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Effects of anticholinergics on serial-probe recognition accuracy of rhesus macaques (*Macaca mulatta*)☆

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Abstract

Potential deleterious behavioral effects of the anticholinergics biperiden and scopolamine were examined via the performance of rhesus monkeys on a serial-probe recognition (SPR) procedure. On each trial, six unique stimuli (list items) were presented sequentially followed by a choice phase. In the choice phase, two stimuli were presented, a standard or 'default' stimulus (a white rectangle) and a 'probe' stimulus that differed with each choice trial. Choosing the probe stimulus was considered correct if the probe matched one of the list items; otherwise, choosing the default stimulus was considered correct. Behavior was examined under a range of doses of biperiden (0.001–1.0 mg/kg) and scopolamine (0.0056–0.03 mg/kg). Scopolamine (0.01–0.03 mg/kg) and biperiden (0.3–1.0 mg/kg) reduced overall accuracy. At the highest dose, scopolamine, but not biperiden, reduced the number of trials completed per session. The results suggest that doses of scopolamine and biperiden necessary to prevent or eliminate organophosphate induced seizures may affect performance adversely. However, because the degree of impairment from biperiden was modest, further examination of this anticonvulsant may be warranted.

Keywords: Biperiden; Scopolamine; Operant behavior; Accuracy; Short-term memory; Serial probe recognition (SPR); Rhesus monkeys; Touch screen response

1. Introduction

Organophosphate (OP) compounds such as sarin, soman, tabun and VX are extremely toxic nerve agents and pose a threat to military personnel when used as weapons in combat or to civilian populations when used by terrorist organizations. These agents irreversibly bind cholinesterase (ChE), which normally hydrolyzes acetylcholine (ACh), resulting in excessive accumulation of ACh at cholinergic receptor sites. Excessive amounts of ACh hyperactivate the cholinergic system and can lead to seizures and ultimately death (Clement, 1985; Holmstedt, 1985). An effective treatment regimen including a prophylactic treatment with a carbamate ChE inhibitor, such as pyridostigmine, followed by treatment with atropine and oxime therapy significantly decreases the mortality rate of animals and humans exposed to various nerve agents (Balali-Mood and Shariat, 1998; Xia et al., 1981). Although this treatment strategy increases survival rate, it does not necessarily ameliorate nerve agent-induced motor convulsions and centrally mediated seizures that can produce permanent brain damage (McDonough and Shih, 1997).

Since the early 1990s, the US military has utilized the benzodiazepine diazepam as an advanced anticonvulsant treatment. Unfortunately, the degree of protection afforded by diazepam against OP-induced seizures is not complete, prompting the continued search for more effective anticonvulsant therapies (Clement and Broxup, 1993; McDonough

☆ This research was conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals, National Research Council, National Academy Press, 1996 and the Animal Welfare Act of 1966, as amended. The views of the authors do not reflect the position of the Department of the Army or the Department of Defense (para. 4-3, AR 360-5).

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et al., 2000). Given the selectivity of OPs for the cholinergic system, centrally active antimuscarinics such as biperiden and scopolamine are being evaluated for potential inclusion as anticonvulsants in the standard treatment following nerve agent exposure (McDonough et al., 2000). The ideal anticonvulsant would effectively eliminate seizure activity while producing few or no untoward behavioral effects. This is particularly important because such drugs may be administered in the absence of OP exposure, under ambiguous circumstances (i.e., *possible* nerve agent exposure). The degree of behavioral incapacitation resulting from administration of the anticonvulsant drug alone is a primary issue addressed by the present study. Diazepam, while somewhat effective as an anticonvulsant, reduced accuracy and increased choice latency on a serial-probe recognition (SPR) procedure in rhesus macaques (Castro, 1995), underscoring the need to find anticonvulsants that are less behaviorally disruptive.

The purpose of the present study was to examine the neurobehavioral effects of the antimuscarinic drugs biperiden and scopolamine on a six-item SPR task in rhesus macaques and characterize the dose–response curve for each drug. These drugs have been shown to be effective anticonvulsants in controlling nerve agent-induced seizures in laboratory animals when given 5 and 40 min after seizure onset (Capacio and Shih, 1991; McDonough et al., 2000), and the doses chosen for the present study were based upon these findings. The SPR task has been demonstrated to be a reliable neurobehavioral model for evaluating cognitive function following a challenge to the central nervous system (Castro, 1995, 1997), and was adapted from a task for evaluating memory in humans (Sands and Wright, 1980a,b; Wickelgren and Norman, 1966; Wright et al., 1985).

