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Effects of Triazolam on Human Aggressive, Escape and Point-Maintained Responding

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CHEREK, D. R., R. SPIGA, J. D. ROACHE AND K. A. COWAN. *Effects of triazolam on human aggressive, escape and point-maintained responding.* PHARMACOL BIOCHEM BEHAV **40**(4) 835–839, 1991.—Placebo and triazolam (0.125, 0.25 and 0.5 mg/70 kg of body weight) were administered to male subjects under double-blind conditions prior to experimental sessions which provided three operant response options. These options were: 1) responding maintained by the presentation of points exchangeable for money, 2) responding which ostensibly resulted in the subtraction of points from a fictitious person was termed aggressive since this responding resulted in the delivery of an aversive stimulus to another person, and 3) responding which ostensibly protected the subject's point counter from subtractions initiated by the other person and was termed escape. Aggressive and escape responding were initiated by subtracting points from the subject. Point subtractions were attributed to the other person. Aggressive and escape responding were maintained by initiation of provocation-free intervals (PFI), during which no further point subtractions were presented. Triazolam produced dose-dependent decreases in point-maintained and escape responding. The effects of triazolam on aggressive responding varied across subjects.

Aggression Escape Human Operant Triazolam

BENZODIAZEPINES have varied effects upon human aggressive behavior. Typically, administration of benzodiazepines to psychiatric patients has been reported to diminish aggressive behavior (8,12). At the same time, benzodiazepines, most notably diazepam, have resulted in so-called "paradoxical" increases in aggressive behavior among some patients (4, 10, 13, 15, 17). Since most of these clinical reports were based upon individual cases under less rigorous conditions, some investigators (3) have suggested that studies should be conducted employing objective measures of aggressive behavior under controlled laboratory conditions. Taylor and his colleagues (14,21) have conducted two studies employing the competitive reaction time task (19). Both of these studies observed that ten mg of diazepam increased the intensity of shock settings set for fictitious opponents among college students. Recently, we have published a study (9) in which diazepam produced increased and decreased aggressive responding across different subjects.

The present study was conducted to determine the effects of another benzodiazepine, triazolam, on aggressive responding. In addition, we employed a three-option procedure which provided subjects with an escape response option in addition to the aggressive and point-maintained response options. The escape responding was occasioned by the same stimulus, point subtractions, and maintained by the same consequence as the aggressive responding. The addition of an escape option allows us to compare drug effects on two behaviors maintained by the same consequence, but which differ in their content as established by instructions. Our previous research had indicated that both aggressive and escape responding were maintained over repeated sessions, with large individual differences in the response option selected and frequency of responding (6).

METHOD

Subjects

Five male volunteers (age range 25–36 years) participated after giving their informed consent. Subjects were recruited by newspaper advertisements soliciting participation in behavior research projects. In order to minimize possible interactions among subjects, students and employees of the medical center were excluded. Subjects were given a mental status exam, a structured psychiatric interview using the Schedule for Affective Disorders and Schizophrenia Lifetime Version (SADS-L) and a physical examination. Subjects were excluded if any current or previous psychiatric disorder, including alcoholism and substance abuse, or physical illness was detected. Subjects that reported the use of any licit or illicit drug (except alcohol, caffeine and nicotine) were excluded. These subjects reported little if any drug use history other than alcohol, none of the subjects had previous experience with benzodiazepines.

To avoid problems with drug usage by our subjects during the study, urine samples were collected throughout the study and screened for the presence of drugs. Breath alcohol levels were determined using an Intoximeter Model 3000 III, prior to each daily session. Detection of any drug in the subject's urine sam-

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ple or alcohol in the subject's expired air sample resulted in the removal of the subject from the study.

