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Initial Subsensitivity to Anxiolytic Treatments on Conflict Behavior in Rats: Parametric Studies Across Drug Classes

RANDALL L. COMMISSARIS,*†[1] TIMOTHY J. HILL,* LOVE V. McMILLER, JR.* AND ROBERT J. KLEINSORGE‡

Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, †Department of Psychiatry, School of Medicine, and ‡Department of Psychology, College of Science, Wayne State University, Detroit, MI 48202

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COMMISSARIS, R. L., T. J. HILL, L. V. McMILLER, JR. AND R. J. KLEINSORGE. *Initial subsensitivity to anxiolytic treatments on conflict behavior: Parametric studies across drug classes.* PHARMACOL BIOCHEM AND BEHAV 51(2/3) 391-396, 1995.—In conflict paradigms, benzodiazepines (BZs) often exhibit maximal anticonflict effects only after three to four BZ exposures (anxiolytic initial subsensitivity; AIS). The present experiments examined 1) whether AIS occurs with non-BZ anxiolytics and 2) whether prior exposure to non-BZs prevents the occurrence of BZ AIS. Female rats were trained to stable responding levels on a repeated-measures punished drinking paradigm. In Experiment 1, dose-response curves for the effects of the BZs chlordiazepoxide and diazepam, the barbiturates (BBs) pentobarbital and amobarbital, and the non-BZ, non-BB agent carbamazepine were determined in five groups of rats (one group/drug); dose-response curves were determined on two occasions for each drug. There was an AIS with both BZs, with the anticonflict effect being significantly greater for dose-response determination #2. There was no AIS with the BBs (robust and dose-dependent increases in punished responding on both determinations) or with carbamazepine (weak anticonflict effect on both determinations). In Experiment 2, the rats from Experiment 1 received a single-dose challenge with chlordiazepoxide (10 mg/kg). This challenge resulted in a robust anticonflict effect in subjects with a history of repeated BZ treatment; in contrast, subjects with a history of repeated BB or carbamazepine treatment exhibited smaller anticonflict responses. These data suggest that 1) the AIS does not occur with non-BZ anxiolytics and 2) the BZ AIS cannot be prevented by repeated exposure to non-BZs.

Benzodiazepines Chlordiazepoxide Diazepam Barbiturates Pentobarbital Amobarbital
Carbamazepine Conflict behavior Anxiolytics Initial subsensitivity

ONE INTERESTING characteristic of the effects of benzodiazepines (BZs) on conflict behavior is the observation that these agents often are not maximally effective when administered to drug-naive subjects, with repeated challenges being required for their maximal anticonflict actions. This effect was first reported to occur in conflict paradigms when relatively large doses were used. Specifically, Margules and Stein (7) reported that drug-naive rats exhibited a generalized depression of motor abilities following the administration of a large dose of oxazepam (20 mg/kg, IP). This generalized depression was expressed as a reduction in the rate of unpunished responding in the Geller-Seifter conflict procedure and was found to dissipate over the course of repeated testing following drug administration. Along with the dissipation of the behavioral depression, a gradual increase in punished responding was observed (7). Cook and Sepinwall (2) reported a similar finding (initial sedation masking the anticonflict effect) in squirrel monkeys following administration of 10 mg/kg chlordiazepoxide and termed this effect the Initial Treatment Phenomenon.

Subsequent studies (6,9,12) have demonstrated that increased anticonflict responding with repeated BZ administration also occurs with nonsedating doses of chlordiazepoxide and diazepam. Because both sedating and nonsedating doses of BZs produce similar patterns of behavioral responses in-

[1] Requests for reprints should be addressed to Randall L. Commissaris, College of Pharmacy, Wayne State University, 525 Shapero Hall, Detroit, MI 48202.

volving an increased magnitude of anticonflict effect with repeated treatment, the "initial treatment phenomenon" might be more accurately described as an anxiolytic initial subsensitivity (AIS). It is interesting to note that an initial subsensitivity to anxiolytic effects has also been observed in humans receiving BZs (5,14).

Although the BZ AIS does not appear to be specific to a particular BZ agent, there are no reports regarding the occurrence of the AIS phenomenon in non-BZs. Moreover, whether prior exposure to non-BZ anxiolytic agents would alter the BZ AIS also has not been reported. The present studies were designed to address these two questions.

