Pharmacology Biochemistry & Behavior, Vol. 39, pp. 525–529. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

RAPID COMMUNICATION

Synergism by Caffeine and by Cocaine of the Motor Control Deficit Produced by Midazolam

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Received 19 February 1991

FALK, J. L. AND C. E. LAU. *Synergism by caffeine and by cocaine of the motor control deficit produced by midazolam.* PHARMACOL BIOCHEM BEHAV **39**(2) 525–529, 1991.—To evaluate the effects of caffeine and cocaine on the impairment of discriminative motor control produced by midazolam, rats were trained to hold a force transducer operated with a paw so that it remained between upper and lower limits of a force band for a continuous 1.5-s period to deliver each food pellet. Acute doses of 3 mg/kg midazolam SC impaired motor performance. Except for one animal, caffeine (10–40 mg/kg IP) had little or no effect on performance, while cocaine (3.75–22.5 mg/kg IP) produced dose-related impairment. When each dose of caffeine was combined with 3 mg/kg midazolam, a marked synergism in motor performance impairment occurred. Cocaine plus midazolam produced mainly an additive synergism. The conspicuous synergistic action of caffeine on the motor control deficit produced by midazolam contrasts with the typical antagonism found between the benzodiazepines and methylxanthines when performance is evaluated by psychomotor tests not requiring fine motor control.

Motor performance Psychomotor stimulant and benzodiazepine Midazolam Cocaine Caffeine Benzodiazepine synergism

MIDAZOLAM is a benzodiazepine possessing a rapid onset and short duration of its pharmacodynamic actions (29). Acute doses of midazolam (0.75–3 mg/kg, SC) produced impaired performance on a discriminative motor control task in rats (21, 33, 36). This impairment was antagonized in a dose-related fashion by Ro 15-1788, a competitive benzodiazepine antagonist (21). There is extensive literature on the impairment of human psychomotor performances by benzodiazepines (37) and the synergism of this action by ethanol (25,34). On the other hand, several studies of caffeine's effect on benzodiazepine pharmacodynamics report that caffeine antagonizes the psychomotor impairment and anxiolytic actions of benzodiazepines (34). It has been suggested that some of the actions of the benzodiazepines may be due to their blockade of adenosine uptake in the brain, thereby potentiating the effects of adenosine, and that the blocking effect of the methylxanthines on adenosine receptors could account for their putative antagonism of benzodiazepine action (28). In exploring this suggestion, we found that, although caffeine antagonized the anxiolytic effect of clonazepam (as evaluated by an NaCl solution intake procedure), caffeine itself possessed a mild anxiolytic action (32).

In order to clarify the interaction of caffeine and the benzodiazepines, the present study evaluated the effect of caffeine on the known property of midazolam to disrupt discriminative motor control. A second psychomotor stimulant agent, cocaine, also was used to determine if any observed interactive effects of midazolam-caffeine combinations were perhaps specific to methylxanthines, or whether a stimulant agent from another class might yield similar interactive results.

METHOD

Animals

Eight male albino adult rats of the Holtzman strain with a mean initial body weight of 385 g (range: 377–389 g) were used. They were housed individually in stainless steel cages in a temperature-regulated room with a daily cycle of illumination from 0700–1900 h. They were experimentally naive and were reduced to 80% of their ad lib body weights by limiting daily food rations. In addition to food pellets delivered in the daily experimental sessions, food necessary for maintaining body weights was made available in the living cages immediately after each session.

Drugs

Midazolam maleate was obtained from Hoffmann-La Roche, Nutley, NJ, and cocaine hydrochloride from the National Institute on Drug Abuse, Rockville, MD. Each was dissolved in a vehicle of nanopure water for injection. Doses are expressed in

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terms of the salt. Caffeine (Sigma Chemical Co., St. Louis, MO) was dissolved in an aqueous solution of sodium benzoate (37.5 mg/ml). Injection volumes were 1 ml/kg body weight. All drug solutions were prepared immediately before use. Midazolam was given SC into the loose skin at the back of the neck; cocaine and caffeine were administered IP.

