Pharmacology Biochemistry and Behavior, Vol. 56, No. 1, pp. 139–143, 1997
Published by Elsevier Science Inc.

0091-3057/97 $17.00 + .00

PII S0091-3057(96)00170-0

Behavioral Comparison of the Oximes TMB-4, 2-PAM, and HI-6 in Rats Using Operant Conditioning

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Received 29 July 1995; Accepted 27 February 1996

GENOVESE, R. F. AND B. P. DOCTOR. *Behavioral comparison of the oximes TMB-4, 2-PAM, HI-6, and in rats using operant conditioning.* PHARMACOL BIOCHEM BEHAV **56**(1) 139–143, 1997.— It has recently been shown that oximes can amplify the ability of cholinesterases to scavenge organophosphorus (OP) agents. Since both OP agents and oximes can disrupt performance, behavioral evaluation of *bioscavenger* therapies using oximes can be hindered. Therefore, we investigated the ability of three oximes, administered alone, to disrupt performance. The effects of trimedoxime bromide (TMB-4) (3.16-56.2 mg/kg), pralidoxime chloride (2-PAM) (10.0-237.1 mg/kg), and, 1-([[4-amincarbonyl)pyridino]-methoxy]-methyl)-2,4-bis[(hydroxyimino)methyl] pyridinium dichloride monohydrate (HI-6) (10.0-237.1 mg/kg) were evaluated in rats using a variable-interval 56 (VI 56) s schedule of food reinforcement. Under control conditions, the VI 56 s schedule produced a constant rate of responding (i.e., lever-pressing). All three oximes produced dose-dependent decreases in responding, and the largest doses of TMB-4 and 2-PAM produced complete or nearly complete suppression of responding in all rats. Only the largest dose of HI-6 suppressed responding. Analysis of the dose-effect functions demonstrated that TMB-4 was substantially more potent than 2-PAM, which was slightly more potent than HI-6, for producing response suppression. These results establish doses of each oxime that will not contribute to disruption of responding, and thus, facilitate future evaluation of bioscavenger therapies against OP toxicity. **Published by Elsevier Science Inc., 1997**

2-PAM Cholinesterases Bioscavenger HI-6 Operant behavior Oxime Rats TMB-4

STANDARD treatment following exposure to anti-cholinesterases such as organophosphorus (OP) agents typically includes administration of a cholinergic receptor antagonist along with an oxime. The cholinergic antagonist is delivered to counteract the effects of increases in acetylcholine, whereas the oxime is administered to reactivate the inhibited acetylcholinesterase (AChE). It is notable, however, that the degree of enzyme regeneration provided by an oxime depends both on the type of oxime and the type of OP (19,23). A novel approach to treatment of OP toxicity, currently under development, involves prophylactic administration of cholinesterases that act as bioscavengers, attaching to, and neutralizing, the OP agent before endogenous esterases are inhibited (6). In this regard, studies have shown that a variety of cholinesterases provide significant protection against OP toxicity induced by potent agents such as sarin, soman, and VX, in rhesus monkeys, rats, and, mice (2,3,5,26,29). A limitation of the bioscavenger therapy is the stoichiometry between the enzyme and the OP. That is, assuming a single turnover between the enzyme and the OP, relatively large amounts of enzyme may be necessary to confer protection. Recently, however, our laboratories have demonstrated that in mice, co-administration of an oxime increased the functional efficacy of fetal bovine serum AChE to scavenge the OP, sarin, by greater than fifty-fold (4).

Behavioral assessment of OP toxicity is complex and a variety of tests have been used, including operant behavior (see 7). In rats, operant behavior is sensitive to the effects of cholinesterase-inhibitors, cholinomimetics, and anticholinergics

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In conducting the research described in this report, the investigators adhere to the "Guide for the Care and Use of Laboratory Animals", as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The views of the authors do not purport to reflect the position of the Department of the Army or the Department of Defense, (para 4-3, AR 360-5).

