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BRIEF COMMUNICATION

Self-Administration of Morphine in the Rat: Relative Influence of Fixed Ratio and Time-Out

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WEEKS, J. R. AND R. J. COLLINS. *Self-administration of morphine in the rat: Relative influence of fixed ratio and time-out*. PHARMAC. BIOCHEM. BEHAV. 9(5) 703–704, 1978.—Rats were offered 3.2 mg/kg of morphine sulfate on a continuous reinforcement schedule until the daily injection rate had stabilized. The effect of fixed ratio schedules of 4 and 8 were compared to imposing time-out periods of 5 and 10 sec immediately following each injection. The fixed ratio schedules decreased the injection rate while the time-out schedules had no effect. The hypothesis that the effect of a fixed ratio schedule is a consequence of imposing a time-out period, allowing full effects of the injection to be sensed, is not supported.

Morphine sulfate Time-out schedules

IN THE FIRST STUDY on intravenous self-administration of morphine by rats, Weeks [3] noted that total morphine intake decreased when the schedule was changed from continuous reinforcement (CR) to fixed ratio (FR) 5. We have consistently observed this phenomenon in other studies (unpublished observations). The explanation suggested was that the FR schedule imposed a time-out (TO) after the injection which allowed the full effect of the drug to be sensed. We report here the relative effect of an FR schedule and a TO after injection on the injection rate of rats self-administering morphine.

METHOD

Animals were 14 female Upjohn Sprague-Dawley origin, specific pathogen free rats, 282–336 g. Rats were prepared with chronic venous cannulas [4] and morphine administered using the pneumatic syringe apparatus [5]. Morphine sulfate was dissolved in isotonic saline and injected as a 3.2 mg/kg bolus in a volume of 0.1 ml/kg. The duration of the injection was estimated as less than 0.5 sec. On CR and FR schedules, there was a brief TO, estimated as about 0.5 sec, to allow refilling of the syringe. During TO, responses on the lever had no consequence. Total daily injections were recorded each day at 0800, and any changes in experimental conditions completed by 0930.

Naive rats were offered morphine 3.2 mg/kg on a CR schedule until daily intake had stabilized. Neither stimulus lights nor shaping techniques were used. Stability of intake implies both uniformity from day to day and that there was no further gradual increase in daily intake. For initial stabilization, the criteria were that, based upon the preceding 5 days, the coefficient of variation (standard deviation/mean) must be ≤ 0.2, and when analyzed as a linear regression, the probability of a significant regression must be ≥ 0.2. For re-stabilization, criteria were based only on the preceding 4 days. The significance of schedule changes was evaluated by a paired t-test comparing the mean initial value with the third day on the FR or TO schedules. Since injection rates between rats are log-normally distributed (submitted for publication), values reported are the antilog of the mean of the logarithms of values for individual rats.

RESULTS

Fourteen naive rats were given access to morphine 3.2 mg/kg on a CR schedule until the daily injection rate had stabilized. The number of days exposure was 20.2 ± 6.1 (SD). Half of the rats were then placed on an FR-4 schedule for 3 days and then FR-8 for 3 more days. The other half of the rats remained on a CR schedule but a 5 sec TO was imposed following each injection for 3 days, and then a 10 sec TO for 3 more days. After this series, rats were returned to the original schedule and allowed at least 5 days for intake to re-stabilize. Re-stabilization was rapid, requiring exposure of 5.8 ± 0.79 days (SD, N=10). Injection rates after re-stabilization did not differ significantly from initial rates ($p > 0.2$). The schedules were then repeated as a cross-over test. Of the 7 rats in each group, 5 in each completed the cross-over test. Since the results were the same regardless of which schedule was tested first, all results were pooled.

Results are summarized in Table 1. The FR-4 schedule caused a highly significant decline in injection rate which decreased still further at FR-8. On the contrary, neither the 5 sec nor 10 sec TO had any effect on the injection rate.

DISCUSSION

Garcin *et al.* [1] offered rats 3.2 mg/kg of morphine on a

TABLE 1

EFFECT OF FIXED RATIO AND TIME-OUT SCHEDULES ON MORPHINE SELF-INJECTION IN RATS

Schedule	Mean inj/day	Confidence Limits L 95%	Confidence Limits U 95%	Mean Coefficient of Variance	Mean Regression Probability
Initial CR	145	117	180	0.11	0.55
FR-4	57*	42	77		
FR-8	37*†	23	61		
Initial CR	146	123	174	0.13	0.51
TO-5 sec	137	111	169		
TO-10 sec	127	107	150		

*Significantly different from initial; $p<0.001$.
†Significantly different from FR-4; $p<0.005$.

CR schedule for 30 days. Daily morphine intake stabilized in an average of 14 days, which agreed with the 15 days noted in this study. However, their stabilized rate was 75 inj/day compared to 120 inj/day in this study. The speed of the injection may explain this difference. In their experiments, morphine was delivered as an infusion, while in ours it was a bolus. Smith *et al.* [2], using brief bolus injections and 10 hr daily access to morphine, reported 80 inj/day after 5 days at 0.3 mg/kg, an hourly rate about double that of Garcin *et al.* However, in another of our studies (submitted for publication) in which morphine was administered by infusion for 6 days at 3.2 mg/kg, the mean intake was 33.5 inj/day, which agrees fully with the 35 inj/day found by Garcin *et al.* on the sixth day.

The observation that injection rates decrease on changing from CR to FR schedules of reinforcement is confirmed. However, the hypothesis that the FR schedule enforces a time-out, allowing full effects of the injection to be sensed, is not supported. Time-outs of 5 and 10 sec are more than adequate for a rat to emit 4 and 8 responses respectively. We propose that responses during short time-out periods would still be associated with the effects of the injection. However, under an FR schedule, if the ratio is not completed within a short time after an injection, some of the responses would not be reinforced and the drive reduced. It is possible that an extended TO, of sufficient duration to allow acute effects of the injection to dissipate, would decrease drug intake.

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