2. Method

The experimental protocol was approved by the Animal Care and Use Committee at the Walter Reed Army Institute of Research and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals, National Research Council, National Academy Press, 1996 and the Animal Welfare Act of 1966, as amended.

2.1. Subjects

Six adult male rhesus monkeys (*Macaca mulatta*) weighing between 8.0 and 12.0 kg served. All monkeys had experience with the six-item SPR task. The monkeys were housed individually in stainless steel squeeze-back cages (61 cm W × 71 cm D × 86 cm H) with free access to tap water. Certified primate rations (Purina Mills, St. Louis, MO) and fresh fruit were provided daily to maintain desired body weights (approximately 95% of free-feeding weight). The subjects were tested unrestrained in their home cages. The colony was maintained on a 12-h light/dark cycle with no twilight (lights on at 0600 h) and at 20–22 °C with a relative humidity of 50% (±20%), using at least 10 complete air changes per hour of 100% conditioned fresh air. The sessions began at approximately 1030 and were conducted during the light part of the cycle, but room lights were off during each experimental session.

2.2. Apparatus

A 14-in. capacitive touchscreen monitor (Mitsubishi Diamond Scan, model MITS 381, Microtouch Systems, Methuen, MA) was attached to the front wall of each cage. Banana-flavored food pellets (750 mg, Bio-Serv, Frenchtown, NJ) were delivered by a pellet dispenser (BRS/LVE Model QNB-400 1) into a food well positioned in the front of the test chamber, centered directly under the touchscreen and 2 cm from the chamber floor. A computer, running a custom-written Pascal routine, was used to control experimental events and collect all data.

2.3. Behavioral procedure

Each daily session consisted of 240 trials, with a 10-min rest period separating each 60-trial block. On each trial, six list stimuli were presented sequentially with a 0.5-s interstimulus interval (ISI). Each list item was a compound stimulus comprised of two superimposed, randomly selected ASCII characters of different size and color. The characters ranged from about 2.5 to 5.5 cm in length and 2 to 3 cm in width. Each list stimulus was displayed in the top-center portion of the screen, 14.5 cm from the left edge of the screen and 5 cm from the top of the screen to the center of the stimulus. Each list item was presented for 1.5 s or until the list stimulus was touched, at which point it was terminated and the ISI was initiated. After all six list items had been presented, a 0.5-s probe delay preceded the choice period. During the choice period, a ‘probe’ stimulus was displayed in the lower-left or lower-right portion of the screen and a standard or ‘default’ stimulus (a 3.5 × 4.5 cm white rectangle) was presented in the other portion of the screen, with equal frequencies of presentation on both sides. The probe item was a compound stimulus that matched a list item on half of all trials. Across these “matching” trials, probe items matched list items at each of the six serial positions with equal frequency. On matching trials, touching the probe stimulus was considered correct. In contrast, on “nonmatching” trials, the probe stimulus was novel and touching the default stimulus was considered correct. Correct responses always produced an immediate tone (4000 Hz, 0.25-s duration) and, 50% of the time, a food pellet. Touching the opposite stimulus was considered incorrect. Choice periods that elapsed without a response ended after 10 s and were excluded from calculations of accuracy. A 1.5-s intertrial interval (during which the screen was blank)

separated each trial, regardless of whether a choice was correct or incorrect. Sessions were conducted Monday through Friday.

2.4. Injection procedure

Scopolamine hydrobromide (Research Biochemicals International, Natick, MA) was mixed with sterile physiological saline and biperiden hydrochloride (Division of Experimental Therapeutics, Walter Reed Army Institute of Research) was mixed with a solution consisting of 50% saline, 40% propylene glycol and 10% ethanol to produce the desired concentration on the day of first administration. The remaining portion was refrigerated until required for the second administration. A Tuesday/Friday injection schedule was used with Thursday serving as a baseline control (noninjection) day. Scopolamine was presented at 0.0056, 0.008, 0.01, 0.017 and 0.03 mg/kg and biperiden was presented at 0.001, 0.01, 0.03, 0.1, 0.3, 0.56 and 1.0 mg/kg. Each drug dose was administered twice during the study and the results of both determinations were aggregated. Injections were given into the posterior thigh muscle (im) in a volume of 0.1 ml/kg 30 min prior to the beginning of the experimental session. The injection site (left vs. right) was alternated across injections. For scopolamine, 7 baseline and 2 vehicle days were conducted. For biperiden, 8 baseline and 4 vehicle days were conducted.