METHOD

Subjects

Female Sprague-Dawley rats (Charles River Farms, Cambridge, MA; 250-300 g at the start of the experiments) were housed two to four per cage in a climate-controlled room with a 12-h light/dark cycle (lights on 0700-1900 h). Initially, food and water were available continuously. Following a 2-week accommodation period and continuing throughout the period of behavioral assessment, all animals were maintained on a restricted water schedule (described below). Food continued to be freely available in the home cage.

General Procedure—Behavioral Conflict Testing

Conflict testing was conducted using the apparatus and methods that have been previously described in detail by Fontana et al. (3). Drug-naive, water-restricted rats were allowed to consume water freely from a metal drinking tube that was recessed into one wall of a standard rodent test chamber (Coulbourn Instruments, Inc.) fitted with a metal grid floor. Subjects were tested individually, 5 days per week, in 10-min sessions. After 1 week of nonshock sessions, test sessions were characterized by periods in which drinking from the tube was occasionally punished. Periods of punishment were signalled by a 7-s tone, which was presented at 30-s intervals to the subjects. Tube contact (i.e., drinking) during the last 5 s of any tone period completed an electric circuit between the floor and the metal drinking spout, which resulted in the delivery of a 0.5-mA shock. Shocks were administered using a Coulbourn Instruments two-pole small animal shocker (model No. E13-02) for the duration of tube contact (less than 200 ms). Punished responding was measured as the number of shocks accepted during each session. Unpunished responding was measured as the volume of water consumed during the session.

In all experiments, subjects were tested individually at the same time of day (1400-1700 h). All subjects achieved stable baselines for punished and unpunished responding (day-to-day coefficients of variation of less than 30% for both shocks received and water consumed) by the end of the second week of conflict sessions with alternating tone on : no tone periods. Nondrug baseline conflict testing was continued for 2 additional weeks before drug testing was initiated. The subjects were tested 5 days per week (Monday-Friday) and free access to water was available from Friday posttest until Sunday a.m.

Specific Experiments Conducted

Experiment 1: Testing for AIS across drug classes. Forty rats were randomly divided into five groups of eight. Over a 6-8 week period, various doses of different classes of antianxiety compounds were administered IP to the groups. Group 1 subjects received 2.5, 5, and 10 mg/kg chlordiazepoxide, 30 min prior to testing; group 2 subjects received 1.25, 2.5, 5, and 10 mg/kg diazepam, 10 min prior to testing; Group 3 subjects received 2.5, 5, and 10 mg/kg pentobarbital, 15 min prior to testing; group 4 subjects received 2.5, 5, 10, and 20 mg/kg amobarbital, 10 min prior to testing; group 5 subjects received 2.5, 5, 10, and 20 mg/kg carbamazepine, 15 min prior to testing. Drug challenges were administered on Thursday and Friday using a 2-day balanced cross-over design as described by Fontana et al. (3) and McCloskey et al. (9). On the Thursday test days, half the subjects (squad 1; $n = 4$) received vehicle treatment and half the subjects (squad 2; $n = 4$) received a dose of the drug under examination. These treatments were reversed on the Friday test days. Thus, each animal served as its own control with respect to the effects of a particular drug dose. To examine for possible residual effects of drug treatment, vehicle treatment scores from squad 1 subjects (vehicle on Thursday) were compared to vehicle treatment scores from squad 2 subjects (vehicle on Friday, 24 h after drug treatment). There were no occasions where the squad 1 and squad 2 scores for vehicle treatment were significantly different. Different doses of the agent under examination were administered each week. After all doses of a particular drug had been examined, the dose-response curves were redetermined in these same subjects in the same manner.

Experiment 2: Effects of prior drug exposure on the sensitivity to chlordiazepoxide. All groups that were used in Experiment 1 were administered 10 mg/kg chlordiazepoxide or vehicle (30 min prior to testing, IP) in a 2-day (Thursday/Friday) cross-over design identical to that described above.

Drugs

Carbamazepine-HCl was purchased from Sigma Chemical Co. (St. Louis, MO); chlordiazepoxide-HCl, diazepam, pentobarbital sodium, and amobarbital sodium were obtained from NIDA. Except for diazepam (free base), doses refer to the salt. Carbamazepine and diazepam were prepared in 0.5% methylcellulose suspensions; chlordiazepoxide, pentobarbital, and amobarbital were dissolved in saline. All drugs were administered intraperitoneally (IP) in a volume of 1 ml/kg body weight.

