintained under a multiple fixed-interval 5-min (F15 min) fixed-ratio 30 response (FR30) schedule of food presentation. A multiple FI FR schedule was chosen because each component of this schedule has been shown to generate characteristic rates and patterns of responding which are uniquely sensitive to the effects of drugs [13] Dose-effect curves were determined for CGS 8216 (PO or IV), diazepam (PO) and pentobarbital (PO) administered alone. In addition, a constant dose of diazepam (3.0 mg/kg) or pentobarbital (3.0 or 10 0 mg/kg) was administered concomitantly with graded doses of CGS 8216.

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TABLE 1
ORDER OF TREATMENT CONDITIONS*†

Treatment Order	Drug	Dose Range	Route	Drug	Dose Range	Route
1	Diazepam	(0 3–17 5)	PO			
2	CGS 8216	(0 1–30 0)	PO			
3	Diazepam	(3 0)	PO and	CGS 8216	(0 3–30 0)	PO
4	Diazepam	(3 0)	PO and	CGS 8216	(0 01–3 0)	IV
5	CGS 8216	(0 01–3 0)	IV			
6	Pentobarbital	(0 1–17 5)	PO			
7	Pentobarbital	(10 0)	PO and	CGS 8216	(1 0, 3 0)	IV
8	Pentobarbital	(3 0)	PO and	CGS 8216	(1 0, 3 0)	IV

*Doses were given 30 min before the start of the session
†When drug combinations were studied, CGS 8216 was given immediately before either diazepam or pentobarbital

METHOD

The subjects were two male pure-bred beagle dogs (D3568 and D3570) and one male beagle-type dog (D3254), obtained from certified suppliers, and weighing 10 4–11 2 kg when given free access to food and water All three dogs had been trained to press a pedal under various schedules of food and/or drug delivery (including sedative/hypnotics and stimulants), but had not been exposed to multiple FI FR schedules The dogs had been drug-free for at least one month before the present experiments began Access to food was restricted until the dogs reached approximately 90% of their free-feeding body weights, they were maintained at this value by giving them limited food supplements following each experimental session Water was available at all times

Experiments were conducted in a wire-mesh chamber within a ventilated, light- and sound-attenuating cubicle (Industrial Acoustics model 400A, Bronx, NY) One black response pedal (20 cm long × 9 cm wide) was horizontally mounted 7 cm above the chamber floor, the pedal could be transilluminated with a 15-W, 28 V DC bulb mounted behind it A minimum downward force of 80 g (0 78N) was required to activate the pedal. A 25-W, 115 V AC bulb was fastened on both the left and right walls of the chamber, adjacent to each bulb was an audio speaker through which low-level masking noise (65 dB) was continuously delivered A food dispenser (Ralph Gerbrands model A, Arlington, MA) was mounted immediately above the chamber and could deliver 1-g food pellets (P J Noyes, formula H, Lancaster, NH) into a receptacle near the response pedal A 15-W, 28 V DC bulb was mounted immediately below the food receptacle Schedule contingencies were programmed and data recorded by a SCAT 3002/PDP8E system (Grason-Stadler, Concord, MA/Digital Equipment, Maynard, MA). Information regarding the temporal distribution of responses within each experimental session was obtained with cumulative response recorders

Procedure

Experimental sessions, conducted Monday through Friday, began with a 5-min timeout during which the chamber was darkened and responses were recorded but had no programmed consequences Each session consisted of 10 FI components (signalled by illumination of the left stimulus light and a 460 Hz, 67 dB tone delivered through the left speaker) alternating with 10 FR components (signalled by illumination of the right stimulus light and a 2800 Hz, 76 dB tone delivered through the right speaker) Initially, during the FI components the first response after 30-sec had elapsed (FI30) produced 5 food pellets accompanied by illumination of the stimulus below the receptacle for 10-sec, during the FR components the second response (FR2) resulted in food delivery Over a period of several weeks the FI duration was increased to 300-sec (FI300) and the FR value was increased to 30 (FR30) The FI component automatically terminated without food delivery if a response did not occur within 60 sec after the 300-sec interval elapsed, and the FR component automatically terminated without food delivery if 30 responses were not completed within 60 sec Successive components were separated by timeout periods of 30 sec during which the chamber was darkened and responses had no programmed consequences Responses during both the FI and FR components briefly (100 msec) transilluminated the pedal

