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Dose-Dependent Effects of Atropine on Behavioral and Physiologic Responses in Humans[1]

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HIGGINS, S. T., R. J. LAMB AND J. E. HENNINGFIELD. *Dose-dependent effects of atropine on behavioral and physiologic responses in humans*. PHARMACOL BIOCHEM BEHAV **34**(2) 303–311, 1989.—Atropine is an antimuscarinic which has been frequently studied with learning and performance tasks using both human and animal subjects. However, interpretation of data from human studies is limited by the relatively narrow range of doses used in most such studies. In the present study a wide range of atropine doses (0, 1.5, 3.0, 6.0 mg/70 kg) were given, intramuscularly, to human volunteers to assess the effects of atropine on a variety of behavioral measures, subject ratings, and physiologic function. The time course of responses was examined over 24 hours. Behavioral measures were a computerized Performance Assessment Battery (PAB) which contained measures of logical reasoning, short-term memory and rapid arithmetic, a Digit Symbol Substitution Test (DSST), and a psychomotor test of hand-eye coordination (Circular Lights). Administration of atropine produced both time- and dose-dependent effects on most measures used, although sensitivity varied across measures. At the 1.5 mg dose, no effects on performance were detected, however, after 6.0 mg reliably and 3.0 mg occasionally, impairments occurred on measures of accuracy and speed of performance. These effects generally began by 1.5 hours postdrug and returned to baseline by 7–9 hours postdrug. In contrast, certain subject ratings and physiologic variables were affected by lower doses of atropine, showing deviations from baseline at 1.5 mg and producing a time course of effects that was both earlier in onset and longer in duration than was observed with the performance measures. The present results have practical implications for the clinical utilization of atropine in situations in which optimal performance is required.

Atropine Drug Performance Behavior Anticholinergic Human study Impairment Psychomotor Abuse liability

ATROPINE is the prototype of the anticholinergics, which antagonize the actions of acetylcholine at muscarinic receptor sites (12). Atropine has been used therapeutically for many years in the treatment of a wide spectrum of conditions including gastrointestinal disorders, respiratory tract disorders, parkinsonism, and as a preanesthetic medication (12). Atropine is also used in cases of poisoning by anticholinesterase agents (12). Despite such long historical and widespread use in research and therapeutics, rela-

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tively limited quantitative information is available on the behavioral effects of atropine in humans. In particular, there are few reports describing the behavioral effects of more than a single atropine dose. One study that involved administration of two low doses of atropine did find dose-related effects: Seppala and Visakorpi (9) examined the effects of atropine (0.85 and 1.7 mg, PO) administered to normal male volunteers using a variety of behavioral tasks. Flicker recognition, reaction time, digit recall, coordination, time anticipation, and standing steadiness were impaired. These effects were dependent on the nature of the task employed. For example, after the 0.85 mg dose, coordination but not choice reaction was impaired, whereas after the 1.7 mg dose both measures were impaired. Administration of neither dose significantly affected performance on the Digit Symbol Substitution Test (DSST). Another study examined the effects of higher dose levels (2.24–12.25 mg/70 kg IM), but only presented quantitative descriptions of the relationship between dose and the effects on heart rate and a simple arithmetic task (5). Heart rate increased and the number of correct calculations decreased as an orderly function of dose in that study. The results obtained using other measures were described only anecdotally or in terms of dose levels needed to produce an effect in 50 percent of the subjects tested.

The importance of obtaining quantitative data on the possible adverse effects of atropine on various aspects of human behavior has increased with the dispensing of atropine in autoinjectors to military troops at risk for exposure to organophosphorus anticholinesterase agents used in chemical warfare (7). Since performance demands of modern military personnel often involve highly skilled and coordinated activity (i.e., learning, remembering, logical reasoning), a joint Army, Navy, and Air Force working group has developed a series of multipurpose behavioral and physiologic testing batteries which are intended to provide qualitative and quantitative data on the possible adverse behavioral effects of drugs (11). Components of these testing batteries were used in the present study to provide a more comprehensive description of the effects of a broad range of doses of atropine (1.5–6.0 mg/70 kg, IM) in normal volunteers. The study also included standard measures used to assess subject ratings of drug effects and abuse liability (3).

