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Behavioral Effects of Chronic Buspirone Administration in the Pigeon: Comparison to Midazolam

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NADER, M. A. *Behavioral effects of chronic buspirone administration in the pigeon: Comparison to midazolam.* PHARMACOL BIOCHEM BEHAV **38**(3) 611–616, 1991.—The effects of acute and chronic administration of buspirone and midazolam were examined in White Carneau pigeons (N = 5) responding under a fixed-ratio 30 (FR 30) schedule of food presentation. Each drug was studied in all pigeons. For three pigeons, buspirone was studied before midazolam, while the order was reversed for the other two subjects. For each drug, a dose-response curve was determined before (prechronic) and two weeks after (postchronic) discontinuation of chronic administration. Prior to chronic drug administration, buspirone (0.3–5.6 mg/kg) and midazolam (0.1–3.0 mg/kg) decreased response rates in all subjects, in a dose-dependent manner. Midazolam was more potent than buspirone; midazolam's ED_{50} (95% C.I.) was 0.53 (0.41–0.69) mg/kg compared to 2.55 (1.48–4.41) mg/kg for buspirone. For each subject, the lowest dose that decreased responding by at least 50% was administered daily, immediately before the session, for up to 6 weeks. At the lowest daily dose of buspirone, complete recovery of baseline rates was observed in 3 pigeons. However, when the buspirone dose was increased, responding remained below control rates in all but one pigeon. During chronic midazolam administration, tolerance developed to the rate-decreasing effects of midazolam in 4 subjects. When saline was substituted for buspirone or midazolam, suppressed responding returned to predrug rates in all subjects. When the dose-response curves were redetermined, the postchronic ED_{50} for buspirone was 3.79 (2.10–6.82) mg/kg, which was not significantly different from the prechronic ED_{50}, suggesting that tolerance did not develop to buspirone's rate-decreasing effects. However, the midazolam dose-response curve was shifted to the right after chronic midazolam administration, with an ED_{50} of 1.18 (0.81–1.72) mg/kg. Thus, while the behavioral effects of acute administration of buspirone and midazolam were similar, the development of tolerance, as determined from shifts in acute dose-response curves and recovery of drug-free response rates during daily administration, was substantially less for buspirone compared to midazolam. Further, consistent with clinical reports, no evidence of withdrawal was seen when daily buspirone treatments were discontinued.

Chronic administration Buspirone Midazolam Schedule-controlled behavior Pigeon

THE nonbenzodiazepine buspirone has been shown to be clinically effective in alleviating many of the symptoms of anxiety (8, 10, 24). Buspirone, unlike the benzodiazepines, has minimal sedative and muscle relaxant effects, suggesting a possible treatment advantage over the benzodiazepines (14, 19, 28). Additionally, buspirone does not appear to interact significantly with other CNS depressants [reviewed by (26)]. A feature of buspirone that is unique for clinically active antianxiety drugs is that it typically takes 2–3 weeks of chronic administration before anxiety symptoms begin to subside (11,20). Further, recent clinical studies have reported a higher drop-out rate for subjects treated chronically with buspirone compared with benzodiazepines (15, 22, 23).

Animal experimentation allows a unique opportunity to examine the rate of tolerance development, cross-tolerance to other drugs and severity of withdrawal from chronically administered drugs. However, in light of the fact that up to 3 weeks are required before buspirone becomes clinically effective in treating anxiety, few studies have examined the behavioral and neurochemical effects of chronic buspirone administration. One purpose of the present study was to examine the behavioral effects of chronic buspirone on responding by pigeons. Previous experiments examining the effects of chronic buspirone have utilized punished responding as a baseline, since performance under this schedule appears to be sensitive to anxiolytic drug action (5,27). Wettstein (30) reported that the behavioral effects of buspirone, administered daily to squirrel monkeys responding under a punishment schedule, were unchanged after 12 consecutive days. Schefke et al. (25) found that administration of buspirone after sessions for 16 consecutive weeks did not significantly affect punished responding of rats. However, the antipunishment effects of acute presession administration of buspirone were enhanced during chronic administration (25). It is not clear whether sensiti-

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zation to the rate-decreasing effects of buspirone would also be observed following chronic administration. To address this issue, the present experiment utilized a fixed-ratio (FR) schedule of food presentation, since buspirone typically decreases responding under this schedule (4).