When responding under the multiple FI300, FR30 schedule became stable, drug treatment began (Table 1) Generally, all three dogs received the same drug treatments in the same order, with doses typically administered in an ascending order within each drug series All drugs were administered in the home cage 30 min before the start of the session When drug combinations were studied, CGS 8216 was administered immediately before either diazepam or pentobarbital Drugs were typically administered on Tuesdays and Fridays; appropriate lactose-filled capsules or vehicles were administered on Thursdays

Measurement of Drug Effects

Average overall rates of FI and FR responding were computed separately in the FI and FR components of the multiple schedule by dividing the total number of responses in each component by the total amount of time the component was in effect For analysis of the temporal pattern of FI responding, the FI component was divided into 10 successive 30-sec segments Responses in corresponding segments were accumulated over the entire session, and the percentage of the interval taken to complete the first one-fourth of responses (i e , the quarter-life statistic [11]) was obtained by the method of linear interpolation Overall and local rates of

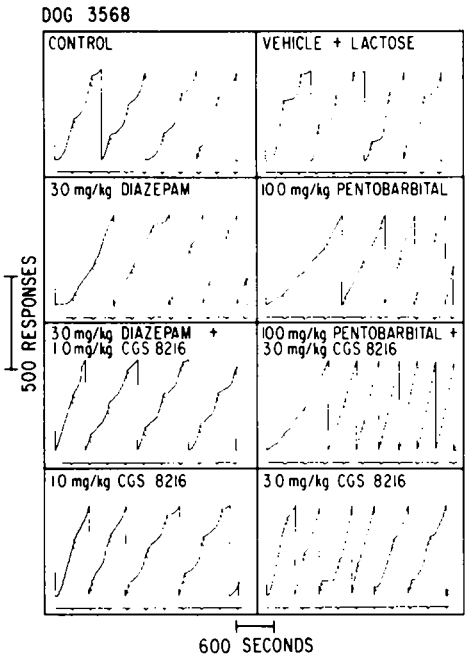

FIG 1 Representative cumulative response records from dog D 3568 depicting behavior under the multiple FI FR schedule of food presentation Abscissae time, ordinates cumulative pedal presses Diagonal marks of the response pen show food delivery, downward deflections of the event pen represent FR components The recorder did not operate during time-out periods

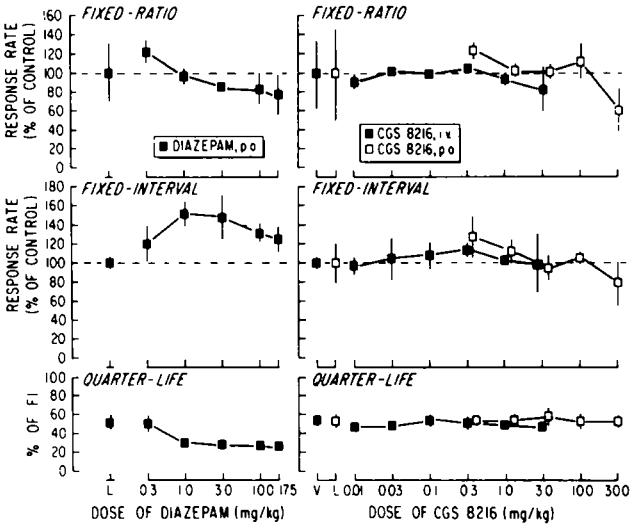

FIG 2 Effects of diazepam and CGS 8216 on responding by beagle dogs under the multiple FI FR schedule of food presentation Abscissae dose, log scale, ordinates overall response rate during FR components (upper panels) and FI components (center panels) expressed as a percentage of response rates during lactose (L) or vehicle (V) sessions, and quarter-life values (lower panels) expressed as a percentage of the FI Vertical lines represent ±S E M

responding and quarter-life values during each session with drug treatment were expressed as a percentage of values from sessions in which lactose-filled capsules or vehicle control injections were administered Since there were some fluctuations in the response rates and quarter-life values across the duration of the study, control values were calculated separately for each of the treatment conditions listed in Table 1 The data were statistically analyzed using an Analysis of Variance and Dunnett's post hoc *t*-test, or the Student's *t*-test, these statistical calculations were performed using the absolute response rate values

