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BRIEF COMMUNICATION

Effects of Chlorpromazine on Avoidance and Escape Responding in Humans[1,2]

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FISCHMAN, M. W., R. C. SMITH AND C. R. SCHUSTER. *Effects of chlorpromazine on avoidance and escape responding in humans.* PHARMAC. BIOCHEM. BEHAV. 4(1) 111–114, 1976. – The effects of chlorpromazine on shock avoidance and escape responding were determined using four human subjects lever pressing on a modified free operant avoidance schedule. Doses of chlorpromazine ranging from 50 to 100 mg and shock levels ranging from 0.35 to 3.0 mA were used. In general, the results showed that chlorpromazine suppressed avoidance responding at doses which did not suppress escape responding.

Chlorpromazine Free operant avoidance Human subjects

IT has been found that certain phenothiazines, such as chlorpromazine, decrease responding which postpones the delivery of electric shock at doses which do not suppress escape responding [5, 9, 14]. Avoidance procedures have been used extensively, and despite considerable differences in experimental design, they have repeatedly been shown to be effective in differentiating drugs with this selective suppressant effect (notably the phenothiazine compounds and narcotic analgesics) from those psychotropic agents which do not have this property [3]. Because the avoidance-escape procedure provides a means of differentiating classes of drugs in infra-human organisms, it is important to determine whether similar selectivity can be demonstrated using man as the experimental organism. Cook [2], using this paradigm in man, reported that chlorpromazine has a specific suppressant effect on avoidance responding but not escape responding. In the present study a free operant avoidance schedule [13] with a provision for shock escape was utilized, and human volunteer subjects were tested over a series of experimental sessions during which shock level and dose of chlorpromazine were varied. The results obtained were similar to data which have been reported using infra-humans.

METHOD

Subjects

Four human female volunteers, ranging in age from 25–35 years were recruited from the local university community by advertising in the campus newspaper. Prior to beginning the series of experimental sessions, all subjects were interviewed and given a complete physical examination.

Procedure

Both behavioral and physiological measures were made during sessions in which either chlorpromazine or placebo were administered. Subjects were instructed to refrain from eating and taking any drugs for 12 hr prior to each 4 hr experimental session, which was carried out in a small (9 × 12 ft) hospital room. Subjects drank a 10 ml chlorpromazine or placebo solution flavored with quinine immediately after arrival. They waited in the experimental chamber for 1 hr while physiological measures (described below) were taken. A 1 hr experimental session, which included both physiological and behavioral measures was

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then conducted. During the third hr, only physiological measures were continued. Subjects remained in the experimental chamber during the fourth hr to insure dissipation of the major effects of the drug.

Physiological Measures

Blood pressure. Blood pressure was measured using an arm cuff at the beginning of the session and periodically during the fourth hr. The subject was free to leave when any hypotensive effects of the drug had dissipated.

Heart rate. Skin surface electrodes were attached to the subject's chest and arm 45 min after ingestion of drug or placebo. Heart rate was recorded on a Beckman Type R polygraph before, during, and for 1 hr after the 1 hr experimental session. Whenever shock was delivered to the subject, the heart rate electrodes were isolated from the polygraph in order to avoid the possibility of current flow through the subject's chest cavity.

Gastric acid secretion. The details of this part of the experiment have been reported elsewhere [15]. Subjects swallowed a Levine tube (No. 16 FR) 30 minutes prior to the measurement period, and gastric acid secretion was measured by continuously aspirating gastric secretions over a two-hour period, during and after the behavioral task.

Behavioral Measures

Prior to the start of the session, surface skin electrodes were firmly affixed to adjacent fingers of the subject's right hand. Shock was delivered by a Lafayette Master Shocker (Model 82401). Subjects, reclining on a hospital bed, pressed a hand-held push-button to avoid or escape shock on a free operant avoidance schedule [13]. If the subject did not respond at all, a 10 sec chain of half second pulses, each separated by 0.5 sec, was delivered every 30 sec (shock-shock interval). If the subject pressed the button during the 30 sec interval (an avoidance response) shock was delayed for 30 sec (response-shock interval). Any response which occurred during the shock (an escape response) terminated the shock and delayed its reoccurrance for 30 sec (response-shock interval).