There is evidence that tolerance can develop to some of buspirone's neurochemical actions. Nader and Barrett (16) examined the neurochemical changes in pigeon cerebrospinal fluid (CSF) associated with daily buspirone (3.0 mg/kg/day) administration over 6 consecutive weeks. Initially, buspirone increased levels of the dopamine metabolites homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) and decreased levels of serotonin's primary metabolite 5-hydroxyindoleacetic acid (5-HIAA); tolerance developed to the effects on the dopamine system by the end of the first week. However, tolerance was not long-lasting since buspirone-induced increases in levels of HVA and DOPAC were obtained two weeks after discontinuation of chronic drug administration. The present study utilized a similar dosing regimen, with buspirone given prior to operant sessions for 6 consecutive weeks. Barrett et al. (4) suggested that buspirone's effects on FR responding may be dopaminergically mediated. Thus, based on neurochemical data, tolerance to the rate-decreasing effects of buspirone on FR responding would be predicted. In addition, for purposes of comparison, the short-acting benzodiazepine midazolam was administered under identical dosing conditions to these subjects.

A second purpose of the present study was to determine whether behavior is further disrupted after termination of chronic buspirone. Schefke et al. (25) did not report data for rats following discontinuation of chronic buspirone, although the dose administered daily did not disrupt responding. Eison (7) examined the effects of food intake and body weight changes in rats that received buspirone daily for 21 days. Chronic treatment with buspirone resulted in significant weight loss. However, the author concluded that no withdrawal signs were evident since discontinuation of daily buspirone did not result in further weight loss (7).

METHOD

Subjects

Five experimentally naive male White Carneau pigeons, maintained at approximately 85% of their free-feeding body weights, served as subjects. The pigeons were individually housed in stainless steel cages, with continuous access to water and grit, in a colony room maintained at a constant temperature (24 degrees centigrade) and lighting (0700:1900 h). Experiments were conducted 5 days/week except during chronic drug administration when subjects were tested 7 days/week.

Apparatus

A standard operant test chamber, equipped with a three-key pigeon intelligence panel (Model 141-10, BRS/LVE, Beltsville, MD) and solenoid-operated feeder (Model 114-10, BRS/LVE), was used. The chamber was placed within a sound-attenuating cubicle and a ventilation fan provided background noise continuously. During the experiment the two outside keys were covered and the center key was illuminated by a white Dialco (6 W) bulb. A peck on the center key which exceeded a force of 0.15 N was recorded as a response. The feeder was illuminated when operated and food (Purina Pigeon Checkers) was presented for 3 s. Programming and data recording were accomplished by a Rockwell Aim 65 microcomputer (Dynatem, Irvine, CA) and associated interface located in an adjacent room.

Procedure

Pigeons' key-peck responses were shaped by the method of successive approximation, with a peck to the center white key producing 3 s access to food and initiating a fixed-ratio 1 (FR 1) schedule. Over a 2-day period, the number of responses required for food delivery was increased to a value of 30 (FR 30). Sessions began with a 5-minute timeout; sessions ended after 20 minutes or after 50 reinforcers were delivered.

After at least 15 sessions under the final schedule requirement (FR 30), and when responding was stable, a buspirone HCl (Bristol Myers, Co., Wallingford, CT) dose-response curve (0.3–5.6 mg/kg) was determined in all subjects. Following completion of the buspirone dose-response curve, three pigeons received buspirone chronically (see below), whereas the other two pigeons (P-678 and P-2421) received midazolam HCl (Hoffmann-La Roche, Nutley, NJ) acutely and chronically. The acute and chronic effects of buspirone and midazolam were studied in all subjects. Buspirone and midazolam were dissolved in saline and injected intramuscularly in a volume of 1.0 ml/kg. During acute drug administration, drugs were prepared fresh before the session; doses were administered in a random order with all doses tested at least twice in each subject, typically on Tuesdays and Fridays.