Statistical Analyses

Dependent variables in the conflict task are shocks received (punished responding) and water intake (unpunished responding). The effects of various treatments on these two dependent variables were analyzed separately. Prior to all statistical analyses, net (drug-vehicle) change scores were determined for the effects of each treatment on these two dependent variables. The data from Experiment 1 were analyzed using factorial ANOVAs with repeated measures [main effects: drug doses (three or four levels), determination number (two levels)], followed by post hoc comparisons using the Student-Newman-Keuls test. The data from Experiment 2 were analyzed using a one-way ANOVA; the Student-Newman-Keuls post hoc test was used to compare the effects of acute chlordiazepoxide challenges in subjects with different drug histories. In all statistical comparisons, $p < 0.05$ was used as the criterion for statistical significance.

RESULTS

Control (i.e., nondrug) conflict behavior was characterized by a stable number of shocks accepted [32 ± 2; values represent mean ± SEM ($n = 40$ subjects)] and a stable volume of

water consumed (10.3 ± 0.3 ml) in each session. There were no significant differences in these baseline values across the five treatment groups for either shocks received, $F(4, 35) < 1.0$, NS, or water intake, $F(4, 35) = 1.12$, NS. It should be noted that nearly all water intake occurred during the unpunished (i.e., no tone) periods. Thus, the volume of water consumed accurately reflects unpunished responding in the conflict procedure.

Experiment 1: Testing for AIS Across Drug Classes

The top panel of Fig. 1 illustrates the results from the two determinations of the dose-response curves for the effects of chlordiazepoxide (left panel) and diazepam (right panel) on shocks received in the conflict task. As can be seen, irrespective of the dose-response determination number, both agents produced increases in punished responding that were dose dependent. For both chlordiazepoxide and diazepam, however, the magnitude of the anticonflict effect was greater for determination #2. This was supported statistically by significant main effects for determination number for both chlordiazepoxide, $F(1, 7) = 4.90$, $p < 0.05$, and diazepam, $F(1, 7) = 18.99$, $p < 0.05$. Post hoc Student-Newman-Keuls tests revealed that doses of 2.5, 5, and 10 mg/kg CDP and 5 and 10 mg/kg DZ exerted greater anticonflict effects in determination #2 when compared to determination #1.

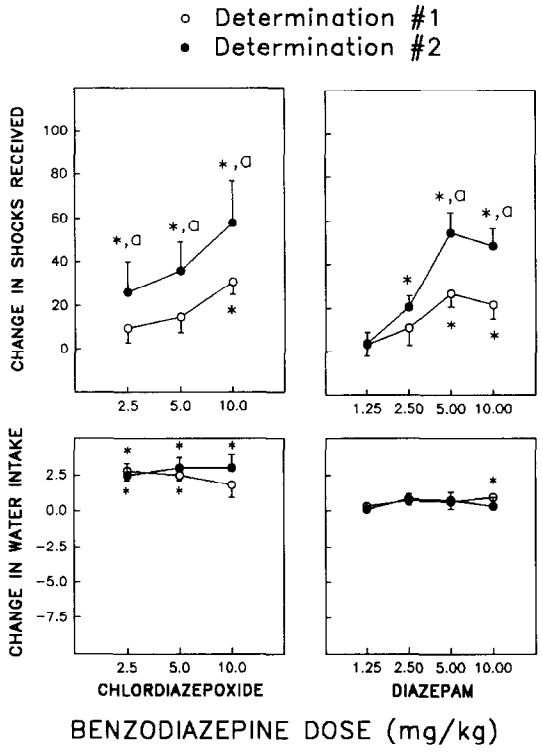

FIG. 1. Chlordiazepoxide and diazepam effects on conflict behavior—the influence of prior drug exposure. Plotted are the mean ± SEM ($n = 8$) change in shocks received (top panels) and the change in water intake (ml; bottom panels) produced by chlordiazepoxide (CDP; left side) and diazepam (DZ; right side). CDP and DZ dose-response curves were determined on two occasions over a period of 2 months. Open circles represent the first dose-response determination, closed circles represent the second dose-response determination. See text for further details. *The effect of the indicated dose is significantly different from vehicle controls, paired t-test. *The effect of the indicated dose in determination #2 is significantly different from that same dose in determination #1, post hoc Student-Newman-Keuls test following repeated-measures factorial ANOVA.