Instructions

The research project was described as a study of the effects of triazolam on motor performance and that the investigators were interested in how efficiently subjects responded on a monetary reinforced task. Subjects were told that it was very important to arrive on time each day because there were several other persons scheduled to arrive the same time, one of whom the subject would interact with during each session. Prior to their first session subjects were read the following instructions:

> Your console will be linked to one of several other consoles just like it during sessions. Other individuals just like you will be seated at the same kind of consoles. These consoles are located at another facility.
>
> When the session starts the light will not be illuminated and the digital counter will be at zero. If you pull lever A, the light labelled A will illuminate. Pulling lever A until the A light goes off advances your counter by one point. Every point is worth ten cents. As your counter advances, the green light just above the counter will flash briefly. When the A light goes off, you can pull lever A, B or C, or do nothing.
>
> During the session the red light below the counter may flash briefly and one point will be subtracted from your counter. The person you were paired with during that session subtracted this point by pulling his B lever. The point that this person subtracted from your counter will be added to his counter.
>
> If you pull lever B, the light labelled B will illuminate. Pulling lever B until the B light goes off results in the subtraction of a point from the counter of the person who is connected to your console. When the B light goes off, you can pull lever A, B or C, or do nothing. If you subtract a point, it will not be added to your counter. Remember, points the other persons subtract from you are added to their counters.
>
> If you pull lever C, the light labelled C will illuminate. Pulling lever C until the C light goes off will protect your counter from point subtractions for some period of time. When the C light goes off, you can pull lever A, B or C, or do nothing.
>
> If you pull a lever while the corresponding light is off, those responses will have no effect. Once you pull a lever, only that lever will be available until the corresponding light is off. You may select another lever only when all the lights (A, B, and C) are off.
>
> At the end of the session you can exchange your points for money. How much you earn depends on how rapidly you pull lever A. As a general rule, the more rapidly you pull lever A, the more points and money you will earn. If lever A responses occur very close together, only the first response will be counted. Thus, very rapid lever A responding may delay point presentations. You will be paid this money at the end of the day.

Response Measures

Subjects were able to pull either lever A, B or C mounted on a response console (HTC-603, BRS/LVE) during six daily experimental sessions. The nonaggressive response option resulted in the presentation of points exchangeable for money. Pulling lever A was maintained by a fixed ratio (FR) 100 schedule of point presentation (i.e., 100 consecutive pulls produced one point). Subjects were paid ten cents for each point remaining on the counter at the end of each session. Lever A responses occurring less than 0.17 s after the previous response did not count toward the completion of the FR 100 response requirement. Subjects typically responded at high rates (4–5 resp/s), and 10–20% of their responses did not count toward the FR 100. This temporal contingency maintained a relatively constant frequency of point presentations despite changes in response rate.

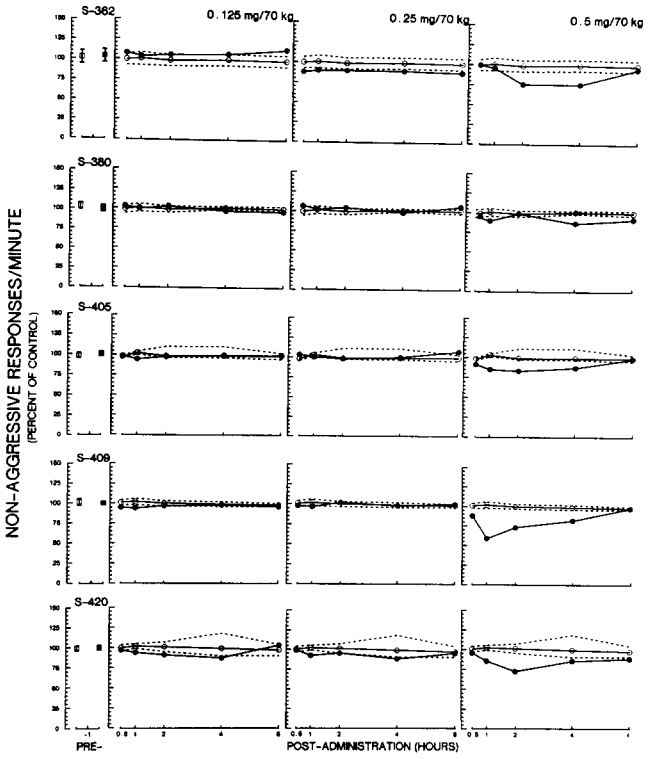

FIG. 1. The effects of placebo (open circles) and triazolam (filled circles) on nonaggressive point-maintained responding. Data points on the far left labelled Pre- and -1 are the mean values of the six sessions preceding placebo sessions the day before triazolam administration and the six sessions preceding administration of triazolam. Mean values for the five sessions following placebo and triazolam sessions are shown on the right and separately for each triazolam dose. The dashed lines represent the 95% confidence intervals for the placebo values.