METHOD

Subjects

Subjects were seven normal, healthy, male volunteers who were medically screened and who provided informed consent to participate in the study. The mean ages and body weights of the subjects were 26.3 years (s.d. = 3.7) and 73.9 kg (s.d. = 19.6), respectively. Their mean number of years of formal education was 11.1 (s.d. = 1.9). All subjects were social drinkers, smoked cigarettes and reported varying histories of occasional illicit drug use, but none had a history of medically significant drug or alcohol abuse other than cigarette smoking; the ethnic composition of the group was 2 white and 5 black subjects. Generally, two subjects participated in the protocol at the same time. They resided for the duration of the study on the residential research unit of the Addiction Research Center. Subject payment was $15.00 daily plus 0.5 cents per point earned via the various behavioral procedures described below. Volunteers typically earned approximately $12.00 per day for their task performance.

General Procedures

During the first 3–5 days on the research unit, subjects were oriented to policies and procedures, received additional medical and psychological screening, and gave written informed consent for their participation in the study. During the informed consent procedures, subjects were informed that they would be receiving atropine and placebo, and that the purpose of the study was to assess the effects of atropine on behavior and physiology. They were informed that they might experience a wide range of drug effects (e.g., arousal, sedation, nervousness, dry mouth, difficulty urinating), but that these effects were dependent on dose, time and could differ across individuals. Upon completion of this familiarization and screening period, subjects were introduced to the general experimental protocol and trained on the behavioral procedures repeatedly each day over 3–5 days to permit acquisition and stabilization of performance on the various tests (described below).

Drug Schedule

Atropine sulfate, dissolved in saline, was administered intramuscularly (shoulder) at doses of 0 (saline), 1.5, 3.0, and 6.0 mg/70 kg. These doses were chosen to be comparable to the three 2 mg autoinjectors of atropine (total of 6 mg) issued to military troops (7). Injections were always 1 ml in volume. Subjects and staff were blind to drug dose. Subjects were exposed twice to each dose condition. The first two subjects tested were exposed to each dose condition in an ascending and then a descending order. These data confirmed that the dose levels and test conditions were safe; the subsequent five subjects were exposed to the dose conditions in two randomized blocks. Subjects were tested two times per week with a minimum of 72 hours between tests.

Daily Experimental Procedures

On test days, subjects were awakened at 0600 hours and a standard breakfast was served. Baseline physiological and behavioral observations were obtained immediately predrug. The intramuscular injection of drug or placebo was given at 0900 hours. Physiological and behavioral measures were repeated 0.5, 1.5, 3.0, 5.0, 7.0, 9.0, and 24 hours postinjection. In addition to the performance battery described below, an evaluation of repeated acquisition and performance of response sequences was conducted and are described in a separate report (4). Electrophysiologic evaluations of passive electroencephalographic responses and evoked cortical potentials were conducted at intervals between the 3.0-, 5.0-, 7.0-, and 24-hour performance tests and will be reported separately.

Physiological Measures

The physiological measures were pupil diameter, as determined from photographs taken at ambient room lighting with a Polaroid camera at 3× magnification, and heart rate and blood pressure, as assessed via a Sentron automatic blood pressure monitor (Bard Electro Medical Systems, Inc., Englewood, CO).

Behavioral Performance Measures

The behavioral performance measures were the Digit Symbol Substitution Test (DSST), the Circular Lights procedure, and four tasks from the Walter Reed Performance Assessment Battery (PAB).

A computerized version of the DSST (6) was used. Briefly, 10 digit-symbol codes were presented at the top of the video screen. Randomly selected digits (0–9) appeared in the center of the screen. The subjects task was to match the digit in the center of the screen with the digit and corresponding symbol code at the top of the video screen and then reproduce the correct 3-response symbol using a 3 × 3 matrix on the numeric key pad. The task was 90 sec

in duration and the subject was instructed to correctly complete as many trials as possible during that time.

