Pharmacology Biochemistry & Behavior, Vol. 31, pp. 779–786. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Assessment of Pimozide's Motor and Hedonic Effects on Operant Behavior in Rats[1]

JOSEPH H. PORTER[2] AND HEIDI F. VILLANUEVA

Department of Psychology, Virginia Commonwealth University, Richmond, VA 23284

Received 3 February 1988

PORTER, J. H. AND H. F. VILLANUEVA. *Assessment of pimozide's motor and hedonic effects on operant behavior in rats*. PHARMACOL BIOCHEM BEHAV 31(4) 779–786, 1988.—The present study examined the effects of the neuroleptic pimozide on several measures of motor capacity and reinforcement efficacy in rats trained to respond according to a multiple random interval (RI) food reinforcement schedule (mean interreinforcement intervals of 10, 20, 40, 80, and 160 sec). Pimozide (0.125, 0.25, 0.5, and 1.0 mg/kg) produced a dose-dependent suppression of response rates for all five RI schedules and a dose-dependent increase in response duration. An independent measure of motor activity in photocell activity chambers also was decreased by pimozide in a dose-dependent manner. Photocell activity was significantly correlated with response duration and with the Matching Equation parameter k. Thus, all three measures of motor performance revealed similar decreases in motor capacity at the high dose of pimozide. Reinforcement efficacy also was reduced by the 1.0 mg/kg dose of pimozide as indicated by an increase in the Matching Equation parameter Re. The parameters k and Re were not significantly correlated, suggesting that these two Matching Equation parameters do provide independent measures of motor capacity and reinforcement efficacy, respectively. The present results demonstrate the importance of obtaining measures other than simple response rates in order to assess drug effects on operant behavior.

Pimozide Neuroleptics Motor capacity Reinforcement efficacy Multiple random interval schedule Response duration Rats Photocell activity Matching equation

WHILE it is well known that neuroleptic drugs suppress operant responding in rats and other laboratory animals [see (4,42)], the mechanism for this effect remains unclear. Many [e.g., (6, 10, 32, 35)] have attributed this disruption of operant behavior by neuroleptics to the motor side effects of these drugs (a motor deficit hypothesis), but Wise (41,42) has proposed the anhedonia hypothesis that neuroleptic drugs "interfere with operant behavior in a more subtle, interesting, and important way than by simply reducing the animal's performance capcity . . . neuroleptics blunt the hedonic impact of rewards . . . before they cause any significant impairment of the performance capability of the animal" [(42, p. 39].

One difficulty with both of these hypotheses is that each predicts the suppression of operant responding maintained by positive reinforcement. Since simple response rate measures do not provide a way to distinguish between motor and hedonic (or other) effects of neuroleptic drugs, additional behavioral measures are needed. Fowler and his colleagues (7–9, 11–13, 15, 16, 39) have suggested that response duration may provide a measure of motor effects that simple response rates cannot. In one study (7) rats were tested on a fixed ratio 10 food reinforcement schedule with haloperidol administration or under extinction testing conditions. While both groups showed similar declines in response rates over six days of testing, the haloperidol-treated rats displayed response durations that were significantly greater than those obtained under extinction conditions in the absence of any drug. According to Faustman and Fowler, these results indicate that neuroleptics and extinction may produce reductions in operant responding by different mechanisms and that haloperidol has pronounced motor effects that cannot be measured simply by changes in response rates.

Another approach (22–26) for measuring the motor and hedonic effects of neuroleptic (and other drugs) uses a curve-fitting technique known as the Matching Equation: $B = kR/R + Re$ [see (20,21)], where B is the response rate (responses/minute), R is the reinforcement rate (reinforcers/hour) and k and Re are constants that measure the asymptotic response rate and the rate of reinforcement needed to maintain half of the asymptotic response rate, respectively. [Note: the constants k and Re are also called B_{max} and R_{half}; see (20).] Heyman (22) argues that k provides a measure of motor capcity [see (30)] and that Re measures

[1]This work was supported by U.S. Public Health Service grant MH 40184-01 to Joseph H. Porter. Pimozide was generously supplied by Janssen Pharmaceutica.

[2]Requests for reprints should be addressed to Joseph H. Porter, Department of Psychology, Box 2018, Virginia Commonwealth University, Richmond, VA 23284-2018.

reinforcement efficacy [see (18)]. Testing rats on a multiple variable interval schedule, Heyman found that a low dose (0.2 mg/kg) of pimozide produced a decrease in reinforcement efficacy (as measured by an increase in Re), but produced no change in motor capacity (as measured by k). At a higher dose (0.6 mg/kg) both reinforcement efficacy and motor capacity were decreased in a dose-dependent manner (i.e., Re increased and k decreased). Heyman and Monaghan (26) also have demonstrated that Re was changed as a function of the deprivation period (with water as the reinforcer) while k was not. When the lever weight was varied, k was changed and Re was not. Other studies have shown that Re was selectively changed when percent body weight was manipulated with water as the reinforcer (2) and when pulse frequency was reduced for electrical self-stimulation in the brain (19), and that k was changed when the weight of the lever was manipulated (1,19). These findings support the contention that k and Re measure motor capacity and reinforcement efficacy, respectively.