Apparatus. The experimental space was a Plexiglas chamber (25 × 30 × 30 cm) with stainless steel front and rear panels and a floor consisting of parallel-mounted, spaced, stainless steel rods. Discriminative motor control was measured using a force-sensitive, stainless steel operandum mounted on the front panel 2.5 cm from the floor. The operandum was surrounded by a thick Plexiglas shield fashioned with a 1.0-cm wide × 4.0-cm high slot so that access to it was limited to a single paw. The front edge of the operandum was recessed 1.2 cm from the front surface of the shield. This prevented lever biting, nose poking or behavior other than paw actuation from operating the lever. The operandum was suspended by a phosphor-bronze leaf spring (0.20 mm thick), and its shaft rested on a drive rod connected to a force transducer (Model UC3 strain gauge, Statham Instruments, Oxnard, CA) through a load cell (Statham Model UL4). The voltage output from the force transducer was conveyed to a customized signal control box (Tri-Tech Services, Hamilton Square, NJ) and sorted into one of three signal regions: above, below or within a window defined by preset lower and upper voltage limits. These limits corresponded to applied forces of 0.147 N (15 g force) and 0.265 N (27 g force), respectively, incident at the paw-placement region of the operandum. A buffer was set so that a minimum force of 0.015 N (1.5 g force) was required for signal recognition. An Apple IIe microcomputer was programmed in assembly language to sample signal input once every 10 ms. When the force applied by the animal was within the 0.147 to 0.265 N band, an audio feedback signal (Sonalert SC648H, P. R. Mallory, Indianapolis, IN) was turned on.

Discriminative Motor Control Measures

The training sequence for producing the final discriminative motor control performance has been described previously (6). A continuously applied in-band force lasting 1.5 s was required for the delivery of a 45-mg food pellet (Bio Serv, Inc., Frenchtown, NJ). If the applied force went above or below the band before 1.5 s had elapsed, then this timer was reset. Thus the behavior reinforced by food pellet delivery was holding the force transducer steadily operated within the force band for a continuous, set period of time. Ordinarily, a session was terminated when the 50th pellet had been delivered, but a session was also terminated if 30 min had elapsed without operation of the transducer. The latter occurrences were associated with some drug-combination doses. They are indicated on the relevant figures in the results.

The raw measures of motor behavior taken for each session were: the *session time* (the time taken to earn 50 pellets), the *total response time* (amount of the session time that the transducer was held operated above the minimum recognition threshold of 0.015 N), the *in-band time* (amount of the session time that the transducer was held operated within the force band, i.e., between 0.147 and 0.265 N), and the *entrances* (the total number of times during a session that the applied force entered the band from either the lower or upper set limits). Except in the case of the entrances measure, these raw measures in isolation are not useful characterizations of motor performance. For example, the in-band time measure is best interpreted in relation to how it compares with the minimum total in-band time that would satisfy the contingencies set for a particular experiment (e.g., in the present case, this value is 1.5 s/pellet for a total of 50 pellets, which yields a minimum possible in-band time of 75 s). Similarly, raw-session in-band time is difficult to interpret unless viewed in relation to total response time.

Two measures of motor behavior were calculated for each session:

$$\text{In-Band Efficiency} = \frac{\text{minimum possible in-band time}}{\text{in-band time}}$$

$$\text{Entrances} = \text{total number of entrances into the force band}$$

(In previous publications, we have calculated four measures of motor behavior, but the above two measures are adequate presentations of the present results.)

The In-Band Efficiency measure has a fixed numerator (50 pellets × 1.5 s), making the minimum possible time in-band to deliver all pellets 75 s. A perfectly efficient performance would yield an efficiency measure of 1.00. The Entrances measure is simply the number of times the applied force enters the appropriate band, with a high count indicating difficulty maintaining steady, in-band holding. It is a different measure than In-Band Efficiency, in which relative inefficiency could indicate that the in-band hold times often fall just short of the appropriate hold time; such a performance would not yield a high Entrances measure.

Procedure

After approximately 4 months, session performances attained a stable, day-to-day session baseline level with respect to the motor control measures. Then animals were divided into two groups (N = 4 each). First, a midazolam dose-effect function was obtained for both groups. Animals received SC injections 30 min presession; 5–7 days separated these and all remaining injection days. Three vehicle injections were administered followed by an ascending dose order of midazolam injections: 0.37, 0.75, 1.5 and 3.0 mg/kg. For one group (Caffeine Group), a caffeine dose-effect function was then obtained. These animals received IP injections 20 min presession in the following order: 0.0 (vehicle), 10, 20 and 40 mg/kg caffeine. This was followed by an evaluation of midazolam-caffeine dose combinations: Midazolam (3 mg/kg, SC, 30 min presession) was given in combination with a repeat of the previous caffeine-dosing sequence. For the other group (Cocaine Group), after the midazolam dose-effect function was completed, a cocaine dose-effect function was obtained. These animals received IP injections 15 min presession in the following order: 0.0, 3.75, 7.5, 15 and 22.5 mg/kg cocaine. This was followed by an evaluation of midazolam-cocaine dose combinations: Midazolam (3 mg/kg, SC, 30 min presession) was given in combination with a repeat of the previous cocaine dosing sequence.

