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Effects of Clozapine and Chlorpromazine Upon Operant Response Measures in Rats

K. E. FORD, S. C. FOWLER AND G. L. NAIL

Department of Psychology, University of Mississippi
University, MS 38677

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FORD, K. E., S. C. FOWLER AND G. L. NAIL. *Effects of clozapine and chlorpromazine upon operant response measures in rats.* PHARMAC. BIOCHEM. BEHAV. 11(2) 239–241, 1979.—Rats responded under a FR20 schedule of water reinforcement by paw-pressing a silent, isometric, force-sensing manipulandum. Two seven-animal groups differed in terms of the force requirement for reinforcer delivery, i.e., a low-force condition (4-g requirement for reinforcer delivery) or a high-force condition (32-g requirement for reinforcer delivery). Oral dose ranges of chlorpromazine (1.0, 3.0, 9.0 mg/kg) and clozapine (2.5, 5.0, 10.0 mg/kg) were evaluated for their effects on intensitive measures of response (i.e., peak force and duration), in addition to the conventional rate measure. Peak force, duration, and rate of response were recorded with a laboratory computer system. Conjoint examination of these three dependent variables revealed that clozapine, a new anti-psychotic agent which produces virtually no extrapyramidal side effects in man, affected FR responding in the same way as did chlorpromazine. More specifically, response rate and peak force declined as a function of dose for each drug. Duration of response tended to be increased at the highest dose for both clozapine and chlorpromazine, but this effect was limited primarily to the high-force condition.

Response force Duration Response rate Fixed-ratio schedule Clozapine Chlorpromazine Rat

THE classical major tranquilizers (e.g., chlorpromazine, CPZ) used in the treatment of schizophrenia produce extrapyramidal motor side effects. Both early-onset Parkinson-like symptoms and late-onset ("tardive") dyskinesias limit the clinical use of these agents [1]. In contrast, a recently developed dibenzodiazepine, clozapine (CLOZ), is reported to alleviate effectively the symptoms of schizophrenia while producing few, if any, extrapyramidal signs [5,12]. Therefore, CLOZ may be an important tool for developing animal test procedures capable of distinguishing between the pharmacological activities of CLOZ and those of other neuroleptics. Currently-used animal tests for neuroleptics emphasize extrapyramidal effects, thereby leading to the selection of anti-psychotic agents with high side effect liabilities [2].

Despite the fact that two previous uses of conventional operant conditioning procedures failed to differentiate CLOZ from CPZ [3,4], it was the purpose of the present study to introduce refinements of measurement to the operant test situation in an attempt to develop contrasting profiles for these two drugs. To this end, the effects of acute dose ranges of CLOZ and CPZ upon force and duration (presumed to reflect motor features) of response, in addition to rate of response, were observed while rats performed on a FR20 schedule of reinforcement. In addition, required force was included as a second independent variable on the basis of previous research which demonstrated that the sensitivity of an operant procedure to drug effects can depend upon the level of force emitted [8].

METHOD

Animals

The animals were 14 male, Sprague-Dawley rats (Holtzman Co.), averaging 334 g in ad lib weight. All of the rats were deprived of water and maintained at 80% of their ad lib body weights. Food was continuously available in the individual home cages.

Apparatus

The apparatus consisted of two simultaneously operative experimental chambers measuring 23 cm long, 20 cm wide and 19 cm high. Each chamber was fitted with a grid floor composed of 6.5 mm-dia. stainless steel rods running parallel to the front of the chamber. The front panels of the chambers were made of aluminum; the remaining sides and the tops were Plexiglas. A stimulus light located in the ceiling of each chamber provided illumination, and also was extinguished for 0.25 sec upon response termination to signal the delivery of water. A rectangular opening, 3.0 cm wide and 1.5 cm high, in the front panel of each chamber, permitted access to the manipulandum positioned outside each chamber. The lower edge of each manipulandum aperture was 6 cm above the grid floor. Two Sanborn force transducers (Model FTA-100) served as the silent, practically isometric, force-sensing manipulanda. The portion of the transducers available to the two concurrently-run animals was a horizontal disk 18 mm in diameter. Each transducer was positioned so that the center of the disk was 2.5 cm from the outside of the chamber wall

and the surface of the disk was 0.5 cm above the lower edge of the aperture. In each chamber a brass water cup, serviced by a solenoid valve calibrated to deliver 0.05 ml water, was mounted on the lower right front panel. White noise was provided for each chamber by means of a General Radio random-noise generator (Model 1390-B). The two experimental chambers, manipulanda, solenoid valves, and speakers providing white noise were separately enclosed in two sound-attenuating boxes in a dark room.