Drugs

2-Phenylpyrazolo[4, 3-c]quinolin-3(5H)-one (CGS 8216, Ciba Geigy, Summit, NJ), diazepam base (Hoffmann-LaRoche, Nutley, NJ) and Na pentobarbital (Abbott, North Chicago, IL) were used For oral administration, the drugs were given via gelatin capsules, for intravenous administration, CGS 8216 was suspended in a mixture of 60% propylene glycol, 20% ethanol and 20% double-distilled water (v/v/v) and given via the cephalic vein in a volume of 0 1 ml/kg

RESULTS

Control Performance

During non-drug control sessions, the multiple FI FR schedule of food presentation maintained rates and patterns of responding characteristic of this schedule [8] Each FI component typically began with a period of little or no responding which was followed by a positively accelerated rate until a response produced food (Fig 1, control) The average response rate during the FI components was 0.49, 0 56, and 0 74 responses/sec, and the average quarter life was 62.8%, 43 7%, and 58.3% for dogs D-3568, D-3570 and D-3254, respectively Each FR component typically began with a brief pause followed by an abrupt change to a steady, high rate of responding that was maintained until food delivery occurred (Fig. 1, control). The average response rate during the FR components was 1 67, 0.99, and 3.83 responses/sec for the same three dogs, respectively The rate during the timeout periods that separated successive components seldom exceeded 0 2 responses/sec, and was typically 0 1 responses/sec or less

Acute Effects of CGS 8216, Diazepam, and Pentobarbital

CGS 8216, given either intravenously or orally, had little effect on either the rate or temporal pattern of responding (Fig 1). For example, the only intravenous dose that produced deviations in response rates greater than 10% from control was 3 0 mg/kg (Fig. 2, right panel) The quarter-life value was not appreciably affected by any intravenous dose of CGS 8216 An oral dose of 0.3 mg/kg moderately increased FI and FR response rates, but did not change the quarter-life value. Only the rates of responding during the early portions of the FI were moderately increased by this dose On the other hand, an oral dose of 30 0 mg/kg decreased both FI and FR rates of responding, the average quarter-life value was unaffected and remained at 53% of the interval

Both diazepam and pentobarbital produced qualitatively similar effects on the rate and temporal pattern of responding (Fig. 1) With few exceptions, both drugs produced dose-

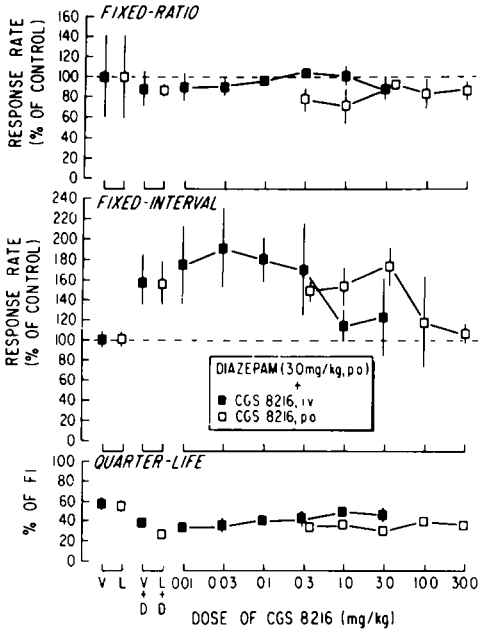

FIG 3 Effects of CGS 8216 given in combination with diazepam on responding by beagle dogs under the multiple FI FR schedule of food presentation See Fig 1 for other details, lactose (L), vehicle (V), diazepam (D)