The present study tested rats on a multiple random interval food reinforcement schedule with the neuroleptic pimozide. In addition to simple response rates, response duration was measured, and, prior to each operant test session, photocell activity was obtained to provide an independent measure of the motor effects of pimozide. The Matching Equation parameters k and Re were calculated from response rate and reinforcement rate data for those animals meeting the criterion for percent variance accounted for (see the Method section). Thus, the purpose of the present study was to evaluate several different behavioral measures to determine if motor and hedonic effects of pimozide could be distinguished and measured independently of each other.

METHOD

Subjects

Fifteen adult male Sprague-Dawley albino rats served as subjects for this experiment (190–260 g). Subjects were individually housed in a temperature-controlled (22°C) animal colony room (7 a.m. light/7 p.m. dark cycle) with water continuously available in the home cage. Body weights were maintained at 80% of free-feeding weights by restricting daily rations of MRH 3000 Rodent Chow.

Apparatus

Operant sessions were conducted in three BRS/LVE operant chambers (Model 020) housed in sound-attenuated cubicles. BioServe food pellets (45 mg) were delivered by a BRS/LVE pellet dispenser to the food cup located in the center of the intelligence panel. A lever was located to the left of the food cup.

Motor activity was measured using three enclosed plastic photocell chambers (19×41×22 cm) that contained two photocell beams that bisected the width and length of the chamber. The chambers had air holes for ventilation. Both operant and photocell sessions were conducted in a darkened room with masking noise and ventilation provided by fans. Solid state programming equipment located in an adjacent room controlled operant and photocell sessions and recorded data.

Drugs

Pimozide (Janssen Pharmaceutica) was dissolved in distilled water with 15 drops of 85% lactic acid plus 0.5 ml Tween 80 to a stock concentration of 1.0 mg/ml. The stock concentration was diluted to concentrations of 0.5, 0.25, and 0.125 mg/ml. All injections, including vehicle, were administered intraperitoneally in volumes of 1 ml/kg four hours prior to operant sessions.

Procedure

All subjects were magazine trained for four days beginning 24 hours after food deprivation was initiated. Subjects were then trained to barpress for food on a fixed ratio 1 (FR1) reinforcement schedule for four days. Next, the reinforcement schedule was changed to a random interval schedule with a mean interreinforcement time of ten seconds (RI 10-sec) for five days. On the third day of RI 10-sec training, an audio cue (approximately 1800 Hz) was presented during the training session. For the next six days, subjects responded on a multiple random interval (MULT RI) schedule consisting of ten minutes of RI 10-sec, a one-minute time-out period, and ten minutes of RI 20-sec. After responding on the RI 10- and RI 20-sec schedules stabilized, additional one-minute time-out and ten-minute RI 40-sec components were introduced. After three days of training, another one-minute time-out and an RI 80 schedule were added. After seven days of training, a final 1-minute time-out and an RI 160-sec component were added. Training on this five component MULT RI schedule continued for 24 days until the response rates stabilized to less than ±10% change over three test sessions.

Thus, the MULT RI schedule consisted of five random interval schedules with mean interreinforcement times of 10, 20, 40, 80 and 160 seconds. Each of the five components lasted for ten minutes and was accompanied by an audio tone cycling on and off at different frequencies. The RI 10-second component was accompanied by a constant tone, RI 20 by a tone cycling on and off at a rate of 1 per second, RI 40 by a tone cycling on and off 2 times per second, RI 80 by a tone cycling on and off 4 times per second, and RI 160 by a tone cycling on and off 10 times per second. Each of the five components were separated by a one-minute time-out period during which the house lights were extinguished, tones were silent, and responding was not reinforced. For nine animals the MULT RI schedules were presented in order of decreasing reinforcer density: 10, 20, 40, 80, 160. For the other six animals the order of the five RI schedules was reversed (RI 160, 80, 40, 20, 10 sec) and the accompanying audio cues were reversed.

Photocell activity data was collected during the last ten days of the 24-day training period in order to adapt the animals to the photocell chambers. Photocell activity was recorded for fifteen minutes immediately prior to operant sessions. Each pimozide and vehicle dose was administered once in a counterbalanced order with a minimum of three nondrug test days between each drug day. The number of responses, number of reinforcers, the total length of time (in seconds) the response lever was held down during each ten-minute component (response duration), and the total number of responses emitted during the time-out periods were recorded for each session. Mean response duration per barpress was calculated for each component by dividing the total length of time the response lever was held down (to the nearest $^1/_{10}$ of a second) by the number of responses during that component. Immediately prior to operant sessions on drug days, subjects were placed in the photocell chambers for 15 min and the number of interruptions of each photocell

beam was recorded. Activity data were not collected on nondrug day (except for the 10-day adaptation period during training).

