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BRIEF COMMUNICATION

Self-Administration of the Isomers of Pentobarbital and Secobarbital by Rhesus Monkeys

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VANOVER, K. E., G. R. WENGER AND W. L. WOOLVERTON. *Self-administration of the isomers of pentobarbital and secobarbital by rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **34**(3) 669–671, 1989.—Previous studies have shown that the isomers of pentobarbital and secobarbital have behavioral effects that are qualitatively similar to those of the racemic mixture, but that the S-(−) isomers are more potent than the R-(+) isomers. The present study was designed to compare the reinforcing effects of the isomers of these compounds to those of the racemic mixtures in monkeys experienced in the intravenous self-administration of barbiturates. Rhesus monkeys (N = 3) were prepared with indwelling intravenous catheters and allowed to self-administer racemic pentobarbital in 1-hour sessions under a fixed ratio 5 schedule. When responding was stable, various doses of (+, −) pentobarbital, (+, −) secobarbital and single doses of both isomers of these compounds were substituted for the baseline drug in a mixed order. All of the compounds functioned as positive reinforcers in all monkeys. R-(+) isomers were self-administered at higher rates than the racemic mixtures which were self-administered at higher rates than the S-(−) isomers. The results demonstrate that both isomers of these barbiturates can function as positive reinforcers.

Rhesus monkeys Self-administration Pentobarbital Secobarbital Stereoisomers

LIKE many of the barbiturates, the racemic mixtures of pentobarbital and secobarbital can be separated into their stereoisomers. As with stereoisomers of, for example, the opiates, the possibility exists that there are behavioral differences between the isomers. However, although potency differences are apparent, behavioral studies have failed to find qualitative differences between the isomers of barbiturates and the racemic mixtures (5, 8–11, 13, 14). The present study was designed to compare the reinforcing effects of the isomers of pentobarbital and secobarbital to those of the racemic mixtures in rhesus monkeys that self-administered pentobarbital under baseline conditions. Reinforcing effects were evaluated using a substitution procedure that has proven predictive of abuse potential in humans (6).

METHOD

Subjects and Apparatus

The subjects were three rhesus monkeys (*Macaca mulatta*), two females (8619 and 8519) that weighed 4.7 mg and 5.5 kg and one male (8524) that weighed 8.4 kg. The monkeys had previous experience with intravenous (IV) self-administration of barbiturates, psychomotor stimulants and anxiolytics. Each was fitted with a stainless-steel restraint harness and spring arm which attached to the rear of the experimental cubicle (70 cm wide × 84 cm deep × 80 cm high) in which each monkey lived for the duration of the experiment. Two response levers (BRS/LVE, PRL-001, Beltsville, MD) were mounted on the inside front of

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each experimental cubicle 10 cm above the floor. Four jewelled stimulus lights, two red and two white, were mounted directly above each lever. Drug injections (1 ml/10 sec infusion) were delivered by a peristaltic infusion pump (Cole-Parmer Co., Chicago, IL). All programming and recording of experimental events was accomplished by solid state equipment located in an adjacent room. Water was available continuously and each monkey was fed 150 to 200 g of monkey chow after each session and was given a chewable vitamin tablet 3 days/week.

Procedure

Following adaptation to the cubicle and restraint system, each monkey was removed from the cubicle and injected with a combination of phencyclidine hydrochloride (1.0 mg/kg, IM) and atropine sulfate (0.04 mg/kg, IM) followed in 20–30 min by sodium pentobarbital (10–20 mg/kg, IV). When anesthesia was adequate, a silicone catheter (0.08 cm i.d., Ronsil Rubber Products, Belle Mead, NJ) was surgically implanted into a major vein. Internal and external jugular and femoral veins could be catheterized. Following surgery the monkey was returned to the experimental cubicle and the catheter was threaded through the spring arm, out the back of the cubicle and connected to the infusion pump. If a catheter became nonfunctional during the experiment, a new catheter was implanted as before following a 1–2-week period to allow any infection to clear.