3. Results

The level of significance for all statistical tests was $P < .05$. Fig. 1 shows mean overall accuracy and the S.E.M. for baseline, vehicle and each drug dose for both biperiden (filled circles) and scopolamine (empty circles). The accuracy data are based only on choice periods in which a response was made. Accuracy obtained under baseline and vehicle did not differ significantly for either drug, and thus the vehicle data were used in all statistical comparisons. A repeated-measures ANOVA revealed a significant effect of dose [$F(5,25) = 11.02$, $P < .05$], and two-tailed Dunnett tests revealed significant reductions in accuracy at the three highest doses of scopolamine, 0.01, 0.017 and 0.03 mg/kg, relative to vehicle performance. For biperiden, identical analyses revealed a significant effect of dose [$F(7,35) = 6.53$, $P < .05$], and two-tailed Dunnett tests revealed significant reductions in accuracy at the three highest doses, 0.3, 0.56 and 1.0 mg/kg, relative to vehicle performance. Although both drugs significantly reduced accuracy at the three highest doses, the degree of reduction was much greater for scopolamine. At the highest dose, accuracy was reduced to chance levels (50%) for scopolamine, but to about only 67% for biperiden. Furthermore, doses producing significant reductions in accuracy under scopolamine (0.01–0.03 mg/kg) produced no such reductions under biperiden.

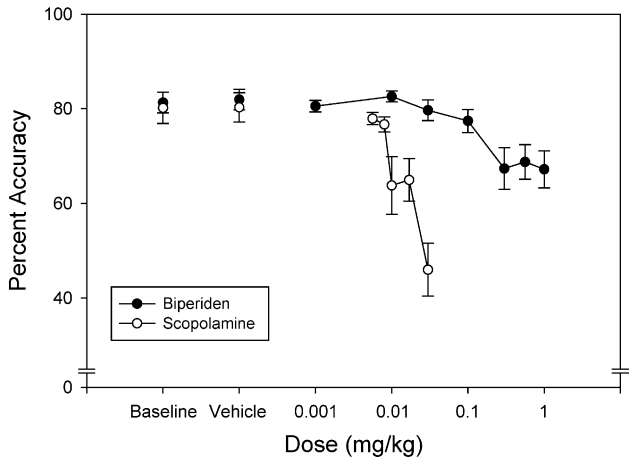

Fig. 1. Mean overall accuracy and S.E.M. for baseline, vehicle and each drug dose for both biperiden (filled circles) and scopolamine (empty circles).

Figs. 2 and 3 show accuracy as a function of serial position for each dose of scopolamine and biperiden, respectively. For both drugs, visual inspection suggests that, across the range of doses, only a recency effect was apparent (i.e., accuracy was higher at the latter, rather than the middle or early, serial positions). For scopolamine, this recency effect was confirmed by a repeated-measures ANOVA that revealed a main effect of serial position [$F(5,25) = 4.55$, $P < .05$], no main effect of dose [$F(5,25) = 2.02$, $P = .11$] and no interaction [$F(25,125) = 1.39$, $P = .12$]. An identical analysis for biperiden also confirmed a recency effect by revealing a main effect of serial position [$F(5,25) = 7.52$, $P < .05$], no main effect of dose [$F(5,25) = 1.48$, $P = .21$] and no interaction [$F(35,175) = 0.78$, $P = .80$]. These analyses did not include data from nonmatching trials because the probe stimuli from such trials have no serial position, therefore a separate repeated-measures ANOVA was performed for each drug to examine the effect of dose on accuracy from nonmatching trials, and a significant main effect of dose was observed for scopolamine [$F(5,25) = 9.31$, $P < .05$] and for biperiden [$F(7,35) = 9.53$, $P < .05$]. Two-tailed Dunnett tests revealed that accuracy on nonmatching trials was reduced significantly only at the highest dose of scopolamine (0.03 mg/kg); for biperiden, accuracy on nonmatching trials was reduced significantly at the three highest doses (0.3, 0.56 and 1.0 mg/kg). To determine whether drug-dependent decreases in accuracy differed as a function of trial type (matching vs. nonmatching), a repeated-measures ANOVA was performed for scopolamine, revealing a significant effect of dose [$F(6,30) = 10.88$, $P < .05$], but no significant effect of trial type [$F(1,5) = 2.03$, $P = .21$] and no significant interaction [$F(6,30) = 1.01$, $P = .44$]. An identical analysis for biperiden revealed a significant effect of dose [$F(8,40) = 5.48$, $P < .05$], but no significant effect of trial type [$F(1,5) = 1.70$, $P = .25$] and no significant interaction [$F(8,40) = 0.76$, $P = .64$]. Taken together, these analyses suggest that the decreased overall accuracy observed at the three highest doses of scopolamine