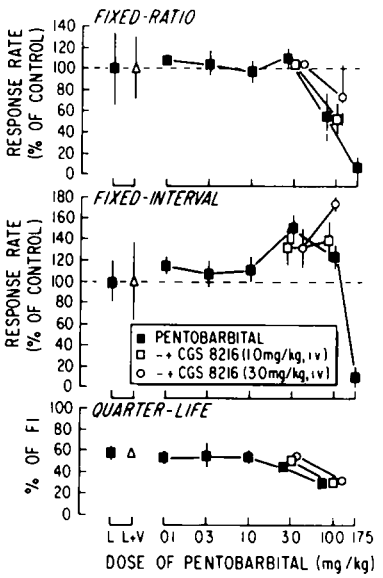

FIG 4 Effects of CGS 8216 given in combination with pentobarbital on responding by beagle dogs under the multiple FI FR schedule of food presentation See Fig 1 for other details, lactose (L), vehicle (V)

related decreases in the rate of responding during the FR components (Figs. 2 and 4). However, only pentobarbital completely suppressed FR response rates Rates of responding during the FI components first increased, then decreased with increasing doses of either drug (Figs 2 and 4) Peak increases, to approximately 50% above control values, were produced by 1.0 mg/kg of diazepam, (Dunnett's $t(10)=4.46$, $p<0.05$) and 3 0 mg/kg of pentobarbital, (Dunnett's $t(10)=2\ 94$, $p<0\ 05$) respectively; thus, diazepam was 3 times more potent than pentobarbital in increasing FI rates. Unlike pentobarbital, which markedly decreased FI rates following a dose of 17.5 mg/kg, diazepam failed to decrease responding below control levels regardless of the dose Both of the drugs also produced decreases in the quarter-life values These decreases were dose-dependent and quantitatively similar. In general, the doses of diazepam and pentobarbital that increased overall FI response rates did so by increasing the low rates of responding that occurred early in the intervals, while only moderately, if at all, affecting the relatively high rates of responding characteristic of the later segments

Effects of CGS 8216 in Combination With Either Diazepam or Pentobarbital

CGS 8216 antagonized some of the behavioral effects of diazepam but not those of pentobarbital (Fig 1) When given alone, a 3.0 mg/kg oral dose of diazepam moderately decreased FR rates, appreciably increased FI rates and also decreased the quarter-life value (Fig. 3) The intravenous administration of graded doses of CGS 8216 in combination with diazepam (3.0 mg/kg, PO) resulted in a dose-related increase in FR response rates to non-drug control values, at doses up to 1.0 mg/kg of CGS 8216. A dose of 3.0 mg/kg IV of CGS 8216 in combination with diazepam decreased FR rates relative to control values None of the changes in FR response rates were statistically significant ($F<1$) Overall FI response rates also returned to baseline when given in combination with the two highest IV doses of CGS 8216 (1.0 and 3.0 mg/kg), statistically significant blockade, $t(2)=3\ 42$, $p<0.05$, was seen only with 1 0 mg/kg CGS 8216 Lower doses of CGS 8216 tended to potentiate the effects of diazepam rather than antagonize them. Although there was a tendency for the quarter-life values to approach the non-drug control level following the highest doses of CGS 8216, the effects of diazepam on this parameter were not appreciably blocked by CGS 8216. Following the oral administration of CGS 8216 in combination with diazepam, FR rates of responding were not unlike those seen when diazepam was given alone, indeed, some doses of CGS 8216 (e g , 1 0 mg/kg) appeared to potentiate the rate-decreasing effects of diazepam during the FR components In contrast, the rate-increasing effects of diazepam seen during the FI components were appreciably attenuated by 10 and 30 mg/kg of CGS 8216 administered orally Statistically significant blockade, $t(2)=15\ 72$, $p<0\ 05$, was seen only with 30 mg/kg, but it should be noted that this same dose given alone appreciably decreased FI response rates The effects of diazepam on quarter-life values were essentially unchanged by the simultaneous oral administration of CGS 8216