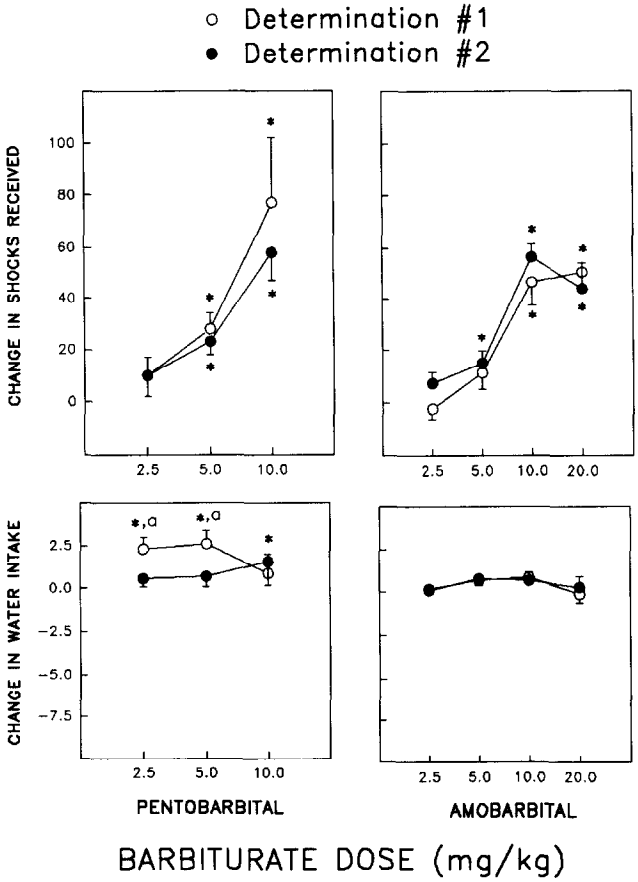

FIG. 2. Pentobarbital and amobarbital effects on conflict behavior—the influence of prior drug exposure. Plotted are the mean ± SEM ($n = 8$) change in shocks received (top panels) and the change in water intake (ml; bottom panels) produced by pentobarbital (PB; left side) and amobarbital (AMO; right side). PB and AMO dose-response curves were determined on two occasions over a period of 2 months. Open circles represent the first dose-response determination, closed circles represent the second dose-response determination. See text for further details. *The effect of the indicated dose is significantly different from vehicle controls, paired t-test. *The effect of the indicated dose in determination #2 is significantly different from that same dose in determination #1, post hoc Student-Newman-Keuls test following repeated-measures factorial ANOVA.

The lower panel of Fig. 1 illustrates the effects of chlordiazepoxide and diazepam on water intake (unpunished responding) for determination #1 and determination #2. As can be seen, chlordiazepoxide increased water intake at several doses; diazepam tended to increase water intake, but this effect was not statistically significant. There was no dramatic dose-effect relationship for either chlordiazepoxide, $F(2, 14) < 1.0$, NS, or diazepam, $F(3, 21) < 1.0$, NS, on this measure, nor was there a significant effect of determination number [chlordiazepoxide, $F(1, 7) = 1.21$, NS; diazepam, $F(1, 7) < 1.0$, NS.

The top panel of Fig. 2 illustrates the results from the two determinations of the dose-response curves for the effects of pentobarbital (left panel) and amobarbital (right panel) on

shocks received in the conflict task. As can be seen, irrespective of the determination number, both agents produced increases in punished responding that were dose dependent. For both agents there was no difference in the magnitude of the anticonflict effect across the two dose-response determinations; this was supported statistically by the lack of a significant main effect for determination number for both pentobarbital, $F(1, 7) = 1.61$, NS, and amobarbital, $F(1, 7) = 2.10$, NS. For both determination #1 and determination #2 the maximal anticonflict effect was approximately 60 shocks, similar to that produced in determination #2 by chlordiazepoxide or diazepam.