Following completion of the dose-response curve for buspirone or midazolam, and prior to chronic administration, saline was administered immediately before testing for 5 consecutive sessions; the average response rate for these 5 sessions was used as the prechronic baseline. The initial dose of buspirone or midazolam tested during the chronic regimen was the lowest dose that decreased response rates by at least 50%, as determined from the acute (prechronic) dose-response curve. If, during daily administration, responding recovered to within 10% of drug-free baseline, the dose was increased. Occasionally, the dose was lowered to see if predrug baseline rates would be recovered. In addition, for some pigeons, sessions were preceded by saline to determine if responding remained decreased in the absence of drug. On such test sessions, the daily dose of drug was administered 30 minutes after the session to try to assure that blood levels remained constant. Drugs were administered chronically for 42 consecutive days. On day 43, and for the next 6 sessions, saline was administered immediately before the session. During chronic administration drugs were prepared in a stock solution every 10 days.

A postchronic dose-response curve was determined after pigeons had been drug-free for at least 2 weeks. Acute administration of the second drug (i.e., prechronic dose-response curve) began immediately after completion of the postchronic dose-response curve for the first drug. Thus approximately 8 weeks separated the end of one chronic regimen from the beginning of the other. The acute effects of midazolam were also tested 3 months after completion of the postchronic dose-response curve, to determine whether the tolerance observed was transient.

Data Analysis

Since the order of drugs tested did not appear to influence the results, dose-response curves are presented as group averages ($N = 5$). All data are presented as responses/second (r/s). For dose-response curves, response rates during Thursday sessions and sessions preceded by saline injections served as control. ED_{50}'s (95% C.I.) for each drug were calculated using the visibly linear portion on the descending limb of the dose-response curve. For each drug, dose-response curves were compared by using a two-way repeated measures ANOVA, with Dose and Time (pre- vs. postchronic) as factors. A third midazolam dose-response curve, 3 months after completion of the postchronic curve, was not determined in P-623. Consequently, when this dose-response curve was compared to the pre- or postchronic midazolam dose-response curve, the ANOVA used only 4 subjects.

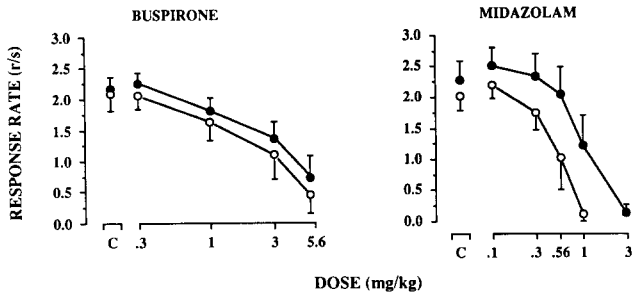

FIG. 1. Response rates (responses/second) before (open symbols) and after (closed symbols) chronic drug administration, as a function of buspirone (left panel) or midazolam (right panel) dose. Each point is the mean of 5 pigeons. Unconnected points represent the average of Thursday control days. Vertical bars represent 1 S.E.

RESULTS

Acute Drug Administration

Responding under the FR 30 schedule was characterized by pauses immediately after food presentation, followed by periods of high rate responding ending in food delivery. The average (± 1 S.E.) rate of responding was 2.10 (0.44) r/s. Under control conditions, subjects typically received 50 food presentations during daily sessions.

Buspirone (0.3–5.6 mg/kg) significantly decreased response rates in a dose-dependent manner [Fig. 1, open symbols; Dose effect: $F(2,8)=7.78$, $p<0.05$]. The prechronic ED_{50} (95% C.I.) for buspirone was 2.55 (1.48–4.41) mg/kg. For one pigeon (P-623), 10 mg/kg was also tested and response rates decreased to 38% of control (data not shown). Beginning two weeks after completion of chronic buspirone administration (see below), the acute effects of buspirone were reexamined (Fig. 1, closed symbols). Buspirone's rate-decreasing effects were not significantly different following chronic administration, as compared to the prechronic dose-response curve, with an ED_{50} of 3.79 (2.10–6.82) mg/kg. In all 5 pigeons, the postchronic ED_{50} (±95% C.I.) overlapped the prechronic ED_{50} (±95% C.I.). When the effects of 10 mg/kg were redetermined in P-623 following discontinuation of chronic buspirone, responding was disrupted to an even greater extent, compared to prechronic rates (0 r/s vs. 0.81 r/s; post- vs. prechronic). However, some tolerance may have developed to buspirone's rate-decreasing effects since there was a trend towards higher ED_{50}'s in the other 4 subjects.

