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Tolerance to Suppressive Effects of Chlordiazepoxide on Operant Behavior: Lack of Cross Tolerance to Pentobarbital[1]

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CESARE, D. A. AND J. W. McKEARNEY. *Tolerance to suppresive effects of chlordiazepoxide on operant behavior: Lack of cross tolerance to pentobarbital.* PHARMAC. BIOCHEM. BEHAV. 13(4) 545–548, 1980.—Pigeons responded under schedules in which either the 60th response (fixed-ratio schedule) or the first response after 3 minutes (fixed-interval schedule) resulted in food delivery. The effects of chlordiazepoxide HCl (1–30 mg/kg) and pentobarbital sodium (1–17 mg/kg) were determined before and during chronic daily exposure to either 10 or 17 mg/kg chlordiazepoxide—doses that markedly suppressed responding when given acutely. After about three weeks of daily injections of chlordiazepoxide, there was at least a three-fold shift to the right of the dose-effect curve for chlordiazepoxide, but not consistent change in the effects of pentobarbital.

Chlordiazepoxide Pentobarbital Tolerance Cross-tolerance Pigeons Schedule-controlled behavior

IN addition to other common effects, many of the behavioral actions of benzodiazepines and barbiturates are very similar. For example, both increase relatively low rates of responding under a variety of conditions [1,3] and both increase behaviors that have been suppressed by response-produced noxious stimuli such as electric shock [2,5]. However, little is known about the extent to which the initially similar effects of these drugs might differ when they are administered on a long-term chronic basis. The present experiments sought to determine the extent to which cross-tolerance to the behavioral effects of pentobarbital might be evident in animals exhibiting tolerance to the behavioral effects of chlordiazepoxide.

METHOD

Four adult male White Carneaux pigeons were maintained at approximately 80% of free-feeding body weights. All had extensive prior experience under a variety of reinforcement schedules and with a variety of drugs, but none had received drugs for several months prior to these experiments.

Experiments were conducted in isolation chambers equipped with stimulus lights, automatic feeding mechanisms, and response keys. Pigeons 111 and 116 responded under a fixed-ratio (FR) schedule in which each 60th peck on the response key resulted in food presentation (4 sec access to mixed grain). Pigeons 106 and 1312 responded under a 3-min fixed-interval (FI) schedule, in which the first response to occur after 3 min resulted in food presentation. Under both schedules there was a 3-min period of darkness in which responding had no consequences following each food delivery (time-out period). If 60 responses were not made within 60 sec under the FR schedule, or if a response was not made within 60 sec of the end of the 3-min period under the FI schedule, the time-out period alone was presented. Experimental sessions were usually conducted 5 days weekly, and were about 45 min in duration.

Chlordiazepoxide HCl (courtesy of Hoffman-LaRoche) and pentobarbital sodium (Abbott) were dissolved in 0.9% sodium chloride solution and injected into the breast muscle immediately before experimental sessions. The injection volume was usually 0.5 ml/kg, and all doses are expressed as the total salts.

During the first phase of the experiments, the effects of various acutely administered doses of chlordiazepoxide and pentobarbital were determined. During this phase, drugs were injected no more than twice weekly (generally on Tuesdays and Fridays, with Thursday's performance serving as control). In the chronic dosing phase of the experiments, rate-decreasing doses of chlordiazepoxide (10 or 17 mg/kg) were injected daily, but experimental sessions were conducted only on Monday through Friday. After 20 or 21 days of chronic dosing, the effects of various doses of both drugs were redetermined (again, on Tuesdays and Fridays). On these test days, animals received either a different dose of