Data Analysis

Dependent measures for operant sessions and photocell activity were analyzed with repeated measures analysis of variance (ANOVA). A preliminary analysis was performed to test for possible order effects for the rats tested with either an ascending or a descending order of RI schedule during the test sessions. The main effect for order was not significant, $F(1,13)=3.99$, $p>0.05$, therefore, the data for these two groups of rats were combined for all further analyses. For responses per minute, reinforcers per hour, and mean duration per barpress (in sec) both Dose and Schedule were included in the ANOVA. Where appropriate, post hoc comparisons were made in a Duncan's Multiple Range Test (3).

The Matching Equation constants k and Re were calculated individually for each subject for each drug dose from the response rate (responses per minute) and reinforcement rate (reinforcers per hour) data in the same manner as Heyman (22). The method of least squares was used to determine the best-fitting values of k and Re for each drug dose. The Matching Equation is a nonlinear equation, and therefore, the least-squares solution produces nonlinear equations for k and Re. The procedure described by Wetherington and Lucas (40) was used for solving these nonlinear equations, representing the best-fitting values to near-machine accuracy. When k and Re are calculated, the percent of variance accounted for (VAF) by the Matching Equation is also determined. Because of the large variability in this measure in the present study, a selection criterion was established that the percent of variance accounted for had to be 50% or greater in order to include the estimates of k and Re for a subject for a given dose. The number of observations included for each dose for analysis is shown in Table 3. The constants k and Re and percent of variance accounted for were analyzed separately with a Dunnett's test (3) in which each dose of pimozide was compared to the vehicle condition. In order to access the relationship between the dependent measures, Pearson product-moment correlation coefficients were calculated between k, Re, responses per minute, response duration, and photocell activity. Because of the limited amount of data (i.e., number of observations) available for each dose of pimozide and vehicle for the analysis of the matching equation constants, the data for all 39 observations (see Table 3) were combined for the calculation of these correlation coefficients. Significant differences for all statistical analyses were at $p<0.05$.

RESULTS

Response Rates

Figure 1 shows the mean responses per minute for each dose of pimozide for each component of the MULT RI schedule. Pimozide produced a significant ($p<0.001$) dose-dependent suppression of responding and there was a significant ($p<0.001$) decrease in response rates as the density of the RI schedules decreased (i.e., from RI 10-sec to RI 160-sec). The Dose × Schedule interaction also was significant ($p<0.001$). Post hoc tests revealed that responding was significantly ($p<0.05$) suppressed by the 0.25, 0.50 and 1.0 mg/kg doses of pimozide relative to vehicle response rates during all five RI schedules. Post hoc comparisons within

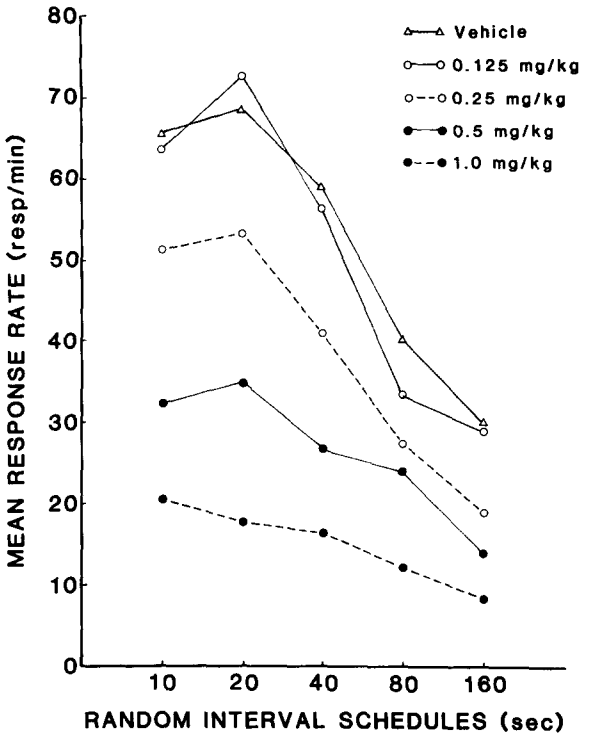

FIG. 1. Mean responses per minute for each dose of pimozide are shown for each random interval schedule.

doses of pimozide revealed that the interaction was due to the lack of significant differences between the RI 20-sec, RI 40-sec and RI 80-sec response rates for the 1.0 mg/kg dose of pimozide. The response rates for these RI schedules were significantly different for vehicle and the 0.125 and 0.25 mg/kg doses. For the 0.50 mg/kg dose the difference between the RI 20-sec and RI 40-sec response rates was not significant.