(11,13–17,28), and has also been used to evaluate protection against OP toxicity conferred by equine butyrylcholinesterase (12). Thus, operant behavior should be a valuable procedure to assess the amplification of bioscavengers by oximes. There is, however, a paucity of modern data examining the behavioral effects of oximes administered alone, and we are unaware of any studies examining these compounds on operant behavior. Since oximes can produce performance deficits, it is necessary to know the doses of oximes producing disruption of operant behavior in order to use the procedure to evaluate the therapeutic efficacy of combinations of bioscavengers and oximes against OP toxicity. That is, it is potentially possible to mask the therapeutic efficacy of the exogenous enzyme by observing performance deficits produced by the oxime alone. Therefore, we investigated the effects of three oximes using a variable-interval 56 (VI 56) s schedule of food reinforcement in rats. We chose to investigate pralidoxime chloride (2-PAM), which is approved for general use in the United States; trimedoxime bromide (TMB-4), an analog of toxogonin, which is currently available for use outside of the United States; and 1-([[4-amincarbonyl)pyridino]-methoxy]-methyl)-2,4-bis[(hydroxyimino) methyl] pyridinium dichloride monohydrate (HI-6), notable because of its efficacy against OP agents, like soman, that rapidly inhibit AChE into an "aged" form that is resistant to reactivation by other oximes (18,24).

METHODS

Animals

Twenty-four adult male Sprague-Dawley rats (Charles River, Wilmington, MA) were used. Rats were individually housed in a temperature-controlled environment under a 12L:12D cycle (lights on at 06:00 h) and water was always available in the home cages. Body weights were maintained at approximately 320 g by food administered during experimental sessions and supplemental feedings (Agway Pro Lab Rodent Chow) occurring several hours after experimental sessions.

Apparatus

Sessions were conducted in twelve standard rodent operant conditioning chambers (model # E-10-10, Coulbourne Instruments, Lehigh Valley, PA), housed in ventilated, light- and sound-attenuating cubicles. Each chamber contained two response levers and a food trough that could be illuminated and was attached to a food dispenser capable of delivering 45 mg food pellets (Bio-Serv, Frenchtown, NJ). Each chamber also contained a houselight mounted on the ceiling and two stimulus lights mounted above each of the response levers. Additionally, a sound generator (Sonalert) was mounted on the chamber wall and was capable of producing a 2.5 kHz tone. A response was considered to occur when either lever was pressed with a downward force of at least 0.3 N. Experimental events were controlled and monitored by a DEC, PDP-11/73 computer, using the SKED-11 (State Systems, Kalamazoo, MI) software system.

Behavioral Procedure

All rats were initially trained to lever-press for food pellets under a continuous schedule of reinforcement. Although two levers were present in each chamber, only one lever produced food reinforcement. During this condition, a single response on the active lever, produced a brief tone and delivery of a food pellet. When lever-pressing was maintained by food presentation, all rats were trained to lever-press under a VI 56 s schedule of food reinforcement. The schedule specifies that the first lever-press following an average interval of 56 s produces food reinforcement (i.e., a single food pellet). Interval values for the schedule were chosen pseudorandomly, without replacement, from normal distributions generated using the procedure of Fleshler and Hoffman (8). The range of intervals was 2.44-198.23 s. The houselight and the stimulus lights above both levers were illuminated during the sessions and each response on the active lever produced a brief (0.1 s) tone. Sessions were 60 min in duration and were conducted at approximately the same time, Monday-Friday.

When responding under the schedule of reinforcement appeared stable (as judged by inspection of the daily response rates and cumulative response records), rats were assigned to one of three groups, each containing eight rats. At least 60 training sessions were conducted before responding was judged to be stable. Groups were matched on the basis of rate of responding. Additionally, groups were also matched such that the number of rats trained on left and right active response levers was nearly equivalent. Dose-effect functions for the three oximes were then determined, with each group of rats receiving doses of a single oxime.

Pharmacological Procedure

TMB-4 (trimedoxime bromide) (mol. wt.=351.2), 2-PAM, (pralidoxime chloride) 2-pyridine aldoxime methochloride (mol. wt.=172.6), and HI-6, 1-([[4-amincarbonyl)pyridino]-methoxy]-methyl)-2,4-bis[(hydroxyimino)methyl] pyridinium dichloride monohydrate (mol. wt.=359.2), were obtained through the Division of Experimental Therapeutics, Walter Reed Army Institute of Research. All compounds were dissolved, on the day of administration, in a solution of 0.9% NaCl, and a solution of 0.9% NaCl was used for vehicle injections. The following doses (in mg/kg) were used: TMB-4, 3.2, 5.6, 10.0, 17.8, 31.6, 42.2, 56.2; 2-PAM and HI-6, 10.0, 17.8, 31.6, 56.2, 100.0, 154.0, 237.1. Dosages are expressed as the salt form of each drug. Injections were given I.M. in the hind limb, in a volume of 1.0 ml/kg body weight, 10 min before the start of behavioral sessions. Drug and vehicle injections were administered on Tuesdays and Fridays, with approximately seven days separating drug injections. Data collected on Thursdays, during dose-effect determinations, served as non-injection control. Single injections of each dose of the oximes and two injections of vehicle were administered to each rat in a group. Drug doses and vehicle injections were administered in a mixed order.

