Pharmacology Biochemistry and Behavior, Vol. 62, No. 2, pp. 209–214, 1999

0091-3057/99 $–see front matter

ELSEVIER

PII S0091-3057(98)00151-8

Acute and Chronic Effects of Morphine under a Progressive-Ratio 25 Schedule of Food Delivery

KIMBERLY JAREMA, CONN MACOMBER, MARK LESAGE AND ALAN POLING

Department of Psychology, Western Michigan University, Kalamazoo, MI 49008

Received 19 December 1997; Revised 21 April 1998; Accepted 30 April 1998

JAREMA, K., C. MACOMBER, M. LESAGE AND A. POLING. *Acute and chronic effects of morphine under a progressive-ratio 25 schedule of food delivery.* PHARMACOL BIOCHEM BEHAV **62**(2) 209–214, 1999.—The present study examined the effects of morphine in pigeons responding under a progressive-ratio 25 schedule of food delivery. Morphine initially reduced response rates and breaking points. With chronic exposure, tolerance developed to these effects. The magnitude of the observed tolerance was not obviously different from that previously reported under a PR 5 schedule of food delivery. In addition, when drug effects were compared under the fixed-ratio 25 and fixed-ratio 100 components comprised by the progressive-ratio schedule, comparable tolerance was observed. Although prior studies using other procedures have shown that ratio size modulates the development of tolerance to morphine and other drugs, the present data suggest that this relation is constrained, and is not easily observed under progressive-ratio schedules. © 1999 Elsevier Science Inc.

Tolerance Morphine Progressive-ratio schedule Pigeons

IN recent years, considerable interest has developed concerning the effects of opiates and of naturally occurring opiate-like substances (e.g., endorphins), on food-related activities [e.g., (4,19)]. Several studies have shown that opioid agonists, such as morphine, increase short-term food intake [e.g., (8,9,11, 17,20,27)]. Given this outcome, it is reasonable to assume that morphine may increase the capacity of food to serve as a reinforcer. This possibility was evaluated in a prior study (25) in which the effects of acute and chronic morphine administrations were evaluated in pigeons responding under a progressive-ratio (PR) 5 schedule of food delivery. The PR schedule is commonly used to quantify the reinforcing capacity of food, drugs, and other stimuli [e.g., (1,10,13,14,18,26)]. It requires the subject to emit an increasing number of responses to earn reinforcement. For instance, under a PR 5 schedule of food delivery, the number of responses required for food delivery in a given session begins at five and is incremented by five every *n*th time food is earned. The value of *n* usually is one, and in this case the response requirements for the first five food deliveries are, in order, 5, 10, 15, 20, and 25. The ratio requirement eventually becomes so long that the subject ceases to respond for a specified period, usually 5 to 15 min [e.g., (14,18, 28,29,31)], at which point the session ends. The largest ratio completed before responding ceases is termed the breaking point, and is used as a measure of the efficacy of the scheduled reinforcer, or of response strength (13,33).

Studies using fixed-ratio (FR) schedules have shown that the development of tolerance to several drugs (6,15,16,22,30, 31), including morphine (23), is influenced by ratio size. Specifically, tolerance develops more quickly and strongly under short FR schedules (e.g., FR 5) than under substantially longer FR schedules (e.g., FR 125). This finding suggests that response effort, defined in terms of the number of responses required to produce reinforcement, generally modulates the development of tolerance. Although this may well be the case, the range of conditions under which the relation has been observed is limited. In all of the studies where ratios size has influenced tolerance, a unique discriminative stimulus was correlated with each ratio value. For example, in the study demonstrating that ratio size influenced tolerance to morphine in pigeons, a different key color was correlated with the FR 5, FR 25, and FR 125 components of a multiple schedule of food delivery (23). Preliminary findings in pigeons responding under mixed-schedules comprising ratio values of 5, 25, 50, 75, and 100, provide no evidence that ratio size modulated tolerance to cocaine or morphine in pigeons (2,3). The mixed schedule was very similar to the multiple schedule used by (25), except that key color (and all other exteroceptive stimuli) remained the same across all schedule values. Comparing results obtained under mixed and multiple schedules suggests that the presence of an antecedent stimulus uniquely correlated with each ratio value may be necessary for ratio size to

Requests for reprints should be addressed to Alan Poling, Department of Psychology, Western Michigan University, Kalamazoo, MI 49008.

modulate tolerance. If this is the case, ratio size should not strongly modulate tolerance under PR schedules, which comprise an ascending series of FR values, all arranged under the same stimulus conditions. To evaluate this hypothesis, the present study compared drug effects under FR 25 and FR 100 schedules when those values were arranged under a PR 25.