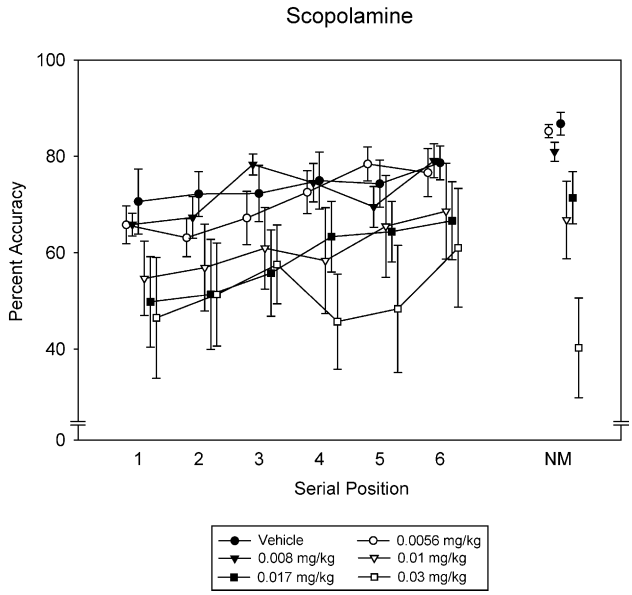

Fig. 2. Mean accuracy and S.E.M. for each dose of scopolamine as a function of which stimulus the probe matched (one of six serial positions). The probe stimulus was not among those listed on nonmatching (NM) trials. For clarity, the different dose functions are displaced slightly along the *x*-axis.

and at the three highest doses of biperiden resulted from drug-induced decreases in accuracy on nonmatching trials in combination with a general downward displacement of the serial-position function, rather than from a change in the form of the function.

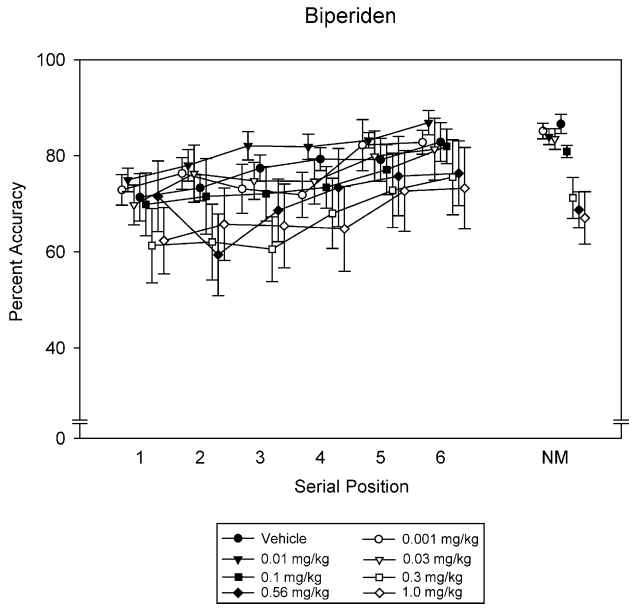

Fig. 3. Mean accuracy and S.E.M. for each dose of biperiden as a function of which stimulus the probe matched (one of six serial positions). The probe stimulus was not among those listed on nonmatching (NM) trials. For clarity, the different dose functions are displaced slightly along the *x*-axis.