Data Analysis

When a response or an experimental event occurred, the elapsed time within the session was recorded. From these data, the total number of responses and the rate of responding (responses per minute) were calculated for each rat. Response rate data from seven non-injection control days were averaged and response rate data from drug and vehicle sessions were then converted to a percentage of the average values obtained during control sessions for each rat (i.e., percent of control).

To assess the effects of drug dose on response rate, repeated measures ANOVA was calculated for each group using the General Linear Models procedure of the SAS (Cary, NC) statistical software package. Two tailed Dunnett's t-tests were used to test the significance of the difference between vehicle and drug effects, for each group. In order to quantify the

relationship between drug dose and response rate, least-squares estimation procedures were used to calculate first through third degree polynomial regression equations. Based, in part, on the analysis of the Type I sum of squares for each regression model (see 9), quadratic polynomial functions were used to interpolate or extrapolate ED_{80} and ED_{50} values for each oxime. That is, values were calculated that represent the dose of each oxime expected to produce suppression of responding equal to 80% and 50% of control response rates, respectively.

RESULTS

Performance maintained by the VI 56 s schedule of reinforcement was characterized by a relatively constant rate of responding throughout the 60 min session in all rats. In general, the performance of each group was similar. The average rate of responding, as responses per minute, (±SEM) and the number of food pellets earned (±SEM), respectively, during the seven non-injection control sessions for each of the three treatment groups was as follows: TMB-4, 24.55 ± 2.4, 56.48 ± 0.5; 2-PAM, 20.63 ± 1.6, 56.00 ± 0.7; HI-6, 21.20 ± 2.4, 56.59 ± 0.5. Responding on the inactive lever was minimal or nonexistent in all rats for the duration of the experiment and those data were excluded from further analysis.

Figure 1 shows the effects of TMB-4, 2-PAM, and HI-6, on the control rate of responding under the VI 56 s schedule of reinforcement. ANOVA revealed a statistically significant effect on responding for TMB-4, $F(7, 49) = 18.86$, $p < .001$; 2-PAM, $F(7, 49) = 20.40$, $p < .001$; and HI-6, $F(7, 49) = 2.85$, $p < .02$. Multiple contrasts revealed that certain doses of each oxime suppressed responding under the schedule of reinforcement. A significant decrease in response rate between vehicle and TMB-4 at doses of 42.2 and 56.2 mg/kg was observed ($p < .05$). Doses of 2-PAM above 56.2 mg/kg were also significantly different than vehicle ($p < .05$). Only the largest dose of HI-6 administered, 237.1 mg/kg, was found to be significantly different than vehicle ($p < .05$). The largest doses of TMB-4 and 2-PAM produced complete or nearly complete suppression of responding in all rats. Small doses of TMB-4, and to a lesser extent, 2-PAM, tended to increase response rate. This effect, however, was not statistically significant. In contrast to TMB-4 and 2-PAM, doses of HI-6 between 10.0 and 154.0 mg/kg, produced very little effect on response rate.

Figure 2 shows regression functions relating drug dose, as μM/kg, and control response rate, for each of the oximes. Differences in the potency of each compound can be seen by separation of the lines of best fit. In this respect, TMB-4 was observed to have a distinctly more potent profile than either 2-PAM or HI-6. Table 1 shows the doses of each oxime, as calculated from the regression functions illustrated in Fig. 2., producing response suppression of 80% (ED_{80}) and 50% (ED_{50}) of control. TMB-4 was observed to be approximately 4-6 times as potent as 2-PAM, and approximately 7-8 times as potent as HI-6, whereas 2-PAM was observed to be less than 2 times as potent as HI-6. It is notable, however, that the extrapolated ED_{50} dose of HI-6 (319.51 mg/kg) was well above the largest dose administered, and, thus, is more subject to error than the interpolated values for the other oximes.