To evaluate further the conditions under which ratio size influences tolerance, the present study used procedures equivalent to those reported in a prior study from our laboratory that examined tolerance to morphine under a PR 5 schedule (25). In that study prechronic administrations of morphine to pigeons responding under a PR 5 schedule of food delivery produced generally dose-dependent decreases in response rates and breaking points. Dose–response curves for both measures shifted substantially rightward with chronic exposure, indicating that tolerance developed. Ratio size increases much faster under a PR 25 schedule than under a PR 5 schedule. Therefore, if ratio size influences tolerance similarly under FR and PR schedules, one would expect less tolerance to develop under the PR 25 than under the PR 5. Such a possibility has not been evaluated, however, and no comparisons of the effects of similar pharmacological manipulations at different PR values have appeared.

METHOD

Subjects

Four experimentally naive White Carneau pigeons, food deprived to 80% of free-feeding body weights, served as subjects. They were individually housed with free access to water and grit in a colony area with controlled lighting (16 L:8 D each day), temperature (22–24°C), and humidity (60–70%).

Apparatus

Four MED Associates (St. Albans, VT) test chambers were used. The chambers were 30 cm long by 25 cm high. They were illuminated by a 7-W white bulb on the ceiling. A 7 by 7 cm opening located 2 cm above the floor allowed access to mixed grain when the food hopper was raised. Three 2.5-cm response keys, which required a force of about 0.2 N to operate and could be illuminated in white, red, or green, were spaced horizontally approximately 5.5 cm apart and 23 cm above the chamber floor. Only the center key, illuminated in white, was used in the present study. A speaker supplied white noise to each chamber and an exhaust fan provided ventilation. Programming of experimental events and data recording were controlled by an IBM-compatible computer equipped with MED-PC software.

Behavioral Procedure

Pecks of the center key when lighted in white initially were autoshaped [as described by (24)]. After a bird consistently pecked the key during autoshaping, it was exposed to an FR 1 schedule of reinforcement. Over several sessions, the FR value was gradually increased to 75. Under the FR 75 schedule, a 3-s food delivery followed every 75th peck of the center key. When all birds responded consistently (no visible trends in overall response rates over 20 consecutive sessions) under the FR 75 schedule, a PR 25 schedule was implemented. Under the PR 25 schedule, food was delivered for 3 s dependent on completing a ratio requirement that began each session at 25 responses and was incremented progressively by 25 following every third reinforcer. Thus, the first 12 ratios in a given session were 25, 25, 25, 50, 50, 50, 75, 75, 75, and 100, 100, 100. Increments of 25 in the PR schedule continued to occur after three ratios were completed throughout the session. Including three ratios at each value was intended to provide sufficient data to allow for a meaningful evaluation of drug effects as a function of ratio size. The session continued until no responding occurred for 5 consecutive minutes. Key illumination and general chamber illumination were present from the beginning of the session to its end, when all chamber lights were darkened. Throughout the study, sessions were conducted daily, 7 days a week, at about the same time every day.

Pharmacological Procedure

Each bird responded under the PR 25 schedule of reinforcement until its breaking point showed no visible trend across 10 consecutive sessions (i.e., was stable). Thereafter, subjects were given intramuscular (IM) injections of isotonic saline solution 30 min prior to four consecutive vehicle-control sessions. Following these sessions, dose–response determinations were initiated. During this phase, each subject received two ascending series of morphine doses. The regimen began with 0.56 mg/kg, and progressively increased until, for a given bird, a dose was reached at which the overall response rate and the breaking point fell to below 10% of the vehicle-control level. Doses were increased in quarter-log units from 0.56 to 5.6 mg/kg (i.e., in the sequence 1, 1.8, 3.2, and 5.6 mg/kg, expressed as the salt), and in eighth-log units above 5.6 mg/kg (i.e., in the sequence 7.5, 10, 13.3, 17.8 mg). Drug injections were given according to a BBBCD design, where B represents baseline sessions (no injection), C vehicle control sessions, and D drug sessions. Morphine sulfate (obtained from the National Institute on Drug Abuse), was dissolved in isotonic saline solution and prepared at an injection volume of 1 ml/kg. Drug and vehicle injections were given via the intramuscular (IM) route 30 min before behavioral testing. Presession injection intervals were determined on the basis of prior reports (21,23).

