Effects of clonazepam and ethosuximide on the responding of pigeons under a fixed-consecutive-number schedule with and without an external discriminative stimulus

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Abstract. The effects of the anticonvulsant drugs clonazepam and ethosuximide were examined in pigeons performing under a fixed-consecutive-number schedule with and without an added external discriminative stimulus. Under these schedules, food was delivered whenever subjects responded between and 8 and 12 times on one response key (work key), and then responded once on a second response key (reinforcement key). For one group, an external discriminative stimulus signalled completion of the response requirement on the work key, while no stimulus change was programmed for the other group. Clonazepam (0.06–0.75 mg/kg) produced dose-dependent decreases in percentage of reinforced runs and rate of responding for both groups. The magnitude of the accuracy-decreasing effect was generally greater in the group without the external discriminative stimulus. For this group, the higher doses of clonazepam produced pronounced increases in switching to the reinforcement key before completing the minimum requirement of eight consecutive responses on the work key. No consistent patterns of errors were evident for the subjects with the added external discriminative stimulus. Although ethosuximide (20–160 mg/kg) produced dose-dependent decreases in rate of responding, it had little effect on the percentage of reinforced runs or the run length distributions. These findings are consistent with previous reports indicating that clonazepam, but not ethosuximide, substantially disrupts performance under operant tasks requiring conditional discriminations. These data also suggest that the addition of an external discrimination stimulus attenuates the disruptive behavioral effects of clonazepam.

Key words: Fixed-consecutive-number – Clonazepam – Ethosuximide – Stimulus control – Pigeons

During the past decade, much attention has been focused on the effects of anticonvulsant medications in humans and nonhumans (see Poling and Picker 1985; Trimble and Reynolds 1976; Woodbury et al. 1982). Although much is currently known about the ability of these drugs to manage seizures, their behavioral effects are not clearly understood (Gibbs et al. 1982). Given that drugs prescribed specifically for their anticonvulsant properties come from diverse chemical classes (e.g., benzodiazepines, barbiturates), it is not surprising that the behavioral effects of these drugs differ quantitatively as well as qualitatively (for reviews see Poling and Picker 1985; Gibbs et al. 1982). Picker and associates (Picker and Poling 1984; Picker et al. 1985a; Poling et al. 1985b), for example, reported that clonazepam, a benzodiazepine effective in managing absence seizures and atypical seizures associated with Lennox-Gastaut’s syndrome and West’s syndrome, produced dose-dependent decreases in accuracy of pigeons performing under repeated acquisition of response chains and delayed-matching-to-sample procedures. Ethosuximide, a succinimide that is also effective in managing absence seizures, produced quite different effects; under both procedures ethosuximide had no effect on accuracy, although the drug was behaviorally active as evidenced by large drug-induced decreases in rates of responding.

Different behavioral effects have also been reported for these drugs when administered to pigeons responding under automaintenance and negative automaintenance procedures, but not under fixed-interval and fixed-ratio schedules of food delivery. Under negative automaintenance and automaintenance procedures, clonazepam typically increases rate of responding, whereas ethosuximide fails to do so (Picker et al. 1985a). Both clonazepam and ethosuximide, however, nonselectively decrease high-rate and low-rate operant responding (Poling and Picker 1985; Poling et al 1985a). Even though it is clear that these drugs posses different behavioral profiles in nonhumans, it has yet to be determined to what extent these effects can be modulated by external discriminative stimuli.

One procedure that has been used to evaluate control by external stimuli as a determinant of drug effects is the fixed-consecutive-number (FCN) schedule. Under this schedule, subjects are required to respond a fixed number of times on one operandum (work operandum), and then respond once on a second operandum (reinforcement operandum). Responding on the reinforcement operandum before the response requirement on the work operandum is completed resets the response requirement. Under one variant of the FCN schedule, an external discriminative stimulus signals the completion of the response requirement on the work operandum, while under the other no external stimulus change is programmed.

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Two experiments have indicated that there are substantial differences in the magnitude of the accuracy-decreasing effects of various neuroleptics under these procedures. Chlorpromazine, a phenothiazine neuroleptic, decreases the percentage of reinforced runs of pigeons responding under both variants of the FCN schedule, whereas pimozide, a neuroleptic of the diphenylbutylamine family, decreases the percentage of reinforced runs only under the FCN schedule without an added external discrimination stimulus (Laties 1972; Szostak and Tombaugh 1981). Such differential effects have also been reported with psychomotor stimulants, such as d-amphetamine, methylphenidate, and caffeine, and the anticholinergic drug scopolamine (Latties et al. 1981; Mechner and Latranyi 1963; Wagman and Maxey 1969). These data clearly suggest that drugs representative of the same therapeutic class can differ substantially in the extent to which their behavioral effects are modulated by external discriminative stimuli.