DISCUSSION

The behavioral effects of the oximes TMB-4, 2-PAM, and HI-6 were evaluated using a VI 56 s schedule of food reinforcement in rats. Under baseline control conditions the schedule of reinforcement produced a relatively constant rate of re-

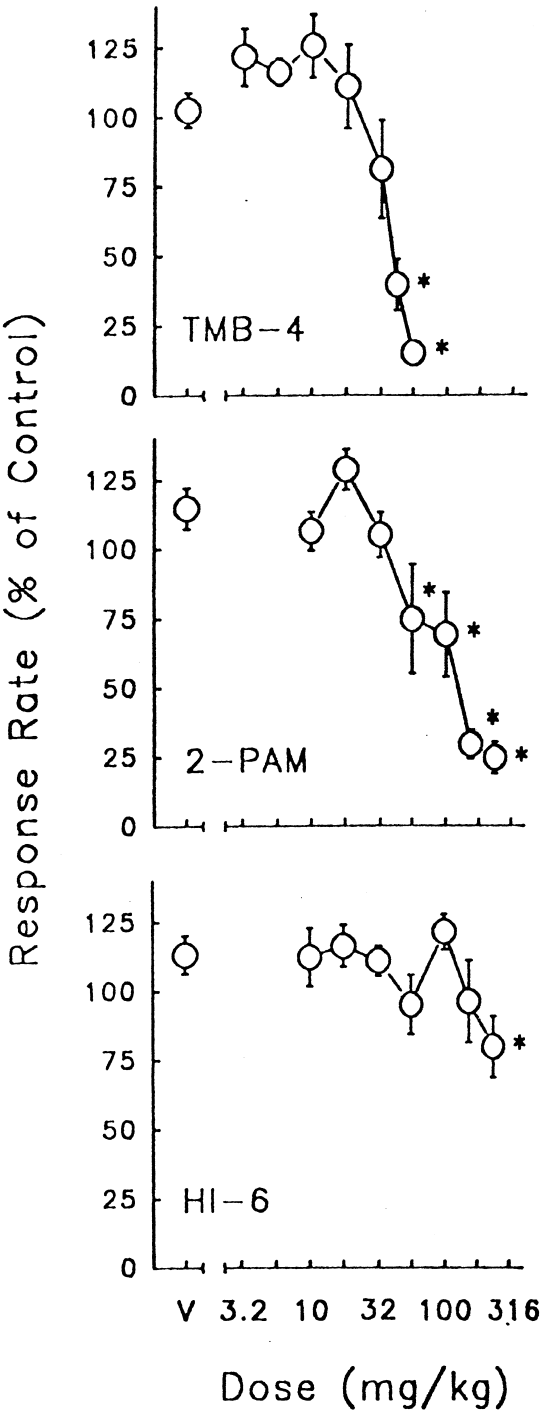

FIG. 1. Effects of TMB-4, 2-PAM, and HI-6 on rate of responding by rats under a VI 56 s schedule of food reinforcement. Response rate is expressed as a percentage of the average values obtained during 7 non-injection control sessions. Each point represents the mean of 8 rats. Drug doses are represented as mg/kg (log scale). Points above V represent vehicle injections. Vertical lines about each point represent ± SEM. Asterisks indicate a statistically significant difference from vehicle (Dunnett's t, $p < .05$, two-tailed).

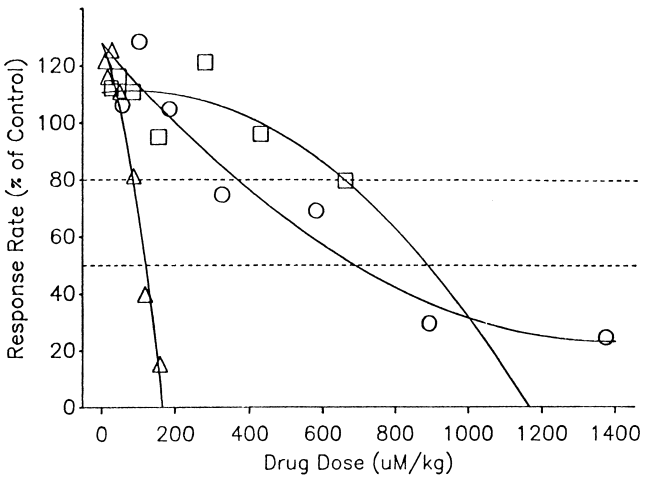

FIG. 2. Dose-effect functions, with regression lines of best-fit, for TMB-4 (triangles), 2-PAM (circles), and HI-6 (squares), on the control rate of responding in rats under the VI 56 s schedule of reinforcement. Each regression line was fitted by calculating a quadratic polynomial using least-squares estimation procedures. Dashed horizontal lines indicate the level of decrease in control performance by 50% and 80%, respectively. Drug doses are represented as μM/kg body weight.