While the significant Dose × Schedule interaction indicates that different doses of pimozide had differential effects on response rates dependent on the RI schedule, it does not address possible rate-dependent effects of the drug. A rate-dependency analysis [see (5)] assesses the effects of a single drug dose over a range of control response rates. Therefore, a rate-dependency analysis on the response rate data was performed separately for each dose of pimozide by plotting ratios of drug response rate/vehicle response rates as a function of vehicle response rates. In this analysis vehicle response rates were used as the control response rates. The results are shown in Table 1 for each dose of pimozide. As the slopes for each dose indicate, there was no rate-dependent effect evident as all four slopes were essentially zero. The decreasing values of the Y-intercept indicate the dose-dependent effect of pimozide that was evident from the ANOVA on response rates (see Fig. 1).

Reinforcement Rates

The ANOVA on mean reinforcers per hour revealed that the only significant factor was Schedule ($p<0.001$). As expected, the mean number of reinforcers per hour decreased as the RI length became longer. The mean reinforcers per

TABLE 1
RATE-DEPENDENCY ANALYSIS ON RESPONSE RATES

Vehicle Response Rates	Pimozide Dose 0.125 mg/kg	0.25 mg/kg	0.50 mg/kg	1.0 mg/kg
30.45 (RI 160-sec)	0.95	0.62	0.46	0.28
40.35 (RI 80-sec)	0.84	0.69	0.60	0.31
59.01 (RI 40-sec)	0.95	0.69	0.45	0.28
68.51 (RI 20-sec)	1.06	0.78	0.51	0.26
65.68 (RI 10-sec)	0.97	0.79	0.49	0.31
Y-Intercept	0.79	0.51	0.53	0.30
Slope	0.003	0.004	−0.0006	−0.0003

Ratios of drug response rates/vehicle response rates as a function of vehicle response rates (responses/minute) are shown for each dose of pimozide. The Y-intercept and slope for each function are also shown. The random interval (RI) schedule for each vehicle response rate is shown in parentheses.

hour for each RI schedule (averaged across all doses of pimozide) were: RI 10-sec=339.1; RI 20-sec=174.1; RI 40-sec=84.5; RI 80-sec=41.0; RI 160-sec=22.2.

Response Duration

Figure 2 shows the mean duration (sec) per barpress for each dose of pimozide for each component of the MULT RI schedule. Pimozide produced a significant ($p<0.001$) dose-dependent increase in mean duration. As the density of the RI schedules decreased, the response duration increased significantly ($p<0.01$). While the increase in duration was most evident for the higher doses of pimozide, the Dose × Schedule interaction failed to reach significance ($p<0.07$) because of the large amount of variability in the data. Duncan's post hoc tests showed that response duration was significantly ($p<0.05$) increased by the 0.50 and 1.0 mg/kg doses of pimozide.

Time Out Responding

Table 2 shows the mean number of responses made during the Time Out components for each dose of pimozide. Pimozide produced a significant ($p<0.02$) decrease in responding during the Time Out components. Post hoc tests showed that Time Out responding for the 1.0 and 0.50 mg/kg doses of pimozide was significantly ($p<0.05$) less than for vehicle.

Photocell Activity

Mean photocell activity (mean number of beam interruptions) for each dose of pimozide also is shown in Table 2. ANOVA revealed a significant ($p<0.001$) decrease in photocell activity, and post hoc tests revealed significant ($p<0.05$) decrease in activity for the 0.50 and 1.0 mg/kg doses.

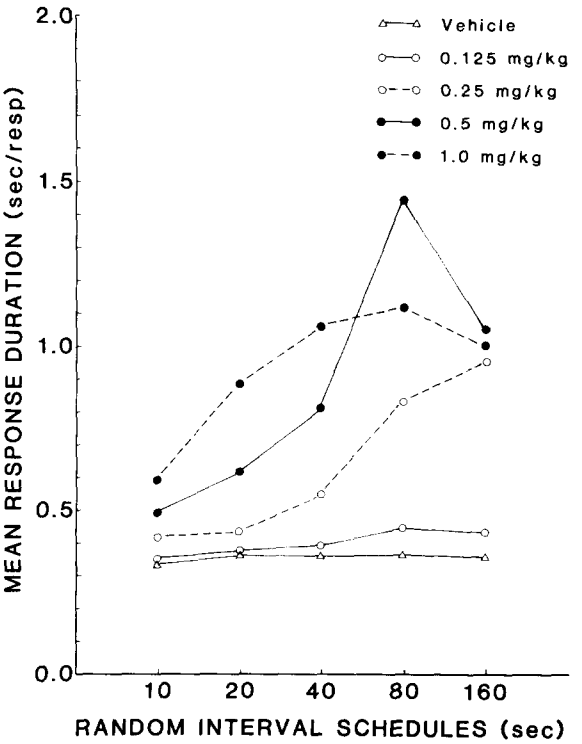

FIG. 2. Mean duration per barpress (sec/response) for each dose of pimozide is shown for each random interval schedule.