After dose–response determinations were completed, 10 consecutive baseline sessions were arranged in which no injections were given. Chronic drug administration immediately followed those baseline sessions. The chronic dose for an individual bird was the highest dose that did not completely eliminate responding during prechronic testing, but did suppress it. During the chronic phase, drug was administered prior to every session. The chronic doses for birds 1 through 4 were 13.3, 10, 10, and 7.5 mg/kg, respectively.

Chronic dosing continued for each bird for at least 30 consecutive sessions and until responding was stable. At that time, dose–response determinations began. During these determinations, every sixth session a substitution dose was administered in place of the chronic dose. Substitution doses were administered in two ascending series as described for initial dose—response determinations. The chronic dose was given prior to all sessions in which a substitution dose was not given. If the substitution dose was lower than the chronic dose, sufficient morphine to make up the difference was administered IM immediately after behavioral testing.

RESULTS

Breaking points (the highest completed ratio) and overall response rates were recorded for each session. Response rates for each individual ratio also were calculated and recorded by the computer. Figure 1 shows dose–response curves for the breaking points of individual subjects before and during chronic exposure to morphine. Figure 2 shows dose–response curves for the overall response rates of individual subjects. In

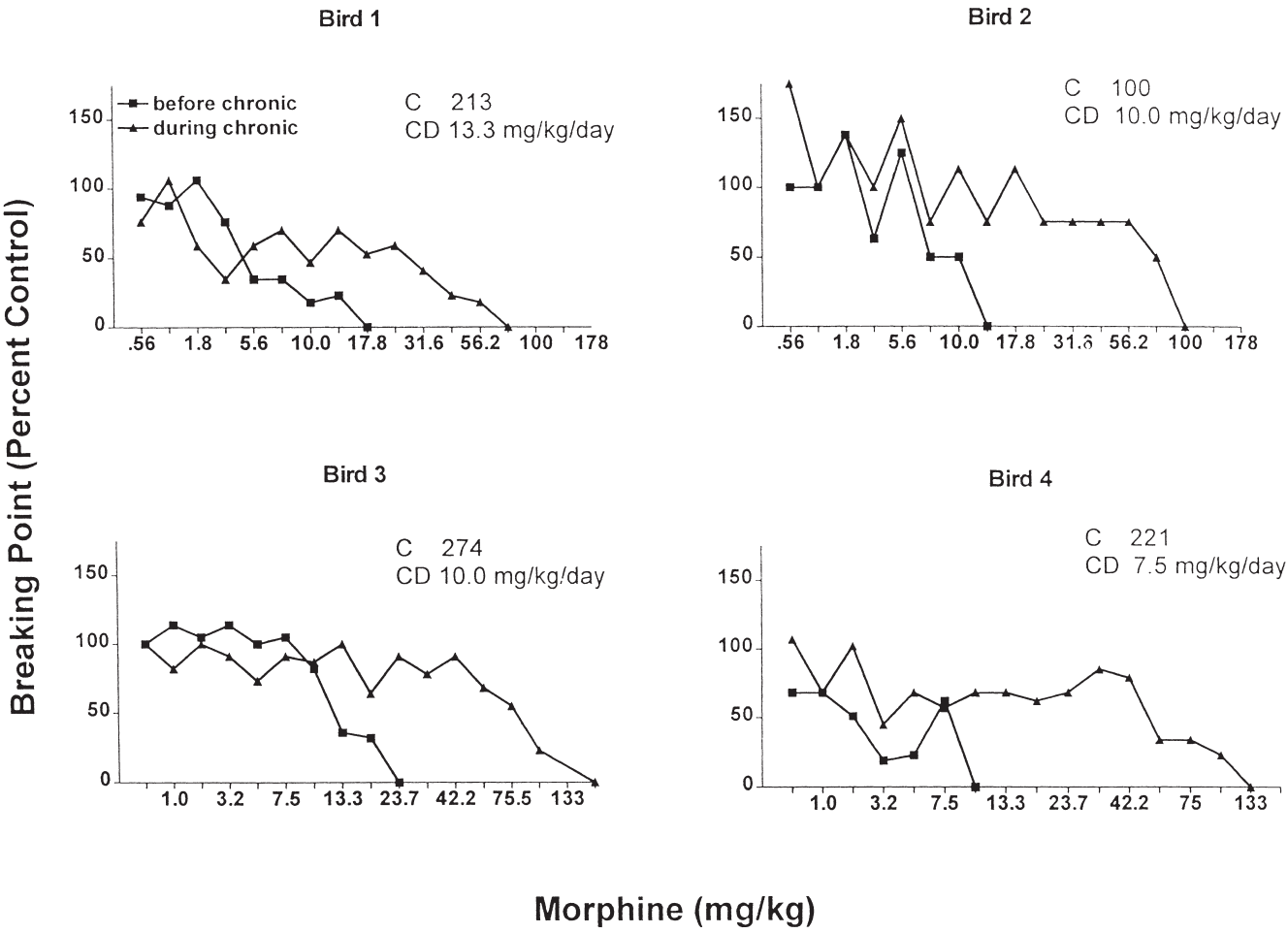


FIG. 1. Effects of morphine before and during chronic exposure on the breaking points of individual pigeons responding under a PR 25 schedule of food delivery. Data are expressed as percentages of mean control breaking points, which are indicated (at C). Each data point represents two drug administrations. The chronic dose received by each bird is indicated as CD.

these and all other figures, data are expressed as a percentage of control values. Control values are based on performance in vehicle control sessions immediately prior to acute drug administrations, therefore, they are based on 16, 12, 19, and 11 sessions for birds 1, 2, 3, and 4, respectively.