RESULTS

Figure 1 shows the results of drugs and drug combinations on discriminative motor control performance for each animal in the Caffeine Group. Baseline values (B) are the grand means of the 3-day mean values preceding each injection. The midazolam dose-effect relation replicated our previous results with this procedure (21, 33, 36), and hence, for simplicity of presentation, only the results for the 3-mg/kg dose of midazolam are shown (cf. black bar). This dose produced a decreased In-Band Efficiency and an increase in Entrances for all animals, i.e., motor performance decrement. The caffeine dose-effect relation (open circles) shows that, for all doses, caffeine had little or no effect

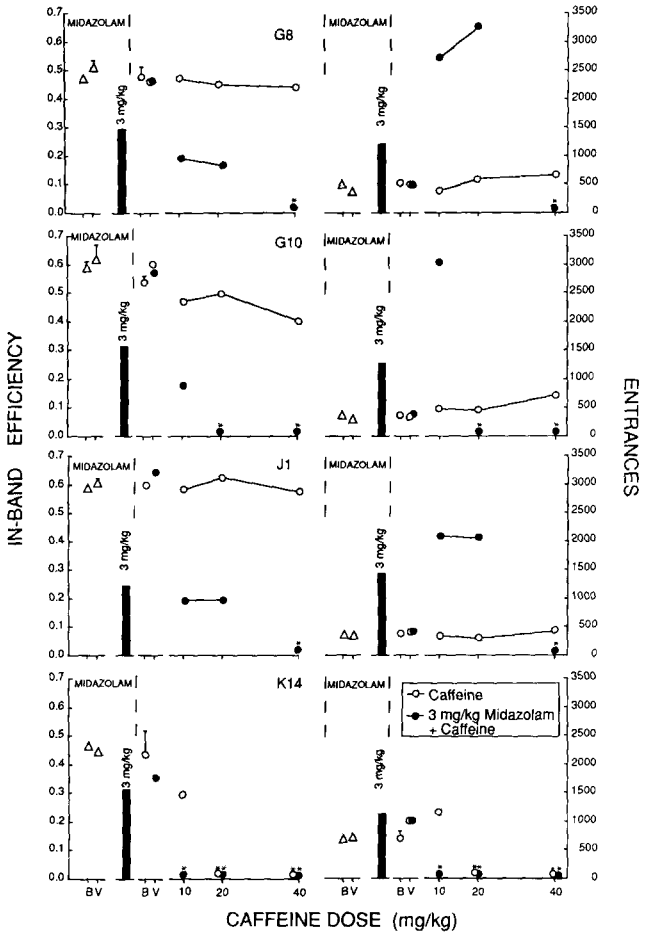

FIG. 1. Acute effects of doses of midazolam (3 mg/kg, SC), caffeine (10–40 mg/kg, IP) and combinations of midazolam + caffeine on 2 indices of discriminative motor performance for individual rats (G8, G10, J1, K14). * = animal did not perform at that dose or dose combination. B = baseline; V = vehicle. Those values of SE for B and V not shown lie within the plotted points.

on the performances of animals G8 and J1, and only a moderate disruptive effect on G10 (much less than the effect of 3 mg/kg midazolam), while, for K14, performance ceased at the 20- and 40-mg/kg dose levels. (As indicated in the Discriminative Motor Control Measures section, a period greater than 30 min without operation of the force transducer terminated the session.) When the 3-mg/kg midazolam dose was given in combination with caffeine doses, a marked synergism occurred at each dose of caffeine. Motor performance was compromised severely; with the combination using the largest caffeine dose (40 mg/kg), performance ceased for all animals.

The magnitude of the synergism can be illustrated by selecting the two animals (G8 and J1) that were unaffected by the lowest dose of caffeine used (10 mg/kg). The In-Band Efficiency performances after a 3-mg/kg midazolam dose were 58% (G8) and 40% (J1) of the vehicle-level performances; the corresponding performance levels when 3 mg/kg midazolam was combined with 10 mg/kg caffeine decreased to 42% (G8) and 30% (J1) of the vehicle levels. Similarly, the Entrances performances after a 3-mg/kg midazolam dose were 324% (G8) and 428% (J1) of the vehicle-level performances; the corresponding performance levels when 3 mg/kg midazolam was combined with 10 mg/kg caffeine increased to 567% (G8) and 512% (J1) of the vehicle levels.