Experimental sessions, signalled by the illumination of all white lights, were 1 hr in length and were conducted 7 days a week. During baseline sessions the animals were allowed to press the right lever to receive IV injections of racemic pentobarbital (0.3 mg/kg/1 ml injection) under a schedule requiring 5 lever presses per injection (fixed-ratio 5; FR 5). During injections the white lights were extinguished and the red lights were illuminated. Responses occurring on the left lever were counted, but had no other programmed consequences. After establishing stable rates of responding under these baseline conditions (less than 10% variation in total number of injections per session for at least three consecutive sessions), 0.9% saline was substituted for pentobarbital until responding declined to low, stable levels (less than 10 injections per session). Subsequently, the animals were returned to baseline conditions for 1 or 2 sessions to ensure that responding approximated previous levels. Then a dose of a test drug was made available (substituted) for intravenous self-administration for at least the same number of sessions as had been required for responding for saline to decline (4–6 sessions) and until there was neither an increasing nor a decreasing trend in total injections per session.

Drugs

The test drugs include the racemic mixture of pentobarbital, both R-(+) and S-(−) pentobarbital, the racemic mixture of secobarbital, and both R-(+) and S-(−) secobarbital. Racemic mixtures were commercially obtained and isomers were provided by the National Institute on Drug Abuse (Rockville, MD). Drugs were dissolved in 0.9% saline, and, when necessary, concentrated sodium hydroxide was added to the drug and saline mixture, until the drug was dissolved (maximum pH of 10). Doses of the test drugs, in the range of 0.03–1.0 (mg/kg/injection), were substituted for the baseline condition in a mixed order with baseline conditions reinstated between doses of test drugs. Only one dose (0.3 mg/kg/injection) of the isomers was tested because amounts of these drugs were limited. This dose was chosen based on peak responding for the racemic mixtures by the majority of the monkeys.

Data Analysis

The number of injections over the last three sessions of a test drug substitution period was used in data analysis. This value was compared to the same values for the last three sessions of the corresponding saline substitution period. A test drug was considered to be a positive reinforcer in a particular monkey if the mean number of injections for the last three sessions of a test period exceeded the mean value for saline injections, and the ranges did not overlap.

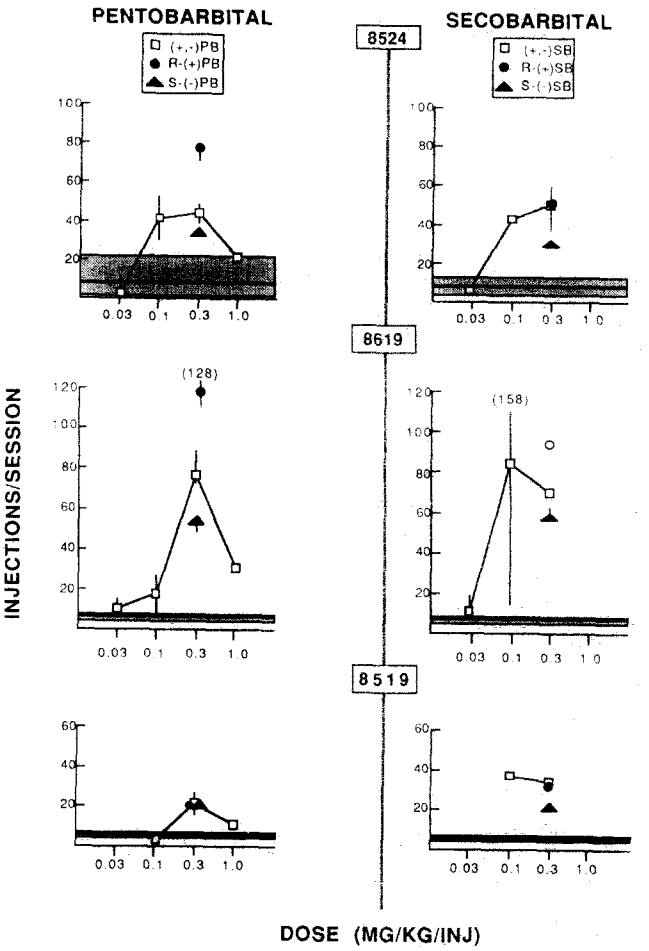

FIG. 1. Dose-response functions for (+,−) (□) pentobarbital (left graphs), and (+,−) secobarbital (right graphs) self-administration as compared to the R-(+) isomers (●) and the S-(−) isomers (▲). The number of injections/session is an average of the last three stable sessions except for (●*) (8619) which is one session only. The vertical bars at each point represent the range self-administered over the three sessions. The shaded area in each graph represents the range of saline self-administered and the bar across the shaded area is the mean.