Neither intravenous dose of CGS 8216 (1.0 or 3 0 mg/kg) significantly antagonized ($F<1$) the effects of pentobarbital on multiple FI FR responding (Fig 4). All of the pentobarbital-produced changes in behavior, including decreased FR response rates, increased FI response rates, and decreased quarter-life values, were present following the concomitant administration of CGS 8216. CGS 8216 was not administered orally in combination with pentobarbital

DISCUSSION

When given alone, CGS 8216 had little effect on the behavior of the dogs responding under the multiple FI FR schedule of food presentation used in the present study. Although an oral dose of 30 mg/kg CGS 8216 decreased overall FR and FI rates of responding, none of the other oral doses (0.3 to 10.0 mg/kg), nor any of the intravenous doses (0.01 to 3 0 mg/kg) appreciably altered either the rates or temporal patterns of responding. The present results are in contrast to some previous reports indicating that CGS 8216 has pharmacologic effects of its own which in many ways appear to be opposite those of benzodiazepines. For example, Bernard *et al* [2] found that CGS 8216 reduced punished responding in rats when administered alone, the ability of benzodiazepines and barbiturates to selectively increase shock-suppressed responding is widely documented [19]. Social interactions in rats were also reduced following a relatively high dose (10.0 mg/kg, IP) of CGS 8216; chlordiazepoxide increased this behavior [10]. In addition, CGS 8216 potentiated the convulsant effects of pentylenetetrazole and picrotoxin in mice, although CGS 8216 alone did not produce convulsions [9] The failure of CGS 8216 to appreciably alter behavior in the present study is not due to a species difference between dogs and rodents in sensitivity to the behavioral effects of CGS 8216. In a previous report from our laboratories [21], CGS 8216 IV produced dose-related decreases in response rates in dogs responding under a very similar multiple schedule. Although the reasons for the differences between the present and the previous study [21] are not entirely clear, response topography appears to be an important factor since the manipulandum was a floor-mounted pedal in the present study whereas a wall-mounted pedal was used in the previous study.

Both diazepam and pentobarbital produced qualitatively similar effects on behavior in the present study. Generally, with increasing oral doses of either drug, rates of responding during FI components first increased, then decreased, while FI quarter-life values and rates of responding during FR components were only decreased Similar results have been previously reported for chlordiazepoxide in monkeys [4], pentobarbital in pigeons [7] and secobarbital in monkeys [22] Information regarding the effects of diazepam on multiple FI FR responding is limited. In one study with pigeons, diazepam did not produce a consistent, dose-dependent change in FI response rates, perhaps due to poor absorption of the compound following IM administration; data regarding the effects of diazepam on FR responding were not presented [3]. However, benzodiazepines generally have been reported to increase FI responding (e.g., [1,23]) and to decrease FR responding [12,18] when these schedules were studied either alone or as one component of a multiple schedule

CGS 8216 antagonized the effects of diazepam, but not those of pentobarbital on responding under the multiple FI FR schedule used in the present study. Intravenously administered CGS 8216 was especially effective in blocking the effects of diazepam under this schedule, diazepam-induced changes in both FI and FR response rates, but not quarter-life values, returned to baseline following the combined administration of diazepam and CGS 8216. These results extend previous findings indicating that CGS 8216 can antagonize many effects of benzodiazepine-like drugs, including their anticonflict, anticonvulsant, ataxic and discriminative stimulus properties [2, 17, 20, 24]. Intravenously administered CGS 8216 was not able to antagonize the effects of pentobarbital on schedule-controlled responding in the present study Although a wide range of CGS 8216 doses were not examined, schedule-controlled responding in the presence of CGS 8216 combined with orally administered pentobarbital was not appreciably different from behavior in the presence of pentobarbital alone. Thus, in the present study, CGS 8216 was a selective benzodiazepine antagonist. In previous reports where CGS 8216 did antagonize the behavioral effects of nonbenzodiazepine anxiolytics [2,15], CGS 8216 administered alone produced dose-related changes in behavior. It is therefore probable in these latter studies that CGS 8216 did not reverse the effects of the nonbenzodiazepines through a pharmacologic (benzodiazepine receptor-mediated) antagonism, but rather through the physiologic summation of opposing behavioral actions

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