Morphine generally produced dose-dependent decreases in breaking points and overall response rates both before and during chronic exposure. Dose–response curves for all subjects were shifted substantially to the right during chronic exposure, which is indicative of tolerance. To quantify the degree of rightward shifting of the dose–response curves and, therefore, the degree of tolerance, regression lines were fitted by the method of least squares to pre- and postchronic dose–response curves for individual bird's overall rates of responding and breaking points. ED_{50} values were determined from the equations that described the regression lines. This was accomplished by solving for x (drug dose) with the value of y set at 50% of the vehicle control level. In regression calculations, the correlation between percent control and log doses were correlated. All doses were used in the calculation, and mean percent control values were used for doses administered twice. Table 1 shows ED_{50} doses before and during chronic exposure to morphine.

Figure 3 compares the effects of morphine on response rates under FR 25 and FR 100 schedules, both arranged as part of a PR 25 schedule. Before and during chronic exposure, the drug generally reduced response rates in dose-dependent fashion at both ratio values. Substantial tolerance developed to morphine's rate-reducing effects, and there was no indication that the magnitude of the rightward shift of the dose–response curve differed as a function of ratio size.

DISCUSSION

As in previous studies involving PR and other ratio schedules [e.g., (5,7,12,21,32)], morphine in the present study produced generally dose-dependent reductions in overall response rates and tolerance developed to the drug's rate-reducing action. Morphine also reduced breaking points in the present study, which is consistent with the results of a prior study that examined its effects on responding maintained by food under a PR 5 schedule (25). Neither study supports the conclusion that morphine increases the reinforcing effectiveness of food, despite the drug's known capacity to increase short-term food intake (8,9,11,17,20,27). As discussed elsewhere (18,25), drugs may influence breaking points through