RESULTS

All monkeys self-administered (+,−) pentobarbital under baseline conditions. Average intake of pentobarbital (0.3 mg/kg/injection) ranged between 22 and 79 injections per session (6.6 and 23.7 mg/kg). Although there was considerable variability between subjects in baseline drug intake, within subjects intake was stable over the course of the experiment. When drug vehicle was substituted, responding declined to less than 10 injections per session over a period of 4–6 sessions.

The racemic mixtures of both pentobarbital and secobarbital functioned as positive reinforcers in all monkeys (Fig. 1). For

(+, −) pentobarbital, each dose-response function was an inverted-U shape typically found for drugs that are positive reinforcers. For (+, −) secobarbital, one animal's (8619) dose-response function was an inverted-U shape. In the two other animals (8524 and 8519) the dose-response function of (+, −) secobarbital was flat between 0.1 and 0.3 mg/kg/inj. The dose of 1.0 mg/kg/injection of secobarbital could not be tested because of solubility limitations. During sessions of self-administration of each of the compounds at doses above 0.03 mg/kg/injection, all animals exhibited ataxia and often fell asleep during the session.

Both the R-(+) and S-(−) isomers of pentobarbital and secobarbital were self-administered by all monkeys. Two monkeys (8524 and 8619) self-administered more of the R-(+) pentobarbital than of the racemic mixture and more of the racemic mixture than of S-(−) pentobarbital. In the third monkey (8519), the amount self-administered was the same for all three compounds. In all three monkeys the amount of S-(−) secobarbital self-administered was lower than the racemic mixture (although there was only enough drug to test in one session in 8619). Only one monkey (8619) self-administered more R-(+) secobarbital than the racemic mixture. Self-administration of both isomers of both compounds also caused ataxia and sleep during the session.

DISCUSSION

The results of this study demonstrate that pentobarbital and secobarbital, as well as the optically pure isomers of both compounds, can serve as positive reinforcers in rhesus monkeys. The results with the racemic mixtures confirm the results of previous intravenous self-administration studies with these compounds (1–3, 12). The results with the isomers of each compound suggest that there were no qualitative differences in reinforcing effects between the isomers, a result which is consistent with previous behavioral studies which found no qualitative differences in discriminative stimulus effects or effects on operant behavior (8–10).

Although there were no qualitative differences between the isomers, quantitative differences were apparent. The S-(−) isomers were generally self-administered at lower rates than the R-(+) isomers for both pentobarbital and secobarbital. Since dose-response functions using this procedure are usually of an inverted-U shape, precise potency comparisons are difficult. However, these observations are consistent with potency differences that have been reported previously using drug discrimination paradigms. In rats and pigeons trained to discriminate pentobarbital from saline, pentobarbital generalized to the isomers of pentobarbital and S-(−) pentobarbital was more potent than R-(+) pentobarbital (5, 11, 13). In rats trained to discriminate diazepam from saline, R-(+), S-(−), and racemic pentobarbital substituted for diazepam and S-(−) pentobarbital was the most potent (14). In pigeons trained to discriminate S-(−) pentobarbital from saline or R-(+) pentobarbital from saline, stimulus generalization occurred to both isomers and the racemic mixtures of pentobarbital and secobarbital, and the S-(−) isomers for both compounds were more potent than the R-(+) isomers and the racemic mixtures (9). The potency differences were also similar to those found in other behavioral experiments. The S-(−) isomers of pentobarbital and secobarbital have been found more potent than the R-(+) isomers in pigeons responding for food under multiple schedules of reinforcement (10), in mice with a spontaneous motor activity paradigm (8) and in rats responding under a variable-interval 60 schedule of reinforcement (8). In assays to determine anesthetic and lethal effects (4,7) the potency of the S-(−) isomers of pentobarbital and secobarbital were greater than the R-(+) isomers. When considered together with the results of these studies, the differences in rate of responding for the isomers observed in the present experiment suggest that the S-(−) isomer is a more potent positive reinforcer than the R-(+) isomer of these barbiturates.

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