Programming of contingencies and recording of data were accomplished with a laboratory computer (PDP8/e) and associated peripherals. The apparatus was programmed to record peak force, duration, and rate of responding. The details of these techniques are described elsewhere [7,9]. Under computer control an analog-to-digital converter sampled the analog voltage from the transducer every 0.01 sec. From these measurements the peak forces of individual response above a 4 g threshold (cf. [14]) were obtained on-line. A response was defined by the force amplitude rising and then dropping below a 4 g threshold. The peak force of a response is simply the maximum force amplitude attained by a response. Duration of response is the amount of time that force remains above threshold. Peak force was recorded with a precision of ± 0.5 g, and response duration was measured with a precision of ± 0.01 sec. Session times, upon which average rate of response measures were based, were taken with a precision of ± 1.0 sec.

Procedure

The animals were shaped to reach through the aperture in the chamber wall to exert downward vertical force on the manipulandum. This procedure was undertaken to develop relatively uniform response topography and to prevent biting of the manipulandum.

The animals were randomly assigned to one of two groups which differed in terms of the force requirement for reinforcer delivery, i.e., a low-force condition (N=7) or a high-force condition (N=7). In the low-force condition, responses of 4 g or more met the requirement for reinforcer delivery and thus advanced the ratio count. For the high-force group, only responses of 32 g or more advanced the ratio count for reinforcer delivery. All responses above or at 4 g were recorded, even though these responses did not meet the 32 g criterion for reinforcer delivery in effect for the high-force group. The reinforcer (0.05 ml water) was delivered upon response termination. The importance of this procedural detail is elucidated elsewhere [8].

Subsequent to shaping, all animals received 10 daily 10-min sessions of CRF training, during which time the force criterion for the high-force group was gradually increased from 4 g to 32 g. Following this training, the CRF component was progressively incremented to FR20 reinforcement. There were 50 daily sessions of FR20, 20 cycles per session, prior to the assessment of drug effects.

Drug dosages were chosen so that the highest doses would be approximately equieffective for antipsychotic action in humans. Chlorpromazine (Smith, Kline and French: 1.0, 3.0, 9.0 mg/kg) and clozapine (Sandoz: 2.5, 5.0, 10.0 mg/kg) were administered by gavage, 45 min before a 10-min session of FR20 reinforcement. Clozapine was dissolved in 0.1 N HCL solution, and chlorpromazine was dissolved in 0.9% saline solution. In all cases drug solutions were diluted with sufficient 0.9% saline to yield a dose volume of 1.0 ml. Drug-evaluation days were separated by at least three days,

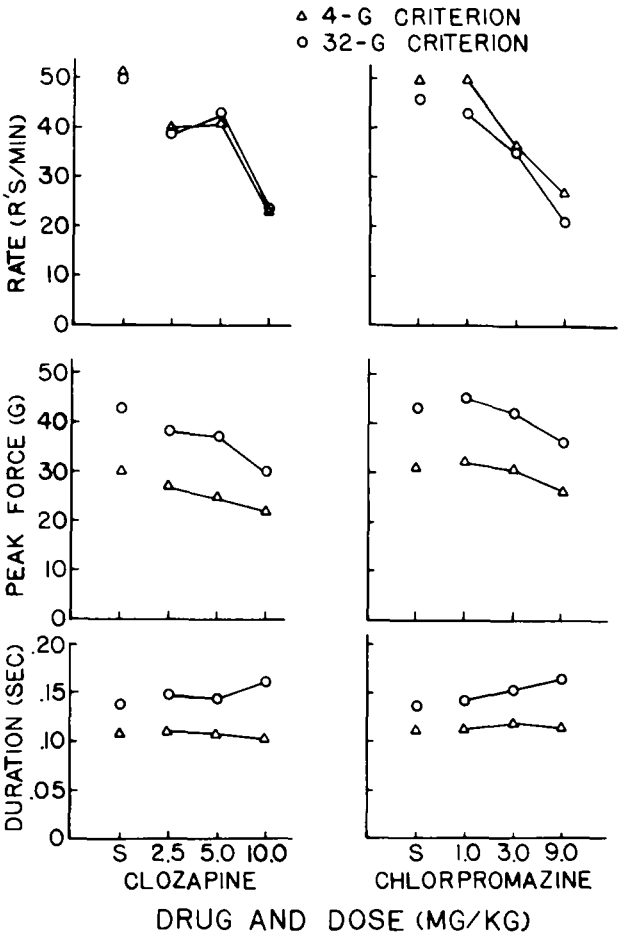

FIG. 1. Dose-response functions for rate, peak force and duration for clozapine and chlorpromazine. Each data point is based on two determinations of the acute effects of the drugs at each dose, except for the saline condition (designated "S") which was based on six saline control sessions. The two separate force-criterion groups consisted of seven subjects each.