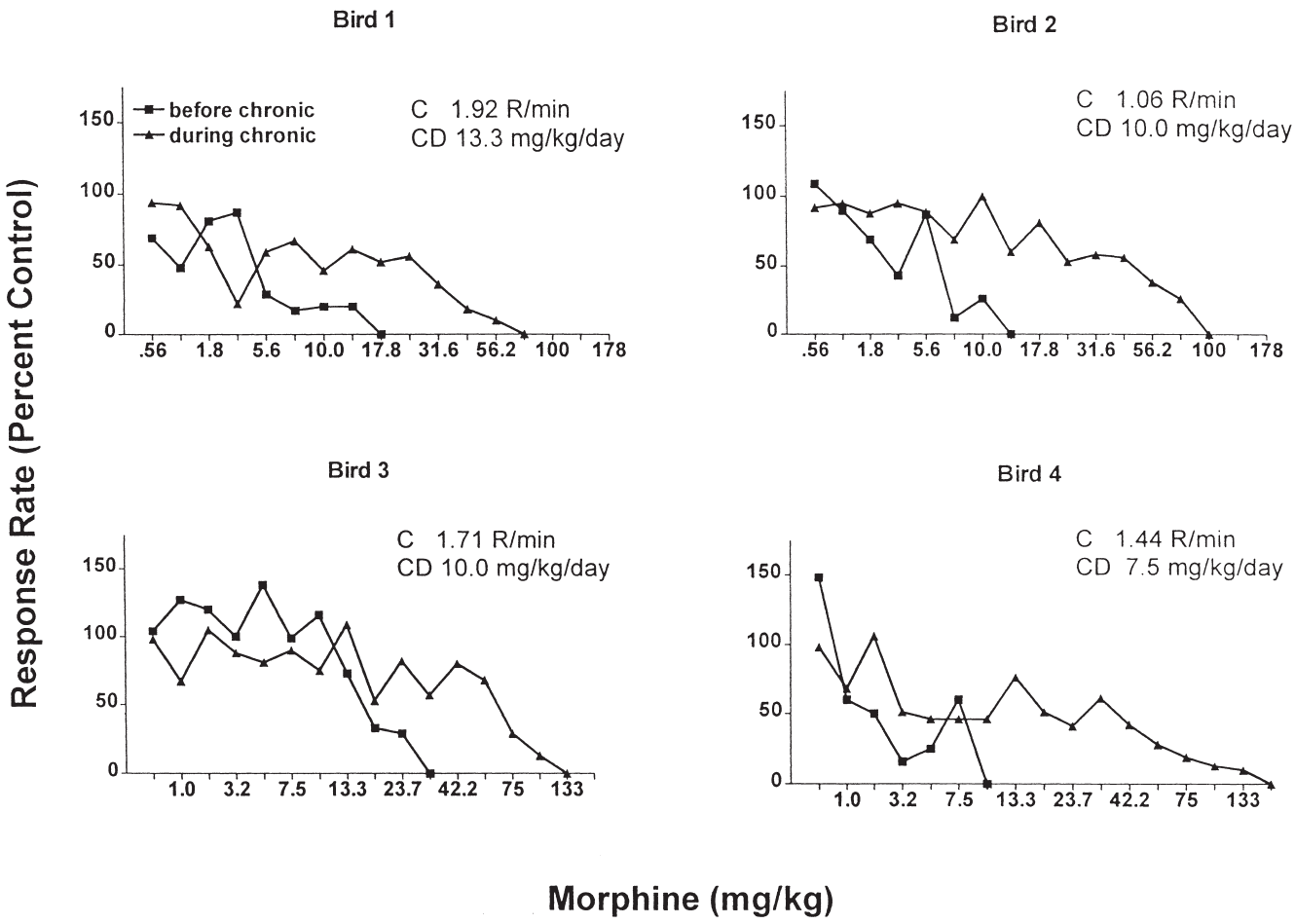


FIG. 2. Effects of morphine before and during chronic exposure on the overall response rates of individual pigeons responding under a PR 25 schedule of food delivery. Data are expressed as percentages of mean control response rates, which are indicated (at C, as responses/s). Each data point represents two drug administrations. The chronic dose received by each bird is indicated as CD.