The purpose of the present experiment was to examine the effects of clonazepam and ethosuximide on the performance of pigeons under FCN schedules. As noted above, previous investigations have indicated that these drugs possess different profiles of behavioral actions, but it is not clear to what extent their effects can be modulated by external discriminative stimuli.

Materials and methods

Subjects. Eight White Carneaux pigeons, maintained at approximately 80% of their free feeding body weights (375–490 g) served as subjects. Each bird was individually housed with free access to grit and water in a constantly illuminated room. Subjects P375, P3333, P2121, and P3286 were experimentally naive at the start of the experiment, whereas subjects P2408, P5153, P10748, and P1236 had previous exposure to simple fixed-ratio (FR) schedules of food delivery.

Apparatus. Four plastic, wood, and aluminum pigeon chambers measuring approximately 32 cm long, 36 cm high, and 35 cm wide, were used as the experimental environments. In each chamber, three response keys 2.5 cm in diameter were located 23 cm from the bottom of the work panel, approximately 5.5 cm apart. Each key could be transilluminated either white or red. An aperture horizontally centered on the work panel 7.5 cm above the floor allowed access to a magazine filled with mixed grain when the magazine was raised. When raised, the magazine was illuminated by a 7-W white bulb. A 7-W bulb centrally mounted 33 cm above the chamber floor provided ambient illumination, and white noise masked extraneous sounds.

Scheduling of experimental events and data collection were controlled by a Digital Equipment Corporation (Maynard, MA) PDP8/A minicomputer using interfacing and software (SUPERSKED) provided by State Systems Inc. (Kalamazoo, MI).

Behavioral procedure. Experimentally naive subjects were initially trained to eat from the raised food magazine, and then keypecking was engendered by a forward pairing autoshaping procedure as described by Brown and Jenkins (1968). Once keypecking was reliably established for these birds, all birds were divided into two groups. Each group consisted of two experimentally naive birds and two birds with previous exposure to FR schedules of food delivery. During the initial training session for the group designated as FCN 8, the two operative response keys were illuminated white and at least one keypeck response on the right response key (work key) followed by a keypeck on the center response key (reinforcement key) produced 3-s access to mixed grain. Twenty consecutive responses (upper limit) on the work key or multiple responses on the reinforcement key produced a 2-s timeout. During the timeout, the houselight and keylights were darkened and responses had no programmed consequences. Over the next few sessions, the number of responses required on the work key before a response on the reinforcement key was reinforced was rapidly increased to eight. Under this final schedule, food was delivered only if the subject responded between 8 and 12 times on the work key and then responded once on the reinforcement key (reinforced run); all other patterns of responding produced a 2-s timeout and reset the response requirement on the work key. Experimental sessions terminated after 40 reinforcers or 40 min, whichever came first. Sessions were conducted 6 days per week at about the same time each day.

For the second group of subjects the color of the work key was changed from white to red when the minimum designated response requirement on the work key was completed; this requirement was initially 1 but was rapidly increased to 8. Responding more than 8 times but less than 13 times on the work key had no effect on the color of key illumination. As under the FCN 8 schedule, at the end of timeouts the response keys were again illuminated in white. This schedule will be abbreviated as FCN 8-Sp.

Pharmacological procedure. When the percentage of reinforced runs for individual birds showed no visually evident trend across five consecutive sessions (a range across subjects from 20 to 44 sessions) five doses of clonazepam (0.06, 0.13, 0.25, 0.5, and 0.75 mg/kg) and five doses of ethosuximide (20, 40, 80, 120, and 160 mg/kg) were administered. Drugs were given in a BBCDBBCD design where B represents baseline sessions (no injection), C vehicle control sessions, and D drug sessions. Drugs and vehicle control were injected IM 30 min prior to the experimental session at an injection volume of 1 ml/kg. Each bird received each dose of clonazepam and then each dose of ethosuximide, and drug doses were administered in an irregular order that varied across birds. Clonazepam (Hoffman-La Roche, Nutley, NJ) was dissolved in a solution consisting of 98% propylene glycol and 2% ethyl alcohol. (Previous studies conducted in our laboratory have indicated that this solution is not behaviorally active when given to pigeons responding under conditional discriminations (Picker and Poling 1984; Picker et al 1985 b). These studies also indicated that repeated administrations of propylene glycol can promote scarring at the site of injection. Thus, to minimize damage at the injection site propylene glycol was not administered as the control vehicle in the present study). Isotonic saline alone served as the vehicle for ethosuximide (Warner-Lambert, Ann Arbor, MI) and as the vehicle control for both drugs. Doses for both drugs are expressed as the base.

Results

Control responding. Control data indicated that the FCN 8-Sp resulted in higher levels of accuracy than the FCN 8 (Figs. 1 and 2). For subjects exposed to the FCN 8 (upper