The lower panel of Fig. 2 illustrates the effects of pentobarbital and amobarbital on water intake (unpunished responding) for determination #1 and determination #2. As can be seen, pentobarbital increased water intake at several doses; amobarbital did not increase water intake. There was no dramatic dose-effect relationship for either pentobarbital, $F(2, 14) < 1.0$, NS, or amobarbital, $F(3, 21) = 2.77$, NS, on this measure; there was no significant effect of determination number [pentobarbital, $F(1, 7) = 1.21$, NS; amobarbital, $F(1, 7) < 1.0$, NS. There was, however, a significant pentobarbital dose × determination number interaction, $F(2, 14) = 3.78$, $p < 0.05$; post hoc Student-Newman-Keuls tests revealed that 2.5 and 5 mg/kg pentobarbital produced a significantly greater increase in water intake in determination #1 when compared to determination #2.

The top panel of Fig. 3 illustrates the results from the two determinations of the dose-response curve for the effects of carbamazepine on shocks received in the conflict task. As can be seen, irrespective of the determination number, carbamazepine produced only a modest increase in punished responding. The main effect for carbamazepine dose was not significant, $F(3, 21) = 1.57$, NS. There was no difference in the magnitude of the anticonflict effect across the two dose-response determinations; this was supported statistically by the lack of a significant main effect for determination number, $F(1, 7) < 1.0$, NS. For both determination #1 and determination #2 the maximal anticonflict effect was approximately 20 shocks over baseline, far less than that produced by the other agents.

The lower panel of Fig. 3 illustrates the effects of carbamazepine on water intake (unpunished responding) for determination #1 and determination #2. As can be seen, carbamazepine did not significantly increase water intake at any dose; rather, a significant and dose-dependent reduction in water intake was observed. There was a significant dose-effect relationship for carbamazepine treatment on this measure, $F(3, 21) = 7.34$, $p < 0.05$; there was, however, no significant effect of determination number, $F(1, 7) < 1.0$, NS, nor was there a significant carbamazepine dose × determination number interaction, $F(3, 21) < 1.0$, NS.

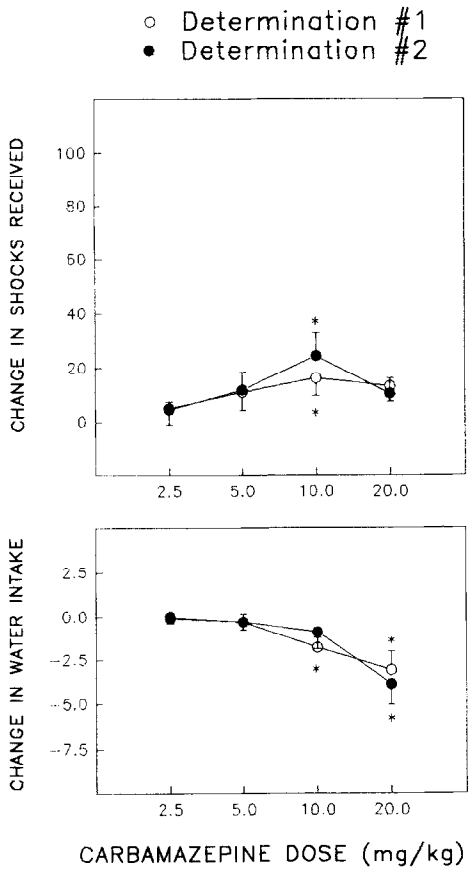

FIG. 3. Carbamazepine effects on conflict behavior—the influence of prior drug exposure. Plotted are the mean ± SEM ($n = 8$) change in shocks received (top panels) and the change in water intake (ml; bottom panels) produced by carbamazepine (CBZ); dose-response curves were determined on two occasions over a period of 2 months. Open circles represent the first dose-response determination, closed circles represent the second dose-response determination. See text for further details. *The effect of the indicated dose is significantly different from vehicle controls, paired t-test. There was no difference in the response to carbamazepine across the two determinations.