sponding. All three oximes produced dose-dependent decreases in responding. In this respect, however, we observed that the potencies of the three compounds differed. The largest doses of TMB-4 and 2-PAM produced complete or nearly complete suppression of responding. In contrast, HI-6 was somewhat notable in producing only moderate suppression, and only at the largest dose administered. However, larger doses of this compound may well have produced the degree of suppression observed with TMB-4 and 2-PAM. We observed the order of potency for producing response suppression to be TMB-4 >> 2-PAM > HI-6. From analysis of the dose-effect functions we were able to calculate doses of each oxime expected to produce a reduction in responding equivalent to 80% and 50% of control responding. Additionally, a range of "sign-free" doses of each oxime was established. The results of the present experiment will, therefore, be particularly useful in evaluating future studies investigating oxime-induced amplification of the therapeutic efficacy of bioscavengers.

Two previous studies have shown that 2-PAM can produce performance changes in rats using behavioral and electrophysiological tests (22,30). For example, Wolthuis, et al., (30) found that 322 μM/kg and 644 μM/kg of 2-PAM were the maximum ineffective, and minimum effective doses (no intermediate dose-effects are reported), respectively, for changing behavioral or neurophysiological parameters using a variety of tests, including open field movements, motor coordination, shuttlebox avoidance and visual evoked potential response. Interestingly, the dose values obtained from the latter study correspond closely to the ED_{80} and ED_{50} values derived in the present study, suggesting that operant behavior may be more sensitive to the effects of 2-PAM than a variety of other tests. In agreement with results from the present study, 2-PAM has been reported to disrupt motor activity in rats at doses below 100 mg/kg (22) and we found that doses of 56.2 mg/kg and above significantly disrupted operant behavior. Leadbeater, et al., (20) found that 2-PAM disrupted swimming in guinea pigs, but only at near-lethal doses. The difference in species, however, makes a meaningful comparison difficult. Wolthius, et al., (30) also reports that 530 μM/kg HI-6 (apparently the largest dose administered) did not affect motor coordination or shuttlebox performance. In this respect, the ED_{80} dose of HI-6 calculated from the present study is somewhat above their noneffective dose, and is, to a certain extent, consistent with the latter study. In contrast, however, the latter study reports that doses as small as 199 μM/kg HI-6 did affect measures from open field and visual evoked potential tests, suggesting that operant behavior is less sensitive to some of the effects of HI-6.

TABLE 1

POTENCIES OF TMB-4, 2-PAM, AND HI-6 FOR PRODUCING RESPONSE SUPPRESSION UNDER THE VI 56 S SCHEDULE OF REINFORCEMENT

Oxime	ED_{80}	ED_{50}
TMB-4	88.21 (30.98)	122.20 (42.92)
2-PAM	365.57 (63.09)	682.70 (117.83)
HI-6	659.31 (236.82)	889.51 (319.51)

Values represent dosages in μM/kg body weight (mg/kg equivalents in parentheses) interpolated or extrapolated from the regression functions illustrated in Figure 2.

In the present study, no attempt was made to investigate the bioavailability of the oximes. Typically, pyridinium aldoximes, like TMB-4, 2-PAM and HI-6, have a rapid onset of action. For example, peak plasma levels, in rats and primates, following I.M. injection of HI-6 occur within 30 min or less (10,18,25). Additionally, these oximes typically are observed to have relatively short elimination half-lives (e.g., 21). In the present experiment we tested rats for 60 min, beginning 10 min following injection, and are therefore relatively confident that a stable behavioral assessment was determined. Additionally, by waiting approximately seven days between injections, we are also relatively confident that the behavioral assessments were not influenced by residual drug effects. In this regard, it is notable that visual inspection of the cumulative response records of individual sessions did not suggest a systematic diminution of drug effect during the course of the session, for any of the oximes. Moreover, no obvious response suppression was observed on the testing days following even the largest doses administered. Nevertheless, pharmacokinetic differences can not be ruled out as influencing the observed differences in the potencies of the three oximes to produce response suppression.

Finally, the present study did not attempt to identify the pharmacological mechanisms by which the oximes produced response suppression. It has been suggested that hydrogen cyanide is formed during the metabolism of some oximes (1). It is, perhaps, more likely that the disruption of responding produced by the oximes in the present study was the result of weak inhibition of AChE as described by Taylor (27). Further investigation, however, is needed to evaluate the specific pharmacological processes by which TMB-4, 2-PAM, and HI-6, disrupt responding under schedule-controlled behavior.

ACKNOWLEDGEMENTS

The authors thank SGT Laurence Simmons, Kimberly Gordon, Averi Roberts and William Fantegrossi for technical assistance with the conduct of the experiment.

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