Midazolam (0.1–1.0 mg/kg) significantly decreased response rates in a dose-dependent manner [Fig. 1, open symbols; Dose effect: $F(2,8)=25.8$, $p<0.01$]. The prechronic ED_{50} for midazolam was 0.53 (0.41–0.69) mg/kg. Beginning two weeks after completion of chronic midazolam (see below), the acute effects of midazolam were reexamined (Fig. 1, closed symbols). The midazolam dose-response curve was significantly shifted to the right following chronic treatment [Time effect: $F(1,4)=9.42$, $p<0.05$], with the ED_{50} increasing to 1.18 (0.81–1.72) mg/kg. When midazolam was tested 3 months after completion of the postchronic dose-response curve (data not shown), the ED_{50} was 1.21 (0.90–1.63) mg/kg. The rate-decreasing effects of midazolam, determined 3 months after the postchronic dose-response curve, were not significantly different from the effects obtained 2 weeks after termination of chronic midazolam (i.e., postchronic dose-response curve), but still significantly different from the prechronic effects [Time effect: $F(1,3)=57.61$, $p<0.005$]. There were no significant interactions between Dose and Time, indicating parallel shifts of the dose-response curves.

Chronic Drug Administration

During chronic buspirone administration, responding recovered to prechronic rates within 7 sessions in 3 of 5 pigeons (Fig. 2). The starting doses of buspirone were 3.0 (P-207, P-2421 and P-2803), 5.6 (P-678) and 10 (P-623) mg/kg/day. Response rates by P-2421 showed the most dramatic recovery, since responding was initially eliminated following 3.0 mg/kg but returned to control levels within 6 sessions.

For subjects whose responding returned to baseline (P-678, P-2421 and P-2803), the dose of buspirone was increased by ½ log unit. For P-678, responding in the presence of 10 mg/kg remained below drug-free control rates for the remainder of the chronic phase. In this pigeon, responding during chronic buspirone steadily declined from session 21 to session 41. Responding by P-2421 remained below control rates when the dose was increased from 3.0 to 5.6 mg/kg. When the dose was lowered to 3.0 mg/kg, responding recovered to predrug control rates within 3 sessions. P-2803 was the only pigeon whose responding recovered to prechronic control rates after the dose of buspirone was further increased by ½ log units. For this pigeon, response rates recovered within 12 sessions after the dose was increased from 3.0 to 5.6 mg/kg. Further increases in dose, to 10 mg/kg, resulted in approximately 60% reductions in response rates by the end of the chronic buspirone regimen. For two pigeons (P-623 and P-207), the dose of buspirone remained the same over the 6-week chronic period. In these subjects, complete recovery of drug-free baselines was not evident, although there was a trend towards recovery by P-623. After 42 consecutive days of buspirone administration, saline was substituted and responding returned to prechronic rates within one session, in all subjects. Response rates following saline (Fig. 2, sessions 43–49) were not different after chronic buspirone administration compared to prechronic rates (Fig. 2, shaded areas).

During chronic midazolam administration, only P-623's responding continued to be below prechronic rates throughout the 42 day chronic phase (Fig. 3). The starting doses of midazolam were 0.3 (P-623), 0.56 (P-207, P-678, P-2421) and 1.0 (P-2803) mg/kg/day. For two pigeons (P-207 and P-2803), the dose of midazolam administered at the beginning of the chronic regimen had either no effect or response rate increases compared to prechronic control rates. Since the starting dose was one that decreased response rates by approximately 50%, based on acute dose-response curve data, the effects observed in these two subjects may represent acute tolerance. For P-2803, 1.0 mg/kg midazolam produced response rate increases during the first 3 days of chronic treatment, even though this dose, when tested acutely, resulted in an average rate of 0.5 r/s (approximately 25% of control). When the dose was increased ½ log unit (from 1.0 to 1.7 mg/kg), responding was completely eliminated within 5 sessions. When the dose was returned to 1.0 mg/kg, responding remained near zero. Further decreases in dose (to 0.56 mg/kg) resulted in complete recovery of baseline response rates. For pigeons P-207, P-678 and P-2421, recovery of drug-free baselines was eventually observed after the starting dose of midazolam was increased by ½ log units.