TABLE 1

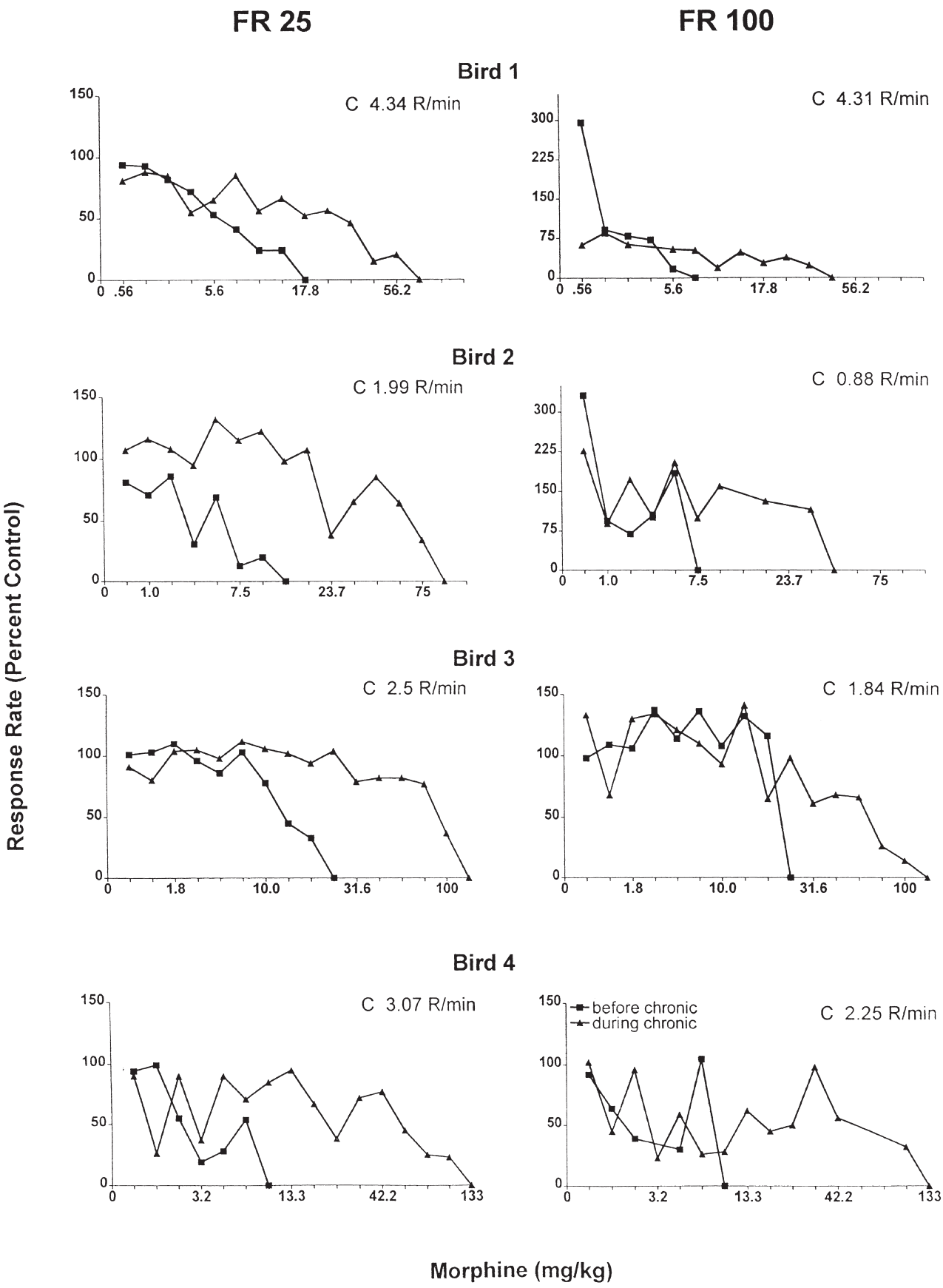
THE ED_{50} DOSES (mg/kg) FOR THE BREAKING POINTS AND OVERALL RESPONSE RATES OF INDIVIDUAL PIGEONS BEFORE AND DURING CHRONIC DOSE-RESPONSE DETERMINATIONS

Measure and Subject Number	Before Chronic ED_{50}	During Chronic ED_{50}
Breaking points		
1	6.0	12.4
2	8.9	44.3
3	13.3	81.5
4	1.8	31.9
Overall response rates		
1	3.3	10.6
2	5.1	30.8
3	18.5	44.9
4	3.4	15.2

several different mechanisms (e.g., sedation, changes in motivation, changes in motor activity), and it is naive to assume that drug-induced changes in PR breaking points index only the effectiveness of the scheduled reinforcer.

The most interesting aspect of the present data is that they provide no evidence that ratio size influenced the development of tolerance to morphine. The absence of such an effect is evident in a cross-study comparison: although data were more variable under the PR 25 schedule in the present study than under the PR 5 used in a prior study from our laboratory (23), there is no evidence that greater tolerance consistently developed under the latter schedule. This finding is inconsistent with prior results demonstrating that ratio size modulates tolerance to morphine and other drugs (6,15,16,22,23). Also inconsistent with the notion that ratio size modulates tolerance to morphine are the present data for FR 25 and FR 100 schedules, both arranged under the PR 25. There was no evidence of differential tolerance under these schedules, although a prior study from our laboratory (23) that involved a

FIG. 3. Effects of morphine before and during chronic exposure on the overall response rates of individual pigeons responding under the FR 25 and FR 100 components of a PR 25 schedule of food delivery. Data are expressed as percentages of mean control response rates, which are indicated (at C, as responses/s). Each data point represents two drug administrations. The chronic dose received by each bird is indicated as CD.