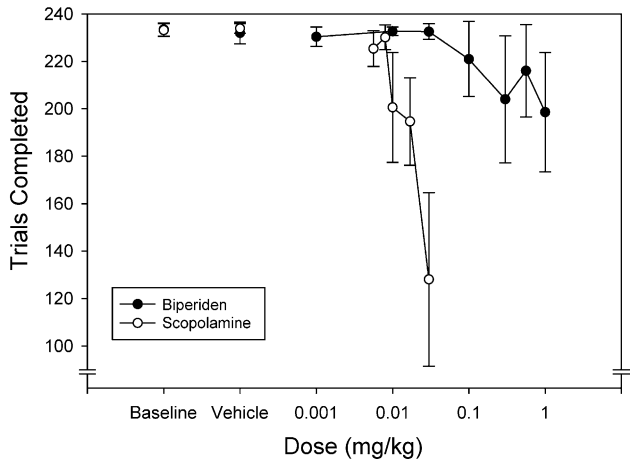

Fig. 4. Mean number of trials completed per session and S.E.M. for baseline, vehicle and each drug dose for both biperiden (filled circles) and scopolamine (empty circles).

Recall that each session consisted of 240 trials. Fig. 4 shows the mean number of trials completed per session and S.E.M. for baseline, vehicle and each drug dose for both biperiden (filled circles) and scopolamine (empty circles). Baseline and vehicle data did not differ significantly; thus, vehicle data were used in all statistical comparisons for both drugs. A repeated-measures ANOVA for each drug revealed a significant main effect of dose for scopolamine [$F(5,25) = 6.39$, $P < .05$], but not for biperiden [$F(5,25) = 1.32$, $P = .27$]. Two-tailed Dunnett tests were used to compare the number of trials completed under vehicle to those under each dose of scopolamine, and the number of trials completed was significantly lower than vehicle only at the highest dose (0.03 mg/kg). In general, the trial completion data resemble the accuracy data (Fig. 1), with a much greater reduction observed for scopolamine despite a smaller range of doses.

4. Discussion

Both scopolamine and biperiden reduced SPR performance accuracy, but only at the higher doses. At the highest dose, scopolamine (but not biperiden) reduced the number of trials completed per session. The present study extends previous findings relating rhesus monkeys' performance deficits to drugs that act upon the cholinergic system. For example, Genovese and Elsmore (1989) found that accuracy on a delayed match-to-sample task and on a simple detection task decreased with increasing doses of the anticholinergics atropine and azaprophen. Similarly, Penetar and McDonough (1983) demonstrated that atropine and benactyzine reduced match-to-sample performance accuracy. Scopolamine has been shown to reduce the accuracy of rhesus monkeys on a delayed nonmatching-to-sample task (Aigner and Mishkin, 1986) and to disrupt simple visual discrimination and delayed match-to-location performance (Bartus

and Johnson, 1976). Thus, the disruptive effects of anticholinergic drugs on visual discrimination and memory are well established, and the present study extends these findings to include the SPR procedure.

Although studied much less often, biperiden has been implicated in related performance decrements. Chronically medicated schizophrenics had low scores on tests of visual memory following biperiden administration, even at common clinical doses (Silver and Geraisy, 1995). Compared to placebo, biperiden increased reports of dizziness and sedation and decreased saliva production and the number of words recalled in a selective reminding task among healthy volunteers (Guthrie et al., 2000). In rats, immediate biperiden administration has been shown to disrupt memory consolidation of one-trial inhibitory avoidance behavior (Roldan et al., 1997). Kurlan and Como (1988) reported that an elderly man's biperiden treatment for Parkinson's disease led to progressive behavioral and cognitive declines that were reversed upon withdrawal of biperiden treatment. In sum, biperiden, like scopolamine, appears to adversely affect the execution of tasks involving memory.

The present study extended the use of the SPR procedure to the examination of anticholinergic drugs and replicated the disruptive effects of scopolamine observed in other procedures. Doing so provides further support for the use of the SPR task as a behavioral assay sensitive to pharmacological challenges in general and anticholinergic action in particular. One of the advantages of the SPR procedure is that it includes several classes of behavior. Specifically, accurate performance of the SPR task requires attending to visual stimuli, remembering what was recently observed, and making a choice by executing a simple motor response. Unfortunately, like many operant procedures, the complexity of the SPR task precludes precise specification of the behavioral component(s) responsible for observed reductions in accuracy. For example, anticholinergics may disrupt attention rather than (or in addition to) disrupting memory, and separating these effects procedurally is often difficult (for a review, see Sahakian, 1988). Nevertheless, the SPR task is sensitive to the disruptive effects of cholinergic drugs and seems to provide a real-world analogue of important human operant behavior (attending, remembering and decision making).