Placebo was administered to subjects until responding became stable. Doses of 50, 75 and 100 mg of chlorpromazine, interspersed with placebo, were administered over 8 experimental sessions for each of the shock intensities used. The intensities of shock that were used were: 0.35 mA, 0.70 mA, 1.5 mA and 3.0 mA. The shock intensities used for 3 subjects were 0.35 mA and 0.70 mA. One of these subjects was also tested with 3.0 mA. A fourth subject was tested only using intensities of 1.5 and 3.0 mA

RESULTS

In general, as the dose of chlorpromazine was increased, the frequency of avoidance responding decreased, with relatively smaller effects on escape responding. In Fig. 1, data from 2 subjects are presented showing the effects of varying dose of chlorpromazine or shock intensity level on behavior maintained by the free operant avoidance schedule. This dose response relationship was not consistent

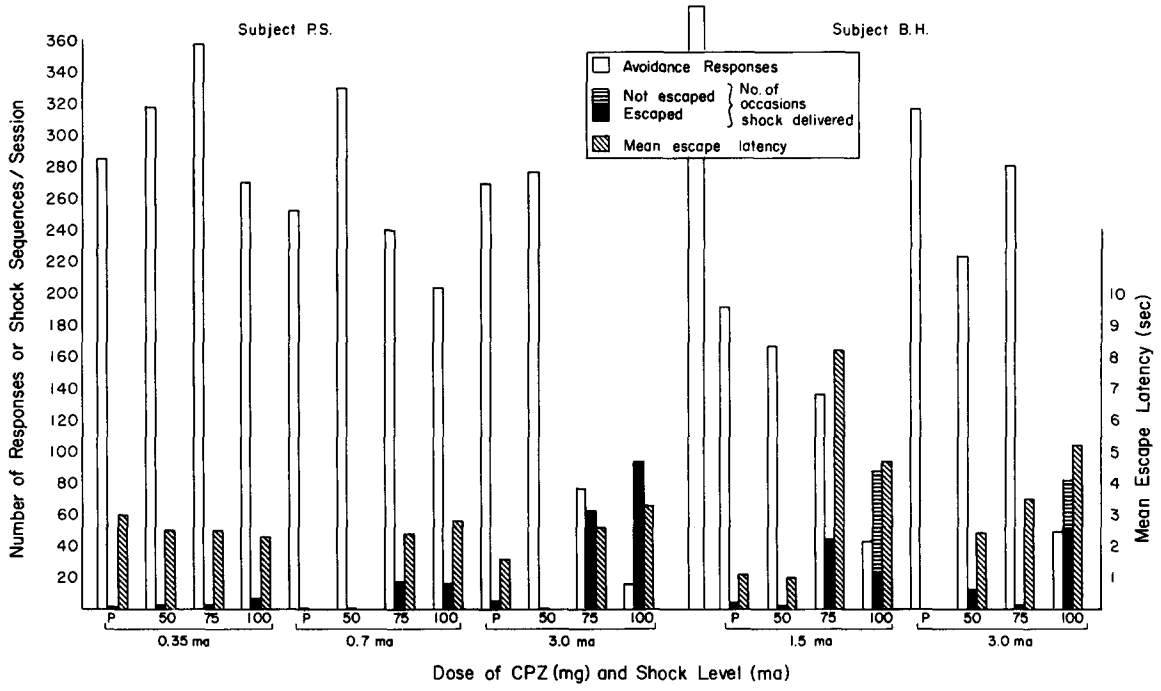

FIG. 1. The effects of varying dose of chlorpromazine and shock intensity level on behavior maintained by a free operant avoidance schedule in 2 humans. Subjects were given placebo (P) or 50, 75, or 100 mg of chlorpromazine and pressed a push button to avoid shock intensities of 0.35, 0.70, 1.5 or 3.0 mA. Baseline response rates were computed for each subject at each shock level using data from those days on which placebo was administered. The open bars represent the number of avoidance responses/session; closed bars represent the number of escape responses/session; horizontally striped bars indicate the number of occasions/session on which the shock was not escaped, and the diagonally striped bars show mean escape latency/session. Escape latency was adjusted to eliminate those occasions on which shock was not escaped.

TABLE 1

DATA FOR THE DOSE AND SHOCK LEVEL AT WHICH A MAXIMAL DIFFERENTIAL EFFECT ON AVOIDANCE AND ESCAPE RESPONDING WAS MEASURED

	Subject			
	P.S.	B.H.	C.D.	S.B.
Shock Level (mA)	3.0	1.5	0.35	0.35
Dose of CPZ (mg)	100	75	100	50
No. of Avoidance Responses				
Placebo	270	192	388	252
CPZ	16	136	161	132
No. of Occasions Shock Delivered				
Placebo	5	4	10	3
CPZ	94	44	57	48
No. of Occasions Shock Series Not Escaped				
Placebo	0	0	0	1
CPZ	0	0	6	1
Escape Latency				
Placebo	1.6	1.1	3.3	8.0
CPZ	3.2	8.1	4.7	4.6