For all pigeons, there was a large degree of between-session variability during chronic midazolam administration. For example, control rate of responding (±1 S.D.) by P-207 was 1.85 (0.30) r/s. The dose administered before session 15 was 1.0 mg/kg, which resulted in complete suppression of responding. On session 16, response rates increased to 1.60 r/s, and on session 18 rates were above prechronic controls (2.12 r/s). However, on session 19 responding was again completely suppressed. When sa-

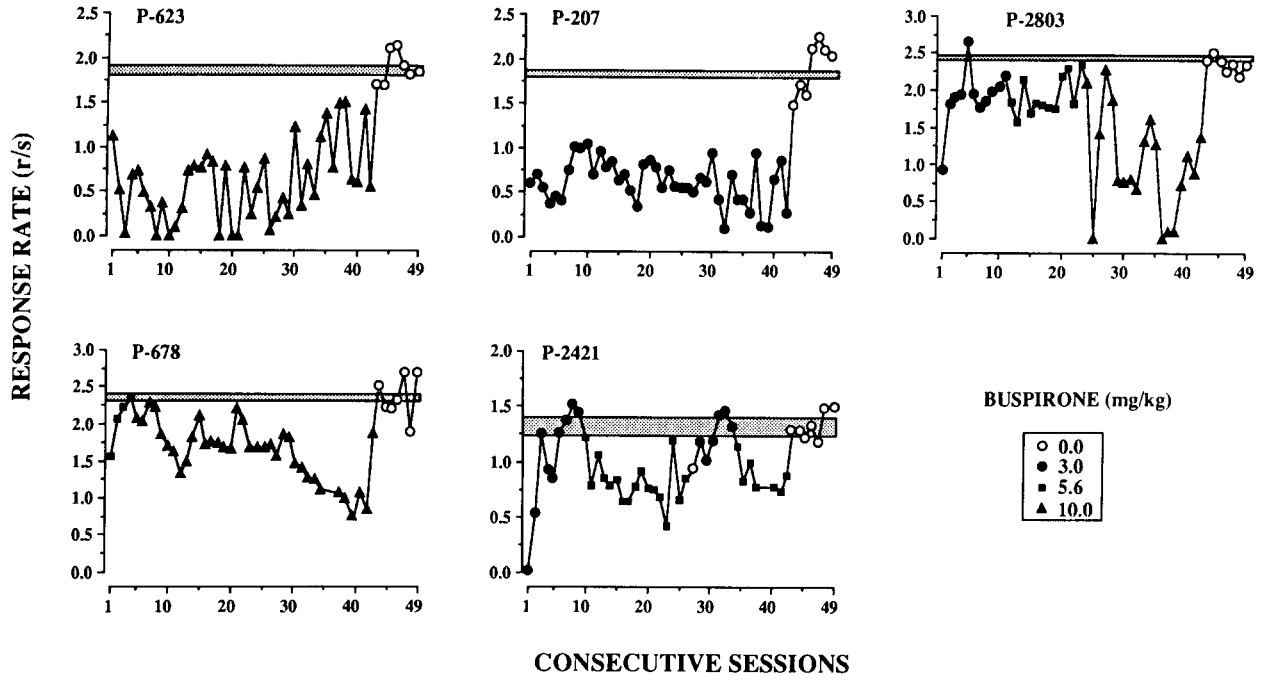

FIG. 2. Response rates (responses/second) for individual subjects, during chronic buspirone administration. Different symbols represent different doses of buspirone. Shaded area represents prechronic control responding (±1 S.D.). The 2 pigeons whose data are represented on the lower panel received chronic midazolam prior to chronic buspirone.

line was substituted for midazolam at the end of the chronic regimen, response rates recovered to prechronic rates in all subjects (Fig. 3). This was especially apparent in P-623 and P-678, in which responding was suppressed by daily midazolam by at least 50% of control rates. Response rates following saline (Fig. 3, sessions 43–49) were not different after chronic midazolam administration compared to prechronic rates (Fig. 3, shaded areas).

DISCUSSION

The behavioral effects of acute and chronic administration of buspirone and midazolam were examined in pigeons responding under a fixed-ratio 30 schedule of food presentation. Tolerance was assessed by comparing pre- and postchronic dose-response curves and by examining the rate of recovery of response rates during daily drug administration. Tolerance, as indicated by a shift to the right of the acute dose-response curve, was not evident with buspirone, although there did appear to be a trend towards tolerance in some pigeons at the end of the chronic buspirone phase. In contrast, the midazolam dose-response curve was shifted to the right after chronic midazolam, and recovery of control rates of responding during chronic administration was observed in 4 of 5 subjects.