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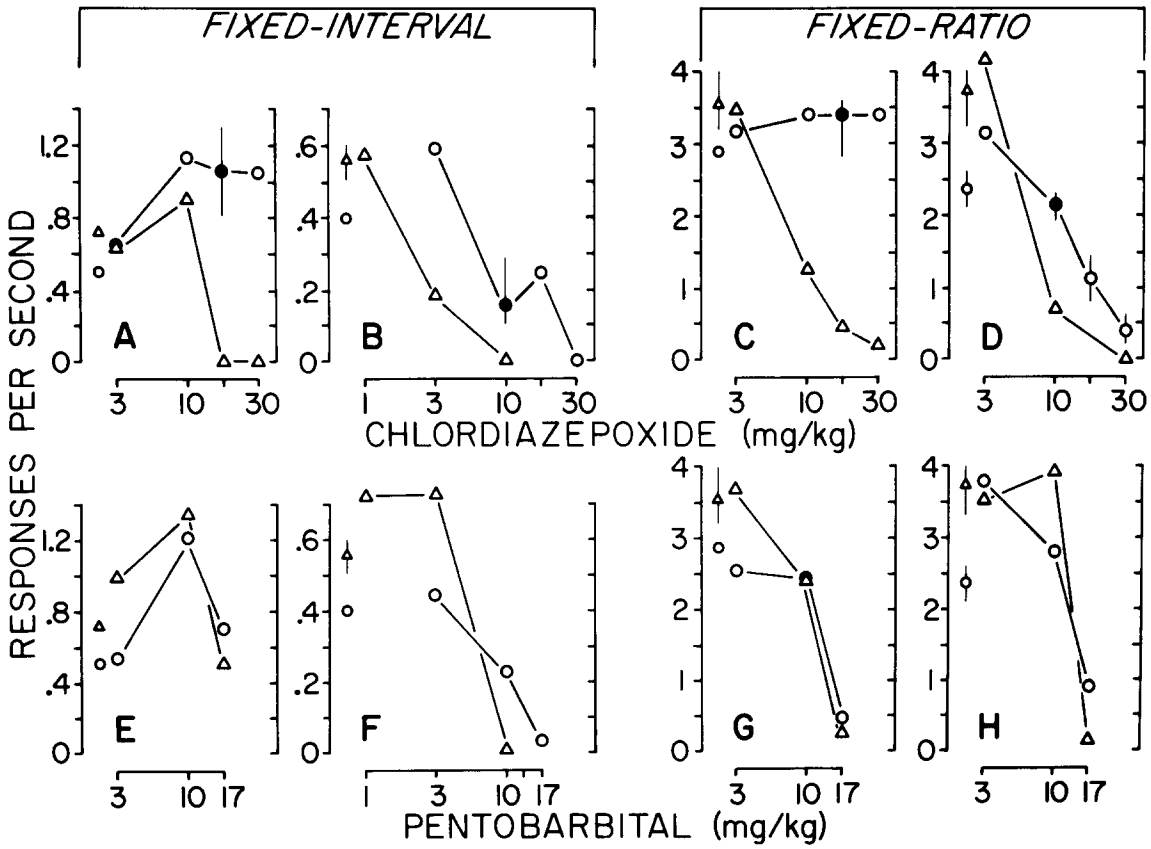

FIG. 1. Effects of chlordiazepoxide (upper) and pentobarbital (lower) on rates of responding before and during chronic exposure to chlordiazepoxide. △———△: effects prior to chronic exposure. ○———○: effects during daily exposure to chlordiazepoxide. Panels A through H summarize individual data for four pigeons. Unconnected triangles at the left are means of 4 non-drug control sessions; vertical lines indicate ranges where falling outside the point. Unconnected circles at the left represent the effects of saline rather than chloridazepoxide administered before sessions during the chronic chlordiazepoxide phase (single determinations for B, F, C, G, and duplicate for others; vertical lines indicate ranges where appropriate). Points are generally single determinations except for the dose of chlordiazepoxide that was chronically administered (●); these are means of 3 or 4 determinations with ranges indicated by vertical lines. The effects of 17 and 30 mg/kg chlordiazepoxide in panel D are means of duplicate observations. Note that there was at least a three-fold shift to the right in the effects of chlordiazepoxide during the chronic chlordiazepoxide phase, but that there were no marked systematic changes in the effects of pentobarbital.