FR 25
FR 100
Bird 1
C 4.34 R/min
C 4.31 R/min
Bird 2
C 1.99 R/min
C 0.88 R/min
Bird 3
C 2.5 R/min
C 1.84 R/min
Bird 4
C 3.07 R/min
C 2.25 R/min
before chronic
during chronic
Response Rate (Percent Control)
Morphine (mg/kg)

multiple FR 5 FR 25 FR 125 schedule of food delivery found that ratio size influenced tolerance to morphine. In that study, less tolerance occurred under the FR 125 component than under the FR 5 component. In two of four birds, greater tolerance was observed under the FR 25 than under the FR 125. These findings suggest that it is easiest to demonstrate that ratio size modulates tolerance to morphine when the drug's effects on a very short ratio (e.g., FR 5) are compared to its effects on a much longer ratio (e.g., FR 125). No very short ratio was arranged in the present experiment, and data for individual ratios were not reported for the study (23) that examined the effects of morphine under a PR 5 schedule which, of course, comprised an FR 5 as well as longer ratios. Thus, further research is required to evaluate fully how ratio size influences the effects of morphine under PR schedules. It is, however, clear that the influence of the variable is not pervasive.

ACKNOWLEDGEMENTS

The reported research was supported by Grant DA07869 from the National Institute on Drug Abuse, which also supplied morphine.