Experiment 2: Effects of Prior Drug Exposure on the Sensitivity to Chlordiazepoxide

Figure 4 depicts the effects on conflict behavior of an acute challenge with a single dose of chlordiazepoxide (10 mg/kg, IP; 30-min pretreatment) in subjects with histories of either repeated BZ (chlordiazepoxide or diazepam), BB (pentobarbital or amobarbital), or carbamazepine treatment. This dose of chlordiazepoxide produced a significant anticonflict effect in all subjects, regardless of past treatment history. The magnitude of this anticonflict effect, however, was greatest in subjects with a past history of BZ exposure; in these subjects, the magnitude of the anticonflict effect was comparable to that produced by maximally effective doses of BBs or BZs (in BZ-exposed subjects). In contrast, the magnitude of the anticonflict effect produced by chlordiazepoxide challenges in subjects with a past history of BB or carbamazepine exposure was significantly smaller. A one-way ANOVA demonstrated a significant overall effect between the various groups, $F(4, 35) = 6.88$, $p < 0.05$. Student-Newman-Keuls post hoc comparisons of individual groups revealed that the magnitude of the chlordiazepoxide anticonflict effect did not differ in the subjects with a history of either chlordiazepoxide or diazepam treatment. The magnitude of the chlordiazepoxide anticonflict effect in rats with a history of either BZ treatment was greater than that observed in rats with a history of either pentobarbital, amobarbital, or carbamazepine treatment. There were no differences in the magnitude of the response to this chlordiazepoxide challenge between subjects with a history of pentobarbital, amobarbital, or carbamazepine treatment.

The lower panel of Fig. 4 depicts the effects of acute chlordiazepoxide challenges on water intake in the conflict paradigm in subjects with histories of either repeated BZ (chlordi-

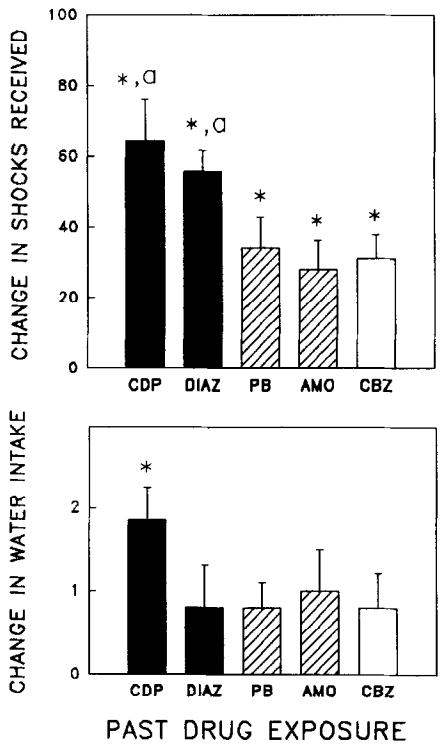

FIG. 4. The effects of an acute challenge with a single dose (10 mg/kg) of chlordiazepoxide (CDP) on conflict behavior in animals with prior exposure to CDP, diazepam (DIAZ), pentobarbital (PB), amobarbital (AMO), or carbamazepine (CBZ). The mean change ± SEM (n = 8) in punished responses (upper panel) and the mean change ± SEM in water consumed (lower panel) are plotted for subjects with each drug exposure history. *Acute CDP treatment is significantly different from vehicle control for subjects with the indicated drug treatment history, $p < 0.05$, t-test for paired values. □The effect of acute CDP treatment in subjects with the indicated drug treatment history is significantly different from the acute CDP effect in subjects with a history of repeated PB, AMO, or CBZ exposure, $p < 0.05$, one-way ANOVA followed by post hoc Student-Newman-Keuls test.

azepoxide or diazepam), BB (pentobarbital or amobarbital), or carbamazepine treatment. Acute chlordiazepoxide challenges increased water intake for all subjects, regardless of past drug history; however, only for chlordiazepoxide-exposed subjects did this effect reach statistical significance. Overall, there were no significant differences in the magnitude of this response across the various treatment histories, $F(4, 35) < 1.0$, NS

DISCUSSION

In Experiment 1 it was found that the BZs chlordiazepoxide and diazepam exert anticonflict effects that are characterized by less-than-maximal efficacy initially, with significantly greater anticonflict efficacy observed during a second determination of the dose-response curves. This observation is similar to earlier findings by Margules and Stein (2) and later by Cook and Sepinwall and coworkers (2,12), and also Rech's group (6,9), that acute treatment with BZs produces an anticonflict effect that is initially submaximal.

An initial subsensitivity was not observed with the barbiturates pentobarbital or amobarbital—the maximal anticonflict effect for these agents was comparable for the two dose-response determinations and was comparable to that produced by BZs in the second determination. Although the anxiolytic-like effects of carbamazepine were weak at best for both determinations, there was no evidence for an increased magnitude of anticonflict effect across determinations. Additional studies (Hill et al., submitted) have revealed that, when compared to BZ and BB agents, the magnitude of the maximal anticonflict effect of carbamazepine is modest under a variety of conditions, even after several weeks of repeated treatment. This finding is consistent with an earlier report by Almeida and Leite (1). The present data suggest that the phenomenon of anxiolytic initial subsensitivity (AIS) is unique to the BZs and does not occur in other drug classes such as the BBs or carbamazepine.