Results from the present study showing that tolerance did not develop to the acute rate-decreasing effects of buspirone after chronic administration are consistent with an earlier result using a different species and a different schedule of reinforcement (30). In that study, squirrel monkeys were trained to respond under a food-maintained fixed-interval (FI) schedule in which responding was also suppressed by shock (punishment). Buspirone decreased response rates at all doses tested and tolerance to the rate-decreasing effects did not develop after 12 days of daily buspirone administration.

However, the present results are in contrast to the sensitization of buspirone's antipunishment effects reported by Schefke et al. (25). The differences in results between Schefke et al. (25) and the present study may be related to species (rat vs. pigeon), to schedule of reinforcement (punished vs. unpunished) or to chronic dosing regimen (postsession vs. presession administration). An additional possibility for the differences is that the buspirone dose-response curves were redetermined at different time points in the two studies. In the Schefke et al. study the buspirone dose-response curve was determined during the chronic regimen, while in the present study subjects were drug free for at least 2 weeks prior to redetermination of the acute effects of buspirone.

Comparison of results from the present study with results from an earlier study examining neurochemical changes in pigeon CSF (16), suggest that the lack of tolerance to buspirone's rate-decreasing effects on FR 30 responding are similar to the buspirone-induced decreases in serotonin metabolism. Although buspirone increased levels of HVA and DOPAC, tolerance developed to these effects within 1 week, while decreases in levels of 5-HIAA persisted throughout the 6-week dosing regimen. Buspirone has been shown to bind to a subtype of serotonin (5-HT) receptors, identified as 5-HT_{1A} (21). The hypothesis that 5-HT mediates the behavioral effects of buspirone during chronic administration is consistent with the discriminative stimulus effects of buspirone (12,18) and buspirone's effects on punished responding (6, 9, 13, 31), which are believed to be mediated through 5-HT_{1A} receptors in the pigeon. However, other evidence suggests that dopamine, rather than serotonin is primarily involved in the behavioral effects of buspirone on FR responding. Barrett et al. (4) compared the rate-altering effects of buspirone to two serotonin agonists, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and gepirone, in pigeons responding under a multiple FI, FR schedule of food presentation. Buspirone decreased responding in both components, while 8-OH-DPAT and gepirone increased FI and FR response rates. The authors suggested that the differences in the behavioral effects of these drugs were due to the dopaminergic