REFERENCES

1. Bedford, J. A.; Bailey, L. P.; Wilson, M. C.: Cocaine reinforced progressive ratio performance in the rhesus monkey. Pharmacol. Biochem. Behav. 9:631–638; 1978.
2. Byrne, T.; LeSage, M.; Poling, A.: Tolerance development to morphine under mixed-ratio schedules. In: Leslie, J., ed. Proceedings of the third European meeting for the experimental analysis of behavior. Cleraine, Northern Ireland: University of Ulster; 1997:2.
3. Christian, L.; LeSage, M.; Makhay, M.; Poling, A.: Tolerance development to cocaine under mixed-ratio schedules. In: Leslie, J., ed. Proceedings of the third European meeting for the experimental analysis of behavior. Cleraine, Northern Ireland: University of Ulster; 1997:23.
4. Cooper, S. J.; Jackson, A.; Birkham, T. C.; Turkish, S.: Endorphins, opiates and food intake. In: Rogers, R. J.; Cooper, S. J., eds. Endorphins, opiates and behavioural processes. London: Wiley; 1988:143–196.
5. Craft, R. M.; Picker, M. J.; Dykstra, L. A.: Differential cross-tolerance to opioid agonists in morphine-tolerant pigeons responding under a schedule of food presentation. J. Pharmacol. Exp. Ther. 249:386–393; 1989.
6. Genovese, R. F.; Elsmore, T. F.; Witkin, J. M.: Environmental influences on the development of tolerance to the effects of physostigmine on schedule-controlled behavior. Psychopharmacology (Berlin) 10:35–43; 1988.
7. Gilbert, R. M.: Microanalysis of fixed-ratio responding in the rat: Behavioral tolerance to morphine. Bull. Psychon. Soc. 3:229–231; 1974.
8. Gosnell, B. A.; Levine, A. S.; Morley, J. E.: The stimulation of food intake by selective agonists of mu, kappa and delta opioid receptors. Life Sci. 38:1081–1088; 1986.
9. Gosnell, B. A.: Central structures involved in opioid-induced feeding. Fed. Proc. 46:163–167; 1987.
10. Griffiths, R. R.; Bradford, L. D.; Brady, J. V.: Progressive ratio and fixed ratio schedules of cocaine-maintained responding in baboons. Psychopharmacology (Berlin) 65:125–136; 1979.
11. Gulati, K.; Ray, A.; Sharma, K. K.: Effects of acute and chronic morphine on food intake in rats: Modulation by oxytocin and vasopressin. Pharmacol. Biochem. Behav. 40:27–32; 1991.
12. Heifetz, S. A.; McMillan, D. E.: Development of behavioral tolerance to morphine and methadone using the schedule-controlled behavior of the pigeon. Psychopharmacologia 19:40–52; 1971.
13. Hodos, W.: Progressive ratio as a measure of reward strength. Science 134:943–944; 1961.
14. Hodos, W.; Kalman, G.: Effects of increment size and reinforcer volume on progressive ratio performance. J. Exp. Anal. Behav. 6:387–392; 1963.
15. Hoffman, S. H.; Branch, M. N.; Sizemore, G. M.: Cocaine tolerance: Acute versus chronic effects as dependent upon fixed-ratio size. J. Exp. Anal. Behav. 47:363–376; 1987.
16. Hughes, C. E.; Branch, M. N.: Tolerance to and residual effects of cocaine in squirrel monkeys depend on reinforcement-schedule parameter. J. Exp. Anal. Behav. 56:345–360; 1991.
17. Jaffee, J. H.; Martin, W. R.: Opioid analgesics and antagonists. In: Gilman, A. G.; Rall, T. W.; Nies, A. S.; Taylor, P., eds. The pharmacological basis of therapeutics. New York: Pergamon Press; 1990:485–521.
18. Jones, C.; LeSage, M.; Sundby, S.; Poling, A.: Effects of cocaine in pigeons responding under a progressive-ratio schedule of food delivery. Pharmacol. Biochem. Behav. 50:527–531; 1995.
19. Levine, A. S.; Billington, C. J.: Opioids: Are they regulators of feeding? Ann. NY Acad. Sci. 575:209–219; 1989.
20. Morley, J. E.; Levine, A. S.; Grace, K. M.; Zengner, H.; Shearman, G. T.: The k-opioid receptor and food intake. Eur. J. Pharmacol. 112:17–25; 1985.
21. Negus, S. S.; Picker, M. J.; Dykstra, L. A.: Kappa antagonist properties of buprenorphine in non-tolerant and morphine-tolerant rats. Psychopharmacology (Berlin) 98:141–143; 1989.
22. Nickel, M.; Alling, K.; Kleiner, M.; Poling, A.: Fixed-ratio size as a determinant of tolerance to cocaine: Is relative or absolute size important? Behav. Pharmacol. 4:471–478; 1993.
23. Nickel, M.; Poling, A.: Fixed-ratio size as a determinant of the development of tolerance to morphine. Behav. Pharmacol. 1:459–462; 1990.
24. Picker, M.; Poling, A.: Effects of anticonvulsants on learning: Performance of pigeons under a repeated acquisition procedure when exposed to phenobarbital, clonazepam, valproic acid, ethosuximide, and phenytoin. J. Pharmacol. Exp. Ther. 230:307–316; 1984.
25. Poling, A.; LeSage, M.; Roe, D.; Schaefer, D.: Acute and chronic effects of morphine in pigeons responding under a progressive-ratio schedule of food delivery. Pharmacol. Biochem. Behav. 54: 485–490; 1996.
26. Roberts, D. C. S.; Loh, E. A.; Vickers, G.: Self-administration of cocaine on a progressive ratio schedule in rats: Dose–response relationship and effect of haloperidol pretreatment. Psychopharmacology (Berin) 97:535–538; 1989.
27. Sanger, D. J.; McCarthy, P. S.: Differential effects of morphine on food and water intake in food deprived and freely feeding rats. Psychopharmacology (Berlin) 72:103–106; 1980.
28. Schulze, G. E.; Paule, M. G.: Acute effects of *d*-amphetamine in a monkey operant test battery. Pharmacol. Biochem. Behav. 35:759–765; 1990.
29. Schulze, G. E.; Paule, M. G.: Effects of morphine sulfate on operant behavior in rhesus monkeys. Pharmacol. Biochem. Behav. 38: 77–83; 1991.
30. Smith, J. B.: Effects of fixed-ratio length on the development of tolerance to decreased responding by l-nantradol. Psychopharmacology (Berlin) 88:296–300; 1986.
31. Smith, J. B.: Effects of fixed-ratio requirement on observed tolerance to decreased responding by clonidine. Pharmacol. Biochem. Behav. 36:993–996; 1990.
32. Smith, J. B.: Prevention by naltrexone of tolerance to the rate-decreasing effects of morphine on schedule-controlled responding in the pigeon. Psychopharmacology (Berlin) 63:49–54; 1979.
33. Young, A. M.; Herling, S.: Drugs as reinforcers: Studies in laboratory animals. In: Goldberg, S. R.; Stolerman, I. P., eds. Behavioral analysis of drug dependence. New York: Academic Press; 1986:9–67.