TABLE 2

MEAN NUMBER OF RESPONSES DURING THE TIME OUT COMPONENTS AND MEAN PHOTOCELL ACTIVITY FOR EACH DOSE OF PIMOZIDE

	Pimozide Dose				
	Vehicle	0.125 mg/kg	0.25 mg/kg	0.50 mg/kg	1.0 mg/kg
Time Out	68.3	54.7	41.0	31.1*	18.9*
Responding	(19.7)	(12.0)	(14.8)	(8.1)	(6.0)
Photocell	341.8	311.1	258.3	214.3*	141.3*
Activity	(25.6)	(31.3)	(28.5)	(34.5)	(19.5)

*Significantly different from vehicle ($p<0.05$).
SEM is shown in parentheses.

TABLE 3

MATCHING EQUATION CONSTANTS k AND Re AND THE PERCENT OF VARIANCE ACCOUNTED FOR (VAF) FOR EACH DOSE OF PIMOZIDE

	Vehicle (N=9)	0.125 mg/kg (N=8)	0.25 mg/kg (N=8)	0.50 mg/kg (N=6)	1.0 mg/kg (N=8)
k	107.95	121.00	96.22	67.12	45.54*
	(13.8)	(14.4)	(13.0)	(15.8)	(2.7)
Re	92.41	130.22	303.85	174.57	386.07*
	(30.0)	(35.4)	(84.1)	(63.1)	(133.7)
%VAF	74.07	81.07	82.65	84.61	85.65
	(4.9)	(4.3)	(1.9)	(4.8)	(3.3)

*Significantly different from vehicle ($p<0.05$).
The number of observations (N) for each dose and SEM are shown in parentheses.

Matching Equation Constants

In addition to determining the constants k and Re, the solutions for the nonlinear equations also determine the percent of variance accounted for (VAF). A selection criterion of 50% or greater was used to determine inclusion of a subject's data for each dose of pimozide. The number of observations included for anlaysis for each dose of pimozide is shown in Table 3, along with mean values for k, Re and percent of variance. The Dunnett's tests revealed that the 1.0 mg/kg dose of pimozide produced a significant ($p<0.05$) increase in Re (i.e., a decrease in reinforcement efficacy) and a significant ($p<0.05$) decrease in k (i.e., a decrease in motor capacity), but there was no significant change in percent VAF across the different doses of pimozide.

Correlations

Table 4 presents the correlation coefficients between k, Re, responses per minute, response duration, and photocell activity for the 39 observations (Table 3) that met the percent VAF selection criterion. There was no significant correlation between k and Re; however, Re was negatively correlated ($p<0.01$) with response rates and positively correlated ($p<0.05$) with response duration. Response rates were positively correlated ($p<0.01$) with k and negatively correlated ($p<0.001$) with response duration. Photocell activity was positively correlated ($p<0.05$) with the constant k and negatively correlated ($p<0.05$) with response duration.

TABLE 4

CORRELATION COEFFICIENTS BETWEEN k, Re, RESPONSES PER MINUTE (R/M), RESPONSE DURATION (DUR) AND PHOTOCELL ACTIVITY (PC) FOR THE 39 OBSERVATIONS USED TO CALCULATE THE MATCHING EQUATION CONSTANTS

	k	R/M	DUR	PC
Re	−0.049	−0.481†	0.404*	−0.176
k		0.464†	−0.259	0.366*
R/M			−0.662‡	0.264
DUR				−0.395*

*$p<0.05$; †$p<0.01$; ‡$p<0.001$.

DISCUSSION

The present results demonstrated that the neuroleptic pimozide impaired both motor capacity and reinforcement efficacy in rats responding for food reward on a MULT RI reinforcement schedule. Significant correlations were found between photocell activity and response duration and the Matching Equation parameter k. All three of these dependent variables are believed to provide measures of the performance (i.e., motor) capacity of the animal. Reinforcement efficacy was significantly reduced (as indicated by an increase in Re) by the 1.0 mg/kg dose of pimozide. Inter-

estingly, the correlation between k and Re ($r=-.049$) was not significant, suggesting that the two Matching Equation parameters do provide independent measures of motor capacity and reinforcement efficacy, respectively.

The dose-dependent reduction of response rates by pimozide in this study confirms numerous previous studies that have demonstrated the suppression of operant responding by neuroleptics [see (4,42)]. While the vast majority of these studies have used a single reinforcement schedule (often fixed ratio 1), the use of MULT RI schedule in this study allowed a rate-dependency analysis to be performed. This analysis showed that there was no rate-dependent effect for any of the pimozide doses tested in this study. Heyman (22) also reported that pimozide did not produce a rate-dependent effect when responding by rats was reinforced according to a multiple variable interval schedule (mean interreinforcement intervals were 10, 20, 40, 80, and 160 sec).