The Cocaine Group (Fig. 2) presents a somewhat more complicated picture than the Caffeine Group. Although most of these animals also had impaired motor performances in response to the 3-mg/kg midazolam dose, animal O8 did not. This dose resulted in a low work rate for O8, lengthening the session (mean vehicle session = 7 min; midazolam = 65 min) with a consequent dissipation of this ultrashort-acting agent's effect. The cocaine doses administered produced a more frequent and dose-related motor impairment than did caffeine. The cocaine dose-effect relation shown is similar to one previously reported (22). In general, the midazolam-cocaine combinations display an additive synergism. Animal N12 is the clearest example of this effect: In the cocaine dose range that impaired performance (15 and 22.5 mg/kg; open circles), these doses also added to the level of impairment produced by a 3-mg/kg midazolam dose (filled circles). The lower cocaine doses that did not affect performance when given alone also had no synergistic action on the effect of midazolam. By comparison, caffeine doses that had little or no effect when given alone synergized the action of midazolam (Fig. 1). For animals O7 and O9, low work rates at the higher end of the midazolam-cocaine combination range again permitted the metabolic elimination of midazolam to proceed so that synergism is not evident for In-Band Efficiency, although it occurs for Entrances (Fig. 2). Interestingly, animal O8, which had the unusually low work rate (described above) with other performance indices unimpaired when under the 3-mg/kg midazolam dose, did not perform under any of the combination doses, which indicates a marked synergism.

DISCUSSION

The effect of the 3-mg/kg dose of midazolam was similar to the discriminative motor control impairment produced by this dose in our previous studies of midazolam (21, 33, 36). Caffeine, in the dose range administered in the present experiment, has produced marked increases in spontaneous motor activity as well as in operant response rates on a variety of schedules of reinforcement in rodents [e.g., (7, 10, 11, 27)]. It impaired hand-steadiness performance in humans (12,24). Even though the animals in the present experiment received acute doses of caffeine and thus had little chance to develop tolerance, only one animal was markedly affected by caffeine when it was administered alone.

In the drug-combination series, caffeine had a conspicuous synergistic effect on the motor impairment produced by midazolam. These results contrast with a great part of the literature on the interaction of the benzodiazepines with the methylxanthines. Although some studies have reported additive, anticonflict action when a benzodiazepine and caffeine were coadministered (1, 4, 35), others find either no effect or an antagonism (5, 30, 32). In mice, IP caffeine doses increased locomotor activity, and this increase was antagonized by alprazolam (20). Further, the impaired performances produced by benzodiazepine administration on a variety of psychomotor tests were antagonized by the coadministration of caffeine or theophylline (9, 12, 15, 24, 26, 31). It is of interest, however, that hand-steadiness performance impaired by caffeine was not antagonized by diazepam (12,24), but neither was it synergized. We suggest that the fine motor control requirement in the present experiment may be an important feature for revealing the observed synergism. Many of the motor performance tasks used in testing humans evaluate the speed of performance of simple, repetitive acts. These may be more useful for detecting the sedative component of the benzodiaz-