The aggressive response option was pulling lever B which ostensibly delivered an aversive stimulus (point subtraction) to another person following the completion of each fixed ratio (FR) 10 on lever B.

The escape response option was pulling lever C which ostensibly protected the subject's counter for some period of time from point subtractions initiated by the fictitious other person following the completion of each fixed ratio (FR) 10 on lever C.

These three response options were concurrently available as nonreversible options. The first response on any lever illuminated the corresponding stimulus light (e.g., pulling lever A illuminated stimulus light A), and inactivated the other two levers. When the ratio requirement for the selected lever was completed (either 100 or 10 responses), the stimulus light for that lever was extinguished and all three response options became available.

Provocations (Point Subtractions)

Aggressive and escape responses were initiated by subtracting points from the research subjects. These provoking point

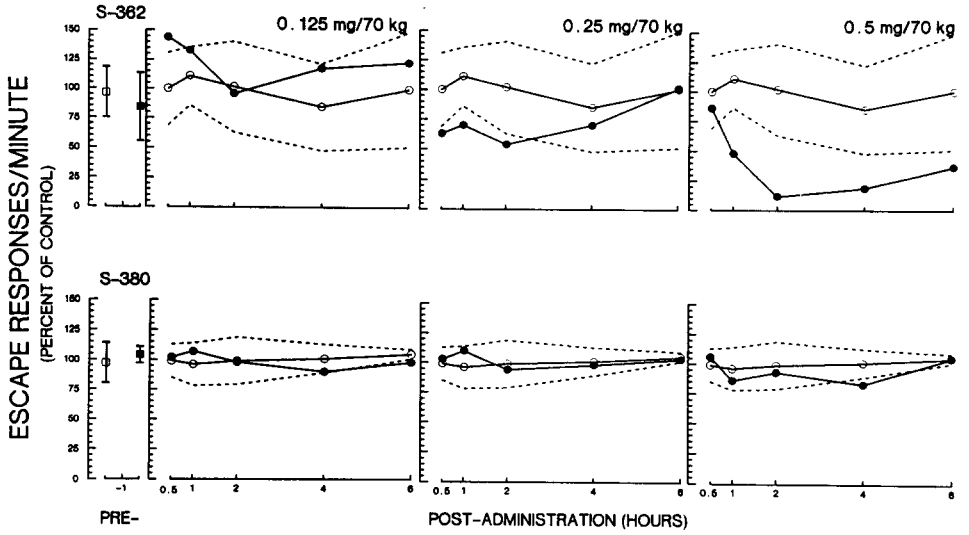

FIG. 2. The effects of placebo (open circles) and triazolam (filled circles) on escape responding. Data points on the far left labelled Pre- and -1 are the mean values of the six sessions preceding placebo sessions the day before triazolam administration and the six sessions preceding administration of triazolam. Mean values for the five sessions following placebo and triazolam sessions are shown on the right and separately for each triazolam dose. The dashed lines represent the 95% confidence intervals for the placebo values.

subtractions were: (a) attributed to the other person, (b) signalled by an audible click and illumination of a stimulus light mounted on the counter, and (c) were scheduled to occur at random times throughout the daily experimental session.

Consequences of the Subject's Aggressive and Escape Responses

Completion of the FR 10 on lever B or C initiated a 125-s provocation-free interval (PFI) during which point subtractions were not presented. At least one point subtraction was presented to the subject before aggressive or escape responses resulted in the initiation of a PFI. Following the termination of the PFI, at least one point subtraction was presented before aggressive or escape responses initiated another PFI. Thus subjects periodically received point subtractions throughout each session (9–17/session).