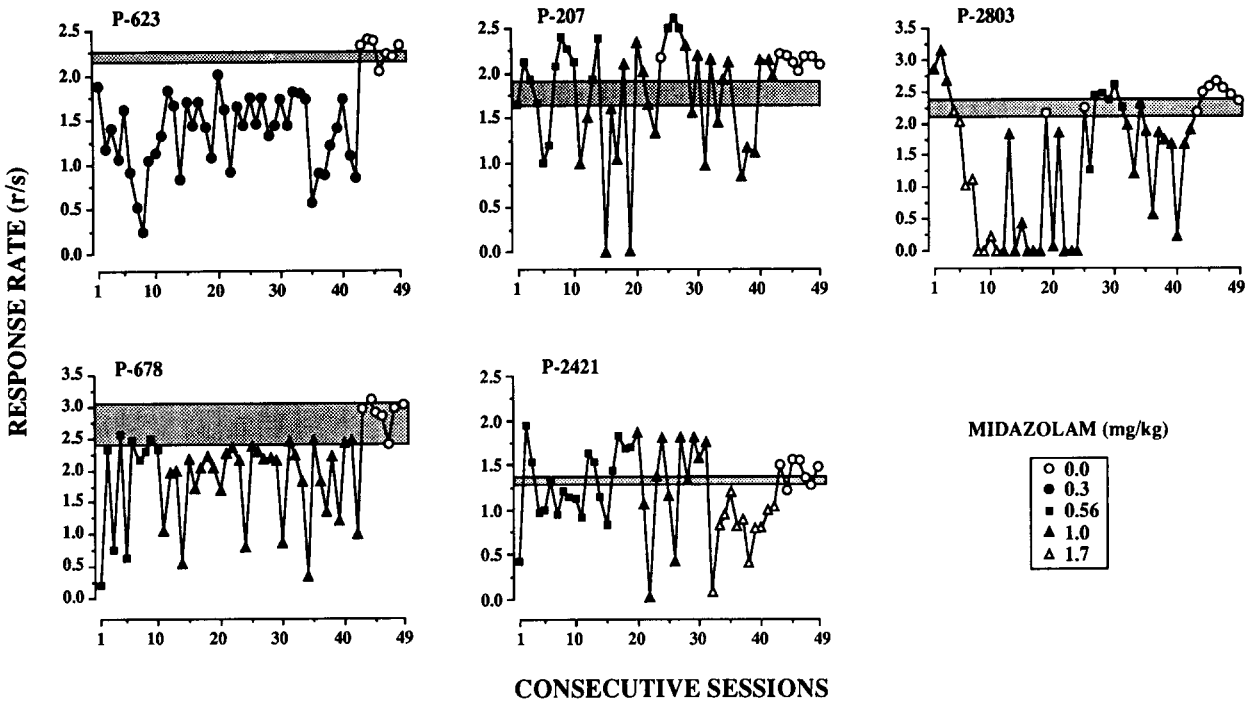

FIG. 3. Response rates (responses/second) for individual subjects, during chronic midazolam administration. Different symbols represent different doses of midazolam. Shaded area represents prechronic control responding (± 1 S.D.). The 3 pigeons whose data are represented on the upper panel received chronic buspirone prior to chronic midazolam.

effects of buspirone. Further studies examining the behavioral effects of chronically administered 8-OH-DPAT and gepirone may provide insight into the neurochemical mechanisms of action of buspirone on operant behavior. If, under identical conditions, tolerance develops to the rate-altering effects of 8-OH-DPAT or gepirone, this effect would most likely be serotonergically mediated and suggest that buspirone's effects under similar schedule conditions were dopaminergically mediated. However, this result would suggest that little correlation exists between drug-induced neurochemical changes and behavioral effects, since tolerance does not develop to decreases in 5-HIAA levels during chronic 8-OH-DPAT administration (16).

In the present study, when daily buspirone administration was discontinued after 6 weeks, responding returned to prechronic control rates in all subjects, suggesting that there were no residual or carry-over effects of the chronic regimen. Eison (7), using food intake as the primary dependent variable, reported that there was no evidence of withdrawal signs following discontinuation of chronic buspirone. Results from clinical studies have also found minimal withdrawal symptoms following discontinuation of chronic buspirone (15). Taken together, the evidence indicates that discontinuation of chronic buspirone treatment does not produce behavioral disruption or evidence of withdrawal.

In addition to examining the effects of acute and chronic administration of buspirone, the effects of midazolam were also assessed to allow for comparisons. Tolerance, as indicated by shifts to the right in the dose-response curve and by recovery of drug-free baseline rates was observed with midazolam. These results are consistent with other reports that tolerance develops to the behavioral effects of benzodiazepines [e.g., (29)]. Also, the rightward shift in the midazolam dose-response curve was still evident 3 months after discontinuation of chronic midazolam, suggesting that the tolerance was not transient. Because all subjects were tested with both buspirone and midazolam, the lack of significant tolerance development following buspirone cannot be attributed to the behavior of these particular subjects under FR schedules. That is, since tolerance developed to midazolam's rate-decreasing effects, behavior maintained under FR schedules can be sensitive to shifts in dose-response curves following chronic drug administration. However, it would be interesting to compare tolerance to the behavioral effects of buspirone and the benzodiazepines when behavior is maintained under other schedules of reinforcement, since it is possible that more complete tolerance would have developed to buspirone's rate-altering effects if behavior had been maintained under a different reinforcement schedule.

There are data indicating that the behavioral effects of buspirone are different from those of the benzodiazepines [see (5) for recent review]. For example, in separate groups of squirrel monkeys responding under second-order schedules of reinforcement, buspirone increased cocaine-maintained responding and decreased food-maintained responding, while chlordiazepoxide produced opposite effects (17). In addition, results from drug discrimination studies have shown that buspirone does not share discriminative stimulus effects with the benzodiazepines (1,12). Furthermore, while benzodiazepines have been shown to function as positive reinforcers in laboratory animals [reviewed by (2)], efforts to maintain self-administration with buspirone have been unsuccessful (3). Results from the present study demonstrate further differences between buspirone and midazolam, i.e., the degree of tolerance that develops to their rate-decreasing effects on operant behavior. Whether the apparent absence of tolerance development during chronic buspirone proves to be an additional therapeutic advantage, compared to the benzodiazepines, remains to be determined.

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