chlordiazepoxide, a saline injection, or a dose of pentobarbital. Chlordiazepoxide was given daily throughout this period when dose-effect relations were being re-established. If an animal received a lower than normal injection of chlordiazepoxide on a test day, a supplementary injection was given after the session. Subjects receiving pentobarbital before the session on test days were likewise given the usual dose of chlordiazepoxide after the session. During all experimental phases, drugs and doses were studied in unsystematic mixed order.

RESULTS AND DISCUSSION

Control Performances

Under the FR schedule there was a brief pause and then a high rate of responding until food was presented. Under the FI schedule, a pause at the beginning of each interval was followed by a gradually increasing response rate. Little or no responding took place during time-out periods.

Acute Effects of Drugs

Figure 1 summarizes the effects of chlordiazepoxide (upper) and pentobarbital (lower) before and during chronic exposure to chlordiazepoxide. For 3 of 4 pigeons, chlordiazepoxide decreased responding with increasing doses during the acute dosing phase (△———△). Pigeon 106 (Fig. 1A) showed an increase in FI responding at 10 mg/kg chlordiazepoxide, but responding decreased at higher doses. Pentobarbital decreased responding under the FR schedules (G and H) but increased responding under the FI schedules at some doses (E and F).

Drug Effects During Chronic Chlordiazepoxide Exposure

Figure 2 summarizes the effects of daily exposure to either 10 mg/kg (B and C) or 17 mg/kg (A and D) over the 20–21 period prior to redetermination of dose-effect relations. In 3 of 4 pigeons (B, C, D) maximum tolerance seemed to develop by the fourth daily injection. For pigeon 106 (A),