While response rates were suppressed in a dose-dependent manner in the present study, rates of reinforcement were not significantly changed. This obviously is in contrast to results seen in studies using fixed or variable reinforcement schedules. Kaempf and Porter (29) found that a 1.0 mg/kg dose of pimozide significantly reduced the number of reinforcers earned on a fixed interval (FI) 60-sec schedule, although the rats still received about two-thirds of the available reinforcers. Also, these rats continued to display a fixed interval pattern of responding (i.e., a FI "scallop"). Greenshaw, Sanger and Blackman (17) reported a similar decrease in response rates for rats responding on a FI 60-sec schedule as a function of increasing pimozide dose. Examination of cumulative records suggests that the FI "scallop" was not disrupted as much as response rates by the 1.0 mg/kg dose of pimozide; also, there was no systematic change in the postreinforcement pause at this dose. However, there was an increase in session length in order to complete 60 fixed intervals. These findings suggest that while response rates are suppressed by pimozide, rats are still capable of earning most or all of the available reinforcers on an interval-based reinforcement schedule by responding in a pattern appropriate for the schedule.

The motor deficit hypothesis (6, 10, 32, 35) attributes the disruption of operant behavior by neuroleptics to the motor side effects of these drugs. The results of the present study clearly support the notion that suppression of operant responding is at least partially attributable to the motor side effects of pimozide (certainly at the higher doses). Photocell activity, which provides a measure of spontaneous motor activity (34,36), was significantly suppressed by the two highest doses of pimozide. This confirms numerous previous reports of the effects of neuroleptics on motor activity measures [e.g., (27–29, 37)] and correlates with clinical reports of the motor side effects of neuroleptics drugs in humans [e.g., (14, 31, 38)]. Fowler and his colleagues (7–9, 11–13, 15, 16, 39) contend that response duration provides a measure of motor effects not obtained with simple response rates. In the present study response duration was significantly increased by the 0.25, 0.50, and 1.0 mg/kg doses of pimozide and there was a significant correlation between photocell activity and duration. There also was a significant correlation between photocell activity and the Matching Equation parameter k. Heyman (22–26) and others [see (30)] have argued that k provides a measure of the motor capacity of the animal and have reported that neuroleptics produce a decrease in the value of k. The present study also found that k was significantly decreased by pimozide (1.0 mg/kg dose).

The anhedonia hypothesis [see (42)] suggests that neuroleptic drugs decrease the reward (hedonic) value of reinforcers. As discussed in the Introduction, the Matching Equation parameter Re is believed to provide a measure of reinforcement efficacy in operant studies [see (18, 22–26)]. Thus, the use of this parameter provides an estimate of changes in the reinforcement efficacy not available from simple response rates. In the present study reinforcement efficacy was significantly decreased by the highest dose of pimozide (as indicated by an increase in the parameter Re). Thus, the highest dose of pimozide produced both reward and motor impairments in rats responding for food reward. These results are in agreement with a study by Hamilton, Stellar and Hart (19) that found similar changes in k and Re in self-stimulating rats with 0.125, 0.25, and 0.5 mg/kg doses of pimozide.

The results of the present study and the study by Hamilton *et al.* (19) differ from studies by Heyman (22) and Heyman *et al.* (24). In these studies, it was found that low doses of pimozide (22,24) and chlorpromazine (24) produced an increase in Re (i.e., decreased reward) without changing k. High doses of both neuroleptics produced changes in both parameters (i.e., both motor and reward deficits). There are a number of procedural differences among these studies that may explain these discrepant results. For example, the Hamilton *et al.* study (19) used self-stimulation as the reward, whereas the other studies used food (22) or water (24) as the reinforcer. In the present study, there was more variability in the percent variance accounted for when the Matching Equation parameters were calculated than in the other studies. Because of this variability, a selection criterion of 50% or greater was used to include estimates of k and Re for a given subject for a given dose. [A similar criterion was used in the Hamilton *et al.* (19) study.] The mean percent VAF in the present study ranged from 74.07% to 85.69%, whereas the other studies typically reported values greater than 90% [although the variability of this measure was greater in the Hamilton *et al.* study (19) than in the Heyman (22) study]. Referring to Table 3, increases in Re were evident at the lower doses of pimozide, although these differences failed to reach significance. With better matching (i.e., greater percent VAF), perhaps these doses of pimozide would have produced significant increases in Re in the present study. As can be seen in Fig. 1, response rates were higher during the RI 20-sec schedule than during the RI 10-sec schedule (except for the 1.0 mg/kg dose of pimozide). We are currently determining if better matching can be obtained by omitting the RI 20-sec schedule and using a four component multiple schedule.