at all shock intensities, as can be seen for subject P.S. at 0.35 mA. When drug was administered, suppression of avoidance responding appeared to increase as intensity of the shock was increased. Escape responding was also related to shock level, increasing as shock intensity was increased. These results were true for all 4 subjects. Subject P.S. terminated all shock series, and therefore shows no occasions on which shock was not escaped. The other 3 subjects generally emitted escape responses when shock was delivered, but for each subject, some occasions occurred during which shock was not escaped. For these subjects, frequency of unescaped shocks was directly related to the dose of chlorpromazine.

The effects of CPZ showed variability; there was, however, for each subject, a dose and shock level which had clear differential effects on avoidance and escape responding. These data are presented in Table 1. It can be seen that at these selected drug and shock levels, CPZ decreased avoidance responding and caused a marked increase in escape responding. Except for subject C.D., who did not escape on 6 occasions, there was no increase in occasions on which shock was not escaped when drug and placebo days are compared. On the other hand, it is apparent that the differential effect of CPZ is not absolute since escape latency did increase in 3 out of the 4 subjects.

Heart rate was sufficiently variable on placebo days so that no consistent drug or intensity effect could be discerned. In addition, the baseline range was such that within session changes were too variable to warrant analysis. Blood pressure remained fairly constant for each subject within placebo sessions. A mild hypotension, which was not dose related, occurred after drug in some subjects; the greatest change in blood pressure was seen approximately 2–3 hr after CPZ and generally returned to baseline within 4–4-1/2 hours after drug ingestion.

DISCUSSION

The results of this study support the frequently reported specificity of the suppressant effect of phenothiazines on

avoidance behavior relative to escape behavior. This specificity has been noted utilizing a wide variety of responses and techniques, primarily with infra-human organisms [3]. There is, however, one report of a similar effect in a human subject when a modified free operant avoidance procedure was employed [2]. The present study, using the same procedure, has corroborated the generality of these results. It was found that avoidance responding in human subjects generally decreased in a dose-related fashion following the administration of chlorpromazine, a result which has also been reported for infra-human organisms avoiding shock on a comparable avoidance schedule [4, 6, 7, 8].

The data obtained in the present study suggest that the suppressant effect of chlorpromazine on avoidance behavior, and the concomittant increase in escape responding was facilitated as shock intensity was increased. These data are contrary to what might be anticipated. Irwin [10] has reported that animals trained on a discrete avoidance task become more resistant to drugs which suppress avoidance behavior as the intensity of the aversive unconditioned stimulus is increased. In addition, Posluns [12], has reported that the effect of CPZ on avoidance responding in rats was the same regardless of whether the shock intensity was 1.2 mA or 2.8 mA. On the other hand, it has been reported that in the absence of drug, avoidance responding increased and shocks delivered decrease as shock intensity is increased [1,11]. It is possible that the data reported here are confounded by a procedural variable. Because this study was designed to explore the parameters of many of the variables involved, shock intensity was started low for each subject and always changed in ascending order. The results obtained may, in fact, represent habituation or adaptation to shock interacting with the change in shock intensity levels. In light of this, before any conclusions based on the effects of increasing shock intensity can be drawn, shock intensity must be varied in a counterbalanced order.

The effects of CPZ on escape responding have traditionally been assesed utilizing discrete avoidance-escape procedures in which shock presentation is signalled by the presentation of a discriminative stimulus for a fixed period of time prior to shock onset. A response during the period of time when the discriminative stimulus is on, is followed by a time-out period, during which no contingencies are programmed. If the subject does not respond, shock, which can be escaped by responding, is delivered. However, it has been pointed out that drug effects obtained with these procedures are confounded by the fact that different stimuli controlling the avoidance response (e.g., light or tone) can effect the sensitivity of the response to drugs [8]. The greater variability in the dose-response relationships seen in the present study as compared to studies utilizing discrete avoidance procedures may be partially due to these procedural differences. In addition, there is always the problem when using human subjects as opposed to laboratory animals, of not having control over all environmental conditions and previous histories. In spite of these differences the similarity of the effect of chlorpromazine on avoidance and escape responding is impressive.

The present study indicates that this procedure, found to be sensitive and selective with respect to specific drug actions in animals, can be utilized to extend the analysis of the behavioral actions of psychotropic drugs in normal humans. The results, although preliminary, were comparable to, if somewhat more variable than, those obtained with infra-human organisms under a wide variety of experimental conditions.

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