i.e., a no-session day, a non-intubation day, and a saline day. Animals were not run on no-session days. On non-intubation days the animals were merely exposed to the conditioning procedures. Saline sessions were held on the day before each drug session, and 1.0 ml saline was intubated. The drugs and dosages were given in randomized order. Two determinations of drug effect were made at each dose. Drug effects were characterized by three dependent variables: mean peak force of all responses (i.e., responses having forces >4 g), mean duration of all responses, and rate of all responses.

RESULTS

The absolute values of the three dependent variables were analyzed by means of Split-Plot Factorial analyses of variance [11]. The results of the statistical analyses revealed that CLOZ and CPZ had significant dose-related effects upon rate, peak force, and duration of response. Figure 1 shows that the effects of CLOZ and CPZ on all three response measures were similar.

Both CPZ and CLOZ significantly decreased response rate, $F(3,36)=20.602$, $p<0.01$ for CPZ, and $F(3,36)=17.526$, $p<0.01$ for CLOZ. Peak force was also lowered significantly for both CPZ, $F(3,36)=11.735$, $p<0.01$, and CLOZ, $F(3,36)=23.860$, $p<0.01$, at the higher doses. There was an interaction effect between the required force condition and the drug dose for both drugs upon the duration measure: $F(3,36)=3.240$, $p<0.10$ for CPZ, and $F(3,36)=6.608$, $p<0.01$ for CLOZ. (For CPZ, $0.05<p<0.10$ as a result of Geisser-Greenhouse conservative F test owing to heterogeneity of the variance-covariance matrix in this case; an ordinary F test would yield $p<0.05$.) Duration of response tended to be increased for each drug at the highest dose, but this effect was limited primarily to the high-force condition (see Fig. 1). Thus the drug effects upon response duration depended upon the baseline values of peak force.

DISCUSSION

The present data indicate that for the *acute* dose ranges used, CLOZ and CPZ have essentially similar, rather than divergent, dose-related effects upon peak force, duration, and rate of FR performance. CLOZ, a relatively new antipsychotic drug with low extrapyramidal side effect liability, demonstrated virtually no behavioral differences from CPZ (an antipsychotic with moderate extrapyramidal effects) at the doses tested. The two compounds increased response duration at the highest doses but decreased mean peak force and rate of response in a dose-related fashion.

With regard to the similarity to the effects of CLOZ and CPZ on operant response measures, the data are in general agreement with previous reports. Canon and Lippa [4] found that CPZ and CLOZ produced similar effects on behavior maintained by a DRL 10 sec schedule of reinforcement. They also concluded that neither adjunctive drinking behavior nor rates of lever pressing under a FR20 schedule were useful in diffferentiating between CLOZ and CPZ [3]. However, Canon and Lippa [3] did report that CPZ and CLOZ produced differential dose-related effects on FI 2 min response rates.

Although the present procedure was not able to differentiate between CLOZ and CPZ, the examination of intensitive response measures during fixed-ratio responding has been shown to be useful in distinguishing between different classes of drugs [8]. Furthermore, although the techniques described herein did not distinguish CLOZ from CPZ when the dosing regimen was acute, it would seem premature to reject these methods for measuring extrapyramidal effects until chronic dosing (which is most analogous to clinical usage for the doses used) and other behavioral parameters have been evaluated. Moreover, a task with more stringent and direct motor-control requirements, such as the force-band duration task (cf. [6,15]), may be sensitive to the differential effects of acute CLOZ and CPZ.

It has frequently been reported that the effects of many drugs upon operant response rate are rate-dependent, i.e., are dependent upon the baseline rate of behavior [13]. The present finding that CPZ and CLOZ increased response duration in the high-force condition, but not in the low-force condition, indicates that a type of force-dependency effect occurred (cf. [8]). This result supports the principle that the procedures used to maintain operant responding are important determinants of the behavioral effects of drugs [10].

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