While the present and other studies (19, 22–26) have found that pimozide changed both k and Re, one study (33) reports a possible exception. Morley *et al.* inferred from their data that pimozide decreased k without changing Re (i.e., a motor deficit only). However, they only tested the rats on two variable interval schedules and therefore did not have enough data points to actually estimate the parameters k and Re. Thus, it is difficult to directly compare these findings with other studies in which k and Re have actually been estimated from the data.

In conclusion, the present study clearly demonstrated the importance of obtaining measures other than simple response rates in order to assess subtle drug effects. Response duration and the Matching Equation parameter k both provided a measure of motor capacity and both were significantly correlated with an independent measure of motor activity (i.e., photocell activity).

The changes in the Matching Equation parameter Re indi-

cated that pimozide also produced reward deficits. Again, because of the small number of observations available for analysis, only the increase in Re for the 1.0 mg/kg dose reached significance. The utility of the Matching Law for interpreting drug action seems to be clear when an analysis of individual subjects is used [see (19, 22–24)]. Its use on analysis of group data as in the present study was hampered in part by the variability evident in the data. Hopefully, as the behavioral procedures are refined and variability in matching is reduced, the usefulness of the Matching Law for interpreting drug effects with group data will be increased.

REFERENCES

1. Bradshaw, C. M.; Szabadi, E.; Ruddle, H. V. Herrnstein's equation: effect of response force requirement on performance in variable-interval schedules. Behav. Anal. Lett. 3:93–100; 1983.
2. Bradshaw, C. M.; Szabadi, E.; Ruddle, H. V.; Pears, E. Herrnstein's equation: effect of deprivation level on performance in variable-interval schedules. Behav. Anal. Lett. 3:267–273; 1983.
3. Bruning, J. L.; Kintz, B. L. Computational handbook of statistics. Glenview, IL: Scott, Foresman & Co.; 1977.
4. Dews, P. B.; Morse, W. H. Behavioral pharmacology. Annu. Rev. Pharmacol. 1:145–174; 1961.
5. Dews, P. B.; Wenger, G. R. Rate-dependency of the behavioral effects of amphetamine. In: Thompson, T.; Dews, P. B., eds. Advances in behavioral pharmacology. vol. 1. New York: Academic Press; 1977:167–227.
6. Ettenberg, A.; Koob, G. G.; Bloom, F. E. Response artifact in the measurement of neuroleptic induced anhedonia. Science 209:357–359; 1981.
7. Faustman, W. O.; Fowler, S. C. Use of response duration to distinguish the effect of haloperidol from nonreward. Pharmacol. Biochem. Behav. 15:327–329; 1981.
8. Faustman, W. O.; Fowler, S. C. An examination of methodological refinements, clozapine and fluphenazine in the anhedonia paradigm. Pharmacol. Biochem. Behav. 17:987–993; 1982.
9. Faustman, W. O.; Fowler, S. C.; Walker, C. H. Time course of chronic haloperidol and clozapine upon operant rate and duration. Eur. J. Pharmacol. 70:65–70; 1981.
10. Fibiger, H. C.; Carter, D. A.; Phillips, A. G. Decreased intracranial self-stimulation after neuroleptics or 6-hydroxydopamine: Evidence for mediation by motor deficits rather than reduced reward. Psychopharmacology (Berlin) 47:21–27; 1976.
11. Ford, K. E.; Fowler, S. C.; Nail, G. L. Effects of clozapine upon operant response measures in rats. Pharmacol. Biochem. Behav. 11:239–241; 1979.
12. Fowler, S. C.; Filewich, R. J.; Leberer, M. R. Drug effects upon force and duration of response during fixed-ratio performance in rats. Pharmacol. Biochem. Behav. 6:421–426; 1977.
13. Fowler, S. C.; LaCerra, M. M.; Ettenberg, A. Effects of haloperidol on the biophysical characteristics of operant responding: Implications for motor and reinforcement processes. Pharmacol. Biochem. Behav. 25:791–796; 1986.
14. Gilman, A. G.; Goodman, L. S.; Gilman, A. The pharmacological basis of therapeutics. New York: MacMillan; 1980.
15. Gramling, S. E.; Fowler, S. C. Effects of neuroleptics on rate and duration of operant vs. reflexive licking in rats. Pharmacol. Biochem. Behav. 22:541–545; 1985.
16. Gramling, S. E.; Fowler, S. C.; Collins, K. R. Some effects of pimozide on nondeprived rats licking sucrose solutions in an anhedonia paradigm. Pharmacol. Biochem. Behav. 21:617–624; 1984.