Experiment 2 examined the effects of repeated exposure to BZ or non-BZ drugs in the conflict task on the response to a subsequent challenge with a BZ. When administered a single 10-mg/kg dose of chlordiazepoxide, subjects previously treated with BBs or carbamazepine demonstrated increases in punished responding (anticonflict effects) that were smaller in magnitude than those that were observed in subjects previously treated with either chlordiazepoxide or diazepam. Thus, repeated administration of non-BZ anticonflict agents, even those with considerable apparent anticonflict efficacy, does not prevent the AIS exhibited by BZs.

In humans, diazepam and chlordiazepoxide exhibit a long duration of biological activity, whereas the duration of action of pentobarbital, amobarbital, and carbamazepine are somewhat shorter. Therefore, it could be hypothesized that the observed differences in the occurrence of the AIS for the various agents result from differences in the duration of action of the agents investigated. According to this hypothesis, the longer duration of action and active metabolites associated with diazepam and chlordiazepoxide per se promote the dissipation of the BZ AIS. This argument is weakened by two findings. First, in contrast to the situation in humans, the duration of action of diazepam in the rat is relatively short, with a biological half-life of less than 2 h. Chlordiazepoxide has a much longer biological half-life in the rat. Thus, the BZs used in the present studies included both long-acting (chlordiazepoxide) and relatively short-acting (diazepam) agents and the BZ AIS was prominent for both agents. Second, acute treatment with a long-acting BB such as phenobarbital exerts a dramatic anticonflict effect initially and repeated occasional treatment with this agent does not result in an enhancement of its anticonflict effects (unpublished data). For these reasons, it seems likely that the observation that the AIS is specific to BZs and not other anxiolytics is not confounded by differences in the duration of action of the various agents studies.

In some, but not all, situations, the dissipation of the BZ AIS may result in part from a learned adaptation to the drug experience during the behavioral task (state-dependent learning). For example, Mokler and Rech (9) have reported that although the AIS associated with low doses of diazepam does not relate to such a learned adaptation, state-dependent learning may play a role in the reduction of the AIS associated with higher doses of diazepam. In Experiment 2, animals with a history of pentobarbital, amobarbital, or carbamazepine administration had several exposures to the conflict task in a drugged state. This past experience in a BB-drugged state or a carbamazepine-drugged state did not prevent the AIS for chlordiazepoxide. Only experience in a BZ-drugged state had an influence on the AIS for chlordiazepoxide. Thus, if the dissipation of BZ AIS in the present studies is indeed the result of state-dependent learning, it appears that a specific anxiolytic-like drugged state induced by a BZ, not simply a

behavioral state induced by any antianxiety drug, is necessary for the reduction of the BZ AIS.

The behavioral actions of benzodiazepines and barbiturates most likely are the result of their interactions at various sites within the γ-amino-butyric acid (GABA)-BZ chloride ionophore receptor complex (13). Differences in the sites where benzodiazepines and barbiturates exert their effects on the GABA-BZ receptor complex might offer a possible explanation for the differences in their effects on the AIS. Barbiturates are believed to act directly on the chloride ionophore within the GABA receptor complex (10,11), whereas BZs interact with BZ receptors to modulate the affinity and accessibility of the GABA binding site (4). It is possible that the strength of the BZ-GABA allosteric interaction is submaximal upon initial exposure to BZs, but is strengthened following repeated exposure to BZs. Because barbiturates presumably do not act via an allosteric interaction with GABA, it is possible that a "priming" dose or exposure is not necessary for the expression of the maximal anticonflict effects of these agents.

In summary, the present studies indicate that the AIS associated with BZs does not occur with the BBs pentobarbital and amobarbital, nor does it occur with the non-BZ, non-BB agent carbamazepine. Also, repeated administration of non-BZ anxiolytics in conjunction with conflict testing cannot prevent the AIS seen with chlordiazepoxide. The mechanism that underlies this phenomenon of BZ AIS remains undetermined.

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