As a result of this contingency, the subject's aggressive or escape responding resulted in a temporary reduction in provocation (i.e., a suppression of or escape from the other person's aggressive responding directed at the subject). This contingency served to maintain the subject's aggressive and/or escape responding over sessions and allowed dose-response determination which required extended periods of time. Without such a contingency, aggressive responding will not be maintained (7).

Triazolam

All research subjects came into the medical center five days per week and participated in six 25-min experimental sessions each day at 0825, 0930, 1000, 1100, 1300 and 1500 h. At 0900, subjects were required to swallow a No. 00 gelatin capsule containing either placebo or triazolam. The triazolam was administered in doses of 0.125, 0.25 and 0.5 mg per 70 kg of body weight. Successive drug doses were separated by at least 96 hours and were administered when the responding during placebo sessions was within variability ranges observed prior to drug administration. All placebo and drug doses were administered double-blind. Drug doses were presented initially in an ascending sequence and then randomly over successive sessions, with each drug dose administered twice.

Questionnaires

Subjects completed the Profile of Mood States (POMS) and the Addiction Research Center Inventory (ARCI) 49-item short form questionnaires before drug administration and at the end of the third session of the day, approximately 1.5 h after drug administration (18).

Debriefing

During their participation, subjects completed questionnaires at the end of each day to determine if the instructional deception had been successful and subjects thought they were paired with other subjects during the experiment. Research subjects were not actually paired with other people, and they were debriefed and informed of this at the end of the experiment.

Statistical Analysis

The effects of triazolam on point-maintained, aggressive and escape responding were evaluated descriptively by calculating the 95% Confidence Intervals for placebo sessions, and the mean values of the two observations at each triazolam dose. Placebo sessions on days immediately preceding drug administration were used. If the mean value for a particular time point following triazolam administration was outside the 95% Confidence Interval then that value was described as significantly different from placebo. POMS and ARCI data were analyzed by repeated measures ANOVA with the factors of drug (triazolam vs. placebo), dose, order (1st or 2nd dose occasion) and time (pre- vs. post-drug). In the absence of significant order effects, this factor was pooled into the error term for all subsequent F-tests (1).