In the present study, a moderate recency effect, but not a primacy effect (i.e., higher accuracy at early positions than at medial positions) was found, and increased doses of both drugs did not change the shape of the serial-position function. Thus, neither biperiden nor scopolamine produced differential memory effects; all serial positions exhibited similar relative decreases in accuracy with increased doses of these anticholinergic drugs. Castro (1995), in contrast, reported differential serial-position effects with a benzodiazepine; high doses of diazepam (1.6 and 3.2 mg/kg) decreased accuracy at latter serial positions but not at the first serial position. However, as in the present study, accuracy from nonmatching trials decreased significantly with increased doses of drug in Castro's study. The different baseline performances produced—one with a pronounced primacy effect and one without—complicate comparisons between Castro's study and the present study. Observed differences in performance may have resulted from differences in procedure. Although procedural features such as intertrial interval, ISI and the consequences of responding were comparable in these two studies, different stimuli were used. Specifically, Castro used a set of 210 picture stimuli, whereas nonrepeating alphanumeric stimuli were used in the present study. Smaller stimulus sets are believed to increase proactive interference and thereby change the form of the serial-position function (Keppel and Underwood, 1962; Sands and Wright, 1980b). The presence of a recency effect in the present study is consistent with similar findings using analogous procedures in a variety of species, including monkeys and humans (Ellis and Hope, 1968; Jahnke and Erlick, 1968; Murdock, 1968; Phillips and Christie, 1977; Roberts and Smythe, 1979; Thompson and Herman, 1977; Wickelgren, 1970). Indeed, a recency effect is commonly observed when short probe delays (retention intervals) are used (Wright et al., 1984, 1985).

One of the primary contributions of the present study is the inclusion of a broad range of doses for both drugs, particularly at the lower end of the ranges. This approach provided a more precise specification of the lowest dose capable of producing a performance decrement. The safety of a compound for anticonvulsant use can be indexed by comparing the minimum behaviorally disruptive dose with the minimum dose needed to provide seizure protection. For example, McDonough et al. (2000) exposed guinea pigs to standard pyridostigmine pretreatment and administration of atropine and oxime immediately following exposure to $2 \times LD_{50}$ of soman. Five minutes later, biperiden or scopolamine was administered to gauge its anticonvulsant effect. The ED_{50} was 0.57 mg/kg for biperiden and 0.12 mg/kg for scopolamine. In rats, with oxime pretreatment, biperiden and scopolamine were administered 30 min prior to soman exposure ($1.6 \times LD_{50}$) resulting in median effective doses of 0.33 and 0.18 mg/kg, respectively (Capacio and Shih, 1991). Doses of scopolamine well below these values have been shown to disrupt behavior in rats. For example, Kirkby et al. (1995) found that scopolamine reduced the delayed matching-to-position accuracy of rats at doses as low as 0.03 mg/kg. Similarly, in the present study, doses of scopolamine as low as 0.01 mg/kg produced behavioral deficits. Taken together, these results suggest that levels of scopolamine likely to afford seizure protection are substantially higher than those doses shown to markedly disrupt behavior. Additionally, the use of scopolamine would appear to be contraindicated from a safety perspective by the relative steepness of the dose–effect curve. Data concerning the effects of biperiden on memory procedures similar to that used in the present study are lacking but, in the present case, doses of biperiden as low as 0.3 mg/kg disrupted performance. Unlike scopolamine, however, this dose is close to that

shown to provide protection from OP-induced seizures. Furthermore, in contrast to scopolamine, biperiden produced smaller reductions in accuracy despite being manipulated over a range of three log units, underscoring the greater relative safety of biperiden. In sum, our findings combined with those from other laboratories suggest that adverse performance effects of scopolamine and potentially biperiden would likely be observed at levels of the drug necessary to prevent or eliminate OP-induced seizures when doses of OP are quite high (about $1.6 \times LD_{50}$ or greater). Unfortunately, complementary data from seizure-protection studies using rhesus monkeys are not available, allowing only tentative suggestions based upon between-species comparisons. Although the present reductions in accuracy were statistically significant at the highest doses of both drugs, for biperiden these reductions were rather small. Thus, further investigation of biperiden as an advanced anticonvulsant treatment and elaboration of its potentially adverse behavioral effects seem warranted. Overall, the current results suggest biperiden may act well as a supplement to the current anticonvulsant therapy for OP exposure.

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