17. Greenshaw, A. J.; Sanger, D. J.; Blackman, D. E. The effects of pimozide and of reward omission on fixed-interval behavior of rats maintained by food and electrical brain stimulation. Pharmacol. Biochem. Behav. 15:227–233; 1981.
18. Guttman, N. Equal-reinforcement values for sucrose and glucose solutions compared with equal-sweetness values. J. Comp. Physiol. Psychol. 47:358–361; 1954.
19. Hamilton, A. L.; Stellar, J. R.; Hart, E. B. Reward, performance, and the response strength method in self-stimulating rats: Validation and neuroleptics. Physiol. Behav. 35:897–904; 1985.
20. Herrnstein, R. J. On the law of effect. J. Exp. Anal. Behav. 13:243–266; 1970.
21. Herrnstein, R. J. Formal properties of the matching law. J. Exp. Anal. Behav. 21:159–164; 1974.
22. Heyman, G. M. A parametric evaluation of the hedonic and motoric effects of drugs: pimozide and amphetamine. J. Exp. Anal. Behav. 40:113–122; 1983.
23. Heyman, G. M.; Seiden, L. S. A parameteric description of amphetamine's effects on response rate: changes in reinforcement efficacy and response topography. Psychopharmacology (Berlin) 85:154–161; 1985.
24. Heyman, G. M.; Kinzie, D. L.; Seiden, L. S. Chlorpromazine and pimozide alter reinforcement efficacy and motor performance. Psychopharmacology (Berlin) 88:346–353; 1986.
25. Heyman, G. M.; Beer, B. A new approach for evaluating the behavioral effects of antipsychotic drugs. Trends Pharmacol. Sci. 8:388–393; 1987.
26. Heyman, G. M.; Monaghan, M. M. Effects of changes in response requirement and deprivation on the parameters of the matching law equation: New data and review. J. Exp. Psychol. [Anim. Behav. Proc.] 13:384–394; 1987.
27. Janssen, P. A.; Neimegeers, C. J. E.; Schellekans, K. H. L. Is it possible to predict the clinical effects of neuroleptics drugs (major tranquilizers) from animal data? Part I: "Neuroleptic activity spectra" for rats. Arzneimittelforschung 15:104–117; 1965.
28. Janssen, P. A. J.; Soudijn, W.; VonWigngaarden, I.; Dresse, A. Pimozide, a chemically novel, highly potent and orally long-lasting neuroleptic drug. Arzneimittelforschung 18:282–287; 1968.
29. Kaempf, G. L.; Porter, J. H. Differential effects of pimozide and clozapine on schedule-controlled and schedule-induced behaviors after acute and chronic administration. J. Pharmacol. Exp. Ther. 243:437–445; 1987.
30. McSweeney, F. K. Prediction of concurrent keypeck and tradle-press responding from simple schedule performance. Anim. Learn. Behav. 6:444–450; 1978.
31. Marsden, D. C.; Jenner, P. The pathophysiology of extrapyramidal side-effects of neuroleptic drugs. Physiol. Med. 10:55–72; 1980.
32. Mason, S. T.; Beninger, R. J.; Fibiger, H. C.; Phillips, A. G. Pimozide-induced suppression of responding: Evidence against a block of food reward. Pharmacol. Biochem. Behav. 12:917–923; 1976.
33. Morley, M. J.; Bradshaw, C. M.; Szabadi, E. The effect of pimozide on variable-interval performance: A test of the anhedonia hypothesis of the mode of action of neuroleptics. Psychopharmacology (Berlin) 84:531–536; 1984.
34. Reiter, L. W.; MacPhail, R. C. Motor activity: A survey of methods with potential use in toxicity testing. Neurobehav. Toxicol. 1:53–66; 1979.
35. Sanger, D. J. Response decrement patterns after neuroleptic and non-neuroleptic drugs. Psychopharmacology (Berlin) 89:98–104; 1986.
36. Siegal, P. S. A simple electronic device for the measurement of the gross bodily activity of small animals. J. Psychol. 21:227–236; 1946.
37. Stille, G.; Lauener, H.; Eichenberger, E. The pharmacology of 8-chloro-11(4-methyl-1-piperazinyl-5H-dibenzo [b,e] [1,4] diazepine (Clozapine). II. Farmaco. Ed. Prat. 26:603–625; 1971.

38. Tyrer, P. J. Drugs in psychiatric practice. London: Butterworths; 1982.
39. Walker, C. H.; Faustman, W. O.; Fowler, S. C.; Kazar, D. B. A multivariate analysis of some operant variables used in behavioral pharmacology. Psychopharmacology (Berlin) 74:182–186; 1981.
40. Wetherington, C. L.; Lucas, T. R. A note on fitting Herrnstein's equation. J. Exp. Anal. Behav. 34:199–206; 1980.
41. Wise, R. A. Neuroleptic attenuation of intracranial self-stimulation: reward or performance deficits? Life Sci. 22:535–542; 1978.
42. Wise, R. A. Neuroleptics and operant behavior: The anhedonia hypothesis. Behav. Brain Sci. 5:39–87; 1982.