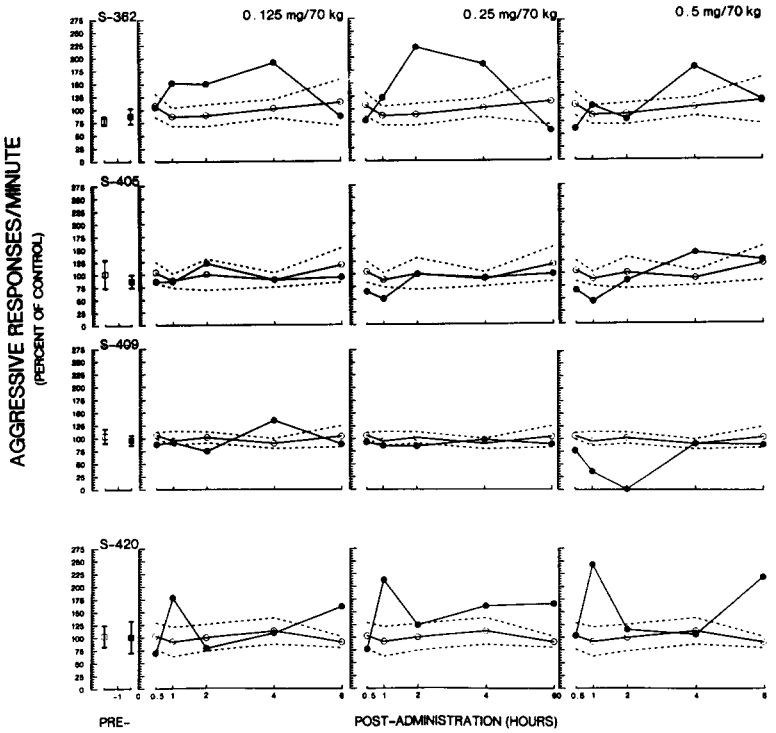

FIG. 3. The effects of placebo (open circles) and triazolam (filled circled) on aggressive responding. Data points on the far left labelled Pre- and -1 are the mean values of the six sessions preceding placebo sessions the day before triazolam administration and the six sessions preceding administration of triazolam. Mean values for the five sessions following placebo and triazolam sessions are shown on the right and separately for each triazolam dose. The dashed lines represent the 95% confidence intervals for the placebo values.

RESULTS

The effects of placebo and three doses of triazolam (0.125, 0.25 and 0.5 mg per 70 kg) on nonaggressive point-maintained responding for all subjects are shown in Fig. 1. Data points for placebo (open circles) and triazolam (closed circles) are expressed as a percentage of responses during the first session of the day prior to placebo or drug administration. Three subjects had a slight decrease in point-maintained responding one hour after triazolam administration at the lower doses (0.125 and 0.25 mg per 70 kg). All five subjects had significant decreases in point-maintained responding which peaked at 1 or 2 hours following administration of the highest dose. Responding remained suppressed until six hours after the 0.5 mg/70 kg dose.

The effects of placebo and three doses of triazolam on escape responding are shown in Fig. 2. Only two of the five subjects responded on the escape option. For subject S-362 the 0.25 and 0.5 mg/70 kg doses produced very large decreases in escape responding, with responding remaining suppressed throughout the day following the highest dose. The other subject was less sensitive to triazolam, but did show slight decreases in escape responding after the highest dose. This subject S-380 also displayed only minimal suppression of point-maintained responding.

The effects of placebo and three doses of triazolam on aggressive responding are shown in Fig. 3. Dose-dependent decreases in aggressive responding following triazolam administration occurred in two subjects (S-405 and S-409). Subject S-362 increased aggressive responding at the two lower doses, while subject S-420 showed dose-dependent increases in aggressive responding one hour following triazolam administration.

ANOVA's conducted on the POMS and ARCI data detected significant ($p<0.05$) drug × dose × time interactions on the PCAG scale of the ARCI and the fatigue and confusion scales of the POMS. On each of these measures, triazolam produced dose-related increases at the postdrug time point indicating that a significant sedative effect of triazolam was reported by subjects. Triazolam-induced sedation was most sensitively detected by the PCAG scale which detected effects of even the lowest (0.125 mg) dose of triazolam.

DISCUSSION

Peak suppression of point-maintained and escape responding were observed at 1–2 hours following triazolam administration. Peak plasma concentrations of triazolam have been observed following oral administration at these same time points (20). The general rate-suppressing effects of triazolam on point-maintained responding are similar to those observed for diazepam (9).

The rate-decreasing effects of triazolam on escape responding are consistent with some reports of benzodiazepine suppression of escape responding in nonhuman subjects (11,16). It is interesting to note that triazolam produced increased aggressive responding in some subjects, while escape responding was not increased, even though both responses were maintained by the same contingency.

The effects of triazolam on aggressive responding in the present study were similar to the effects of diazepam reported in

an earlier study (9). In both studies, the highest doses (10 mg/70 kg diazepam and 0.5 mg/70 kg triazolam) increased aggressive responding of some subjects and decreased aggressive responding of other subjects.

Under controlled laboratory conditions some normal subjects increased aggressive responding following triazolam administration. How this relates to reports (2) of increased hostility following triazolam use in patients is unclear. The small number of patients in these reports, and the small number of subjects in the present study necessitate further research.

The important conclusion is that sedative drugs like triazolam can have predictable effects on certain behaviors such as point-maintained responding and escape responding. Other social behaviors (i.e., aggressive behavior) are not affected by triazolam in a highly predictable manner and can have very different effects across a variety of individuals. With these behaviors, individual subject variables appear to be a major determinant of drug effects rather than the pharmacological profile of the compound.

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