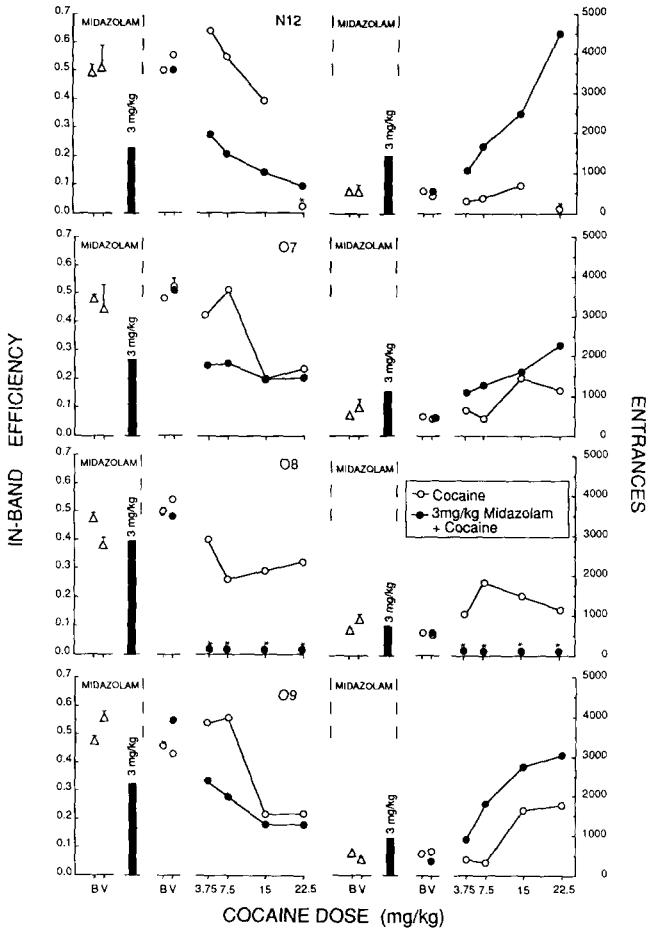

FIG. 2. Acute effects of doses of midazolam (3 mg/kg, SC), cocaine (3.75–22.5 mg/kg, IP) and combinations of midazolam + cocaine on 2 indices of discriminative motor performance for individual rats (N12, O7, O8, O9). * = animal did not perform at that dose or dose combination. B = baseline; V = vehicle. Those values of SE for B and V not shown lie within the plotted points.

epines than for evaluating fine motor control capacity; sedative action may be more readily antagonized by psychomotor stimulants than is fine motor dyskinesia.

Inasmuch as cocaine as well as caffeine synergized the motor impairment produced by midazolam, perhaps there is a shared neurochemical basis for this commonality of action. An acute pretreatment injection of cocaine resulted in region-specific increases in brain benzodiazepine receptor labeling, an effect that may be relevant to midazolam-cocaine synergism (19). We could locate no parallel study on the effect of caffeine on benzodiazepine receptor labeling. A review cites evidence suggesting that caffeine can enhance the release of norepinephrine, perhaps partially through its blockade of adenosine receptors (8). It may also increase dopamine release and enhance dopamine receptor sensitivity. Cocaine facilitates the release and inhibits the reuptake of both norepinephrine and dopamine (18). The portrayal of a partial commonality between these two psychomotor stimulants with respect to catecholamine effects is further enhanced by studies on the discriminative stimulus properties of caffeine. Rats trained to discriminate a 10-mg/kg caffeine dose from saline generalized completely to cocaine, methylphenidate and an alpha-1 adrenergic receptor agonist (16). This caffeine stimulus was blocked dose dependently and completely by alpha-adrenergic receptor antagonists. The complete blockade by phentolamine could be overcome by increasing the caffeine dose, but the partial block produced by diazepam could not. This study indicates the possibility that an alpha-adrenergic mechanism might mediate the actions that caffeine and cocaine have in common.

In groups of hospitalized psychiatric and nonpsychiatric patients, subgroups with high caffeine intakes (>750 mg/day) in both groups also had a higher percentage use of minor tranquilizers (13,14). It was suggested that either the greater frequency of benzodiazepine use might be due to self-medication of an anxiogenic effect produced by high caffeine intake, or that physicians, mistaking caffeinism for an anxiety disorder, might be prescribing benzodiazepines to these subgroups more readily. However, these subgroups also used alcohol and cigarettes more frequently, perhaps indicating a greater probability of co-use of licit, psychoactive agents, rather than a specific association of caffeine with benzodiazepines. On the other hand, the association of high caffeine intake with increased benzodiazepine use might reflect self-medication not of caffeinism, but of a morning sleepiness residual that occurs after benzodiazepine medication to promote sleep. Morning sleepiness occurred particularly with a long-acting benzodiazepine, and morning caffeine administration improved alertness (17). In general, the fact of an association between high daily caffeine intake and an increased probability of benzodiazepine use provides no information on the sequencing of administration. It is not unlikely that the administration of a benzodiazepine can be followed later by caffeine intake as a self-medication which alleviates an unwanted residual sedative component of the benzodiazepine.

There is an interesting relation between the clinical condition manifesting as anxiety attacks (panic disorder) and caffeine. When panic disorder groups were compared to either clinically depressed or normal groups, panic disorder was associated with more coffee abstainers and much lower caffeine intakes (2,23). Further, panic disorder patients report anxiety reactions to the administration of 10 mg/kg caffeine and to as little as one cup of coffee (2, 3, 23). Only one of these studies provides information on the medication status of these patients (2); most of the panic disorder patients were not receiving benzodiazepines. But it is possible, in light of our report of midazolam-caffeine synergism in disrupting motor control, that at least part of the anxiety reaction produced by caffeine in panic disorder is due to the combination of caffeine intake with a currently administered benzodiazepine. Such a relation would account for the low caffeine intake in terms of a conditioned avoidance of the consequences of benzodiazepine-caffeine synergism.

ACKNOWLEDGEMENTS

This research was supported by grants DA 03117 and DA 05305 from the National Institute on Drug Abuse. John L. Falk is the recipient of Research Scientist Award KO5 00142 from the National Institute on Drug Abuse. We thank Dr. Peter F. Sorter of Hoffmann-La Roche, Inc., Nutley, NJ, for generous supplies of midazolam maleate.

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