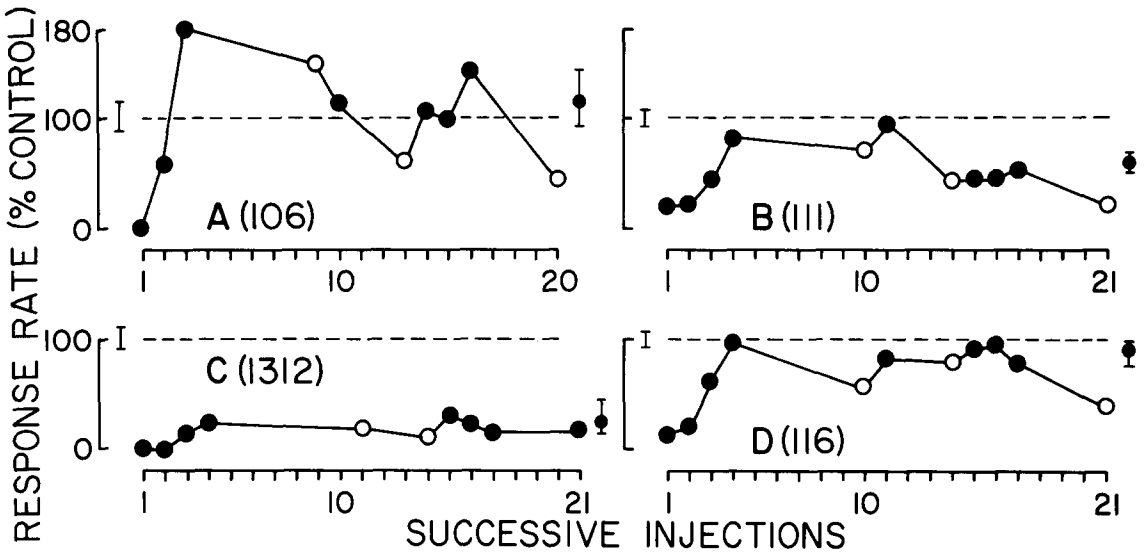

FIG. 2. Effects of daily injections of chlordiazepoxide on responding under fixed-interval and fixed-ratio schedules. A and C: pigeons 106 and 1312, fixed-interval schedules. B and D: pigeons 111 and 116, fixed-ratio schedules. Pigeons received either 10 mg/kg/day (B and C) or 17 mg/kg/day (A and D). Experimental sessions were conducted only on days where points are indicated. Brackets at left indicate mean and standard deviation of performance during 8 or 9 non-drug control sessions. Filled points are for days that were preceded by an experimental session, while open points are from sessions following one or more days with injections but without experimental sessions (e.g., Mondays). Unconnected points with brackets at the right indicate the mean and range of effects of the same dose of chlordiazepoxide when given on 3 (A,B) or 4 (C,D) occasions during redetermination of dose-effect relations (i.e., up to 25 sessions later). Relatively complete tolerance developed in pigeons 106 (A) and 116 (D), but was less complete in pigeons 111 and 1312 (B and C). The extent of tolerance remained stable over the course of the experiment in all pigeons (compare unconnected bracketed points with the connected, filled points during the latter sessions).

however, 17 mg/kg chlordiazepoxide completely suppressed responding on the first day, had a lesser effect on the second, and resulted in increased responding on the third day. By the 10th session, responding was comparable to that during control sessions. It is significant that these rate increases were observed in the pigeon that had shown increases in responding at a lower dose of chlordiazepoxide (10 mg/kg) during the acute dosing phase.

Though 10 or 17 mg/kg chlordiazepoxide given acutely resulted in nearly complete suppression of responding, considerable tolerance developed when these doses were given daily (compare the filled circles in the upper portion of Fig. 1 with the triangles at the same dose). There was complete tolerance to the effects of 17 mg/kg chlordiazepoxide in pigeon 116 (Fig. 1C); pigeon 106 (Fig. 1A) not only showed complete tolerance to the effects of 17 mg/kg, but this dose increased responding when given during the chronic dosing phase. Likewise, pigeons 116 and 106 also showed complete tolerance to the effects of the highest dose of chlordiazepoxide (30 mg/kg). The other two pigeons (Fig. 1B and D) showed clear tolerance, but it was not as marked. Taken together, the results summarized in the upper portion of Fig. 1 show that there was at least a three-fold tolerance to the effects of chlordiazepoxide.

In contrast, there were no marked systematic changes in the effects of pentobarbital when given during the period of chronic exposure to chlordiazepoxide (Fig. 1, lower).

The tolerance to the behavioral effects of chlordiazepoxide observed in these experiments confirms similar observations under other behavioral conditions for this drug and other benzodiazepines (e.g. [4,5]). Unfortunately, we did not redetermine the effects of various doses of chlordiazepoxide at any time periods after cessation of chronic treatment. This would be of interest since there are indications that there may be long-lasting changes in the behavioral effects of benzodiazepines after even relatively infrequent exposure to large doses [5].

Under the conditions of this experiment, however, there was no evidence of cross-tolerance to the effects of pentobarbital. In one recent experiment, McMillan and Leander [4] did observe reciprocal cross-tolerance to certain behavioral effects of chlordiazepoxide and pentobarbital in rats exposed to large daily doses for 7 weeks (50 and 100 mg/kg, respectively). Redetermination of the effects of chlordiazepoxide in the present experiments began after three weeks of chronic exposure. Though this was sufficient time for the development of considerable tolerance to the effects of chlordiazepoxide, it is possible that tolerance and cross-tolerance might develop at different rates and that cross-tolerance might have been observed had we employed larger daily doses of chlordiazepoxide or a more prolonged period of chronic exposure. However, prolonged daily exposure to doses of chlordiazepoxide as high as 50 mg/kg might produce liver enzyme induction (e.g., see discussion in reference [5]) that could mediate an apparent cross-tolerance to the effects of pentobarbital.

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