The Circular Lights procedure was conducted using a commercially available device (Saccadic Fixator and Sequence Rotator, Wayne Engineering, Skokie, IL), which has been described previously (1). In this procedure, subjects earned points by pressing a series of 16 buttons located on a wall-mounted panel. The panel consisted of 16 button-lights mounted in a circle (56 cm diameter). At the start of the 60-sec trial, one of the peripheral lights was illuminated. Pressing the button associated with the illuminated light added 1 point to a counter and resulted in the illumination of a new light at a random position. Subjects were instructed to obtain as many points as possible during the 60-sec trial.

The four tasks from the PAB were Rapid Arithmetic (Serial Addition-Subtraction), Logical Reasoning, Digit Recall, and Two Letter Search; these have been described elsewhere (10,11). In the Rapid Arithmetic procedure, two digits were presented in sequence followed by a "+" or "−" sign. Subjects were to complete the indicated operation. If the answer was a two-digit number, then the correct answer was the second digit. If the answer was a negative number, then 10 was added to the answer. Therefore, correct answers were always single digit positive values. In the Logical Reasoning procedure, a statement was presented at the top of the video screen describing the relation between the two letters (e.g., "A precedes B"). Immediately below the statement, the same letters appeared in the order AB or BA. The subject was instructed to determine whether the statement accurately described the order of the letters. Session duration was 150 sec or when 32 trials were completed, whichever occurred first. In the Digit Recall task, a nine-digit string was presented at the top of the video screen for 1 sec. Subsequently, the screen was blank for 3 sec and then 8 of the 9 digits were re-presented. Subjects were instructed to report which digit was missing from the string. The duration of this task was 120 sec or 20 problems, whichever occurred first. In the Two Letter Search task, 2 alphabetic characters (target letters) were presented at the top of the screen and a random string of 24 letters immediately below. Subjects were instructed to identify the target letters from among those in the string. The duration of the task was 120 sec or 20 problems, whichever occurred first.

Subject-Rated Measures

At each observation period subjects also completed a set of 11 visual-analog scales assessing various aspects of the drug effect and a short form of the Addiction Research Center Inventory (ARCI). The visual-analog scales ranged from 0 ("not at all") to 50 ("extremely"). The ARCI short form consisted of 40 true-false items. The inventory is divided into three empirically derived scales that are sensitive to opioid/stimulant effects (MBG or euphoria scale), sedative effects (PCAG scale), and hallucinogen effects (LSD or dysphoria scale) (2).

Data Analysis

All of the above described behavioral measures, except the Circular Lights task, were conducted using a Corona portable computer (model No. PPC-21). At the end of each session, a hard copy of the data was printed and data were also electronically transferred to files for storage and analysis. Daily data for each subject were averaged across their two observations at each dose condition. Individual subject means were used in a two-way repeated measures, randomized block design with dose and observation time as factors. Duncan's Multiple-Range Test was used for post hoc comparisons. Effects were considered significant at $p<0.05$ and below.

RESULTS

Atropine produced dose- and time-dependent effects on measures of physiologic function, behavioral performance, and subject ratings, although the sensitivity of the measures varies considerably. Data from each of these categories of response measure are described below. Measures that were significantly affected by drug dose are summarized in Table 1.

Physiological Measures

Heart rate. Heart rate increased significantly as a function of atropine dose. Maximal effects on heart rate occurred 0.5 hr postdrug (Fig. 1). The average values at that time were 83.5, 105.8, 114.8, and 116 beats per minute for placebo, 1.5, 3.0 and 6.0 mg, respectively. Heart rate values began to descend towards placebo levels by 1.5 hr postdrug across all three of the atropine doses. By either 7 or 9 hr postdrug, heart rates had decreased below those occurring predrug and at any time point following placebo administration. Heart rates had nearly returned to those obtained following placebo administration by 24 hr postdrug.

Pupil diameter. Pupil diameter increased as a function of atropine dose (Table 2). The three atropine doses increased pupil diameter above placebo levels, but did not differ from each other. Effects began by 0.5 hr and peaked by 1.5 hr postdrug, at which time the average values were 5.8, 6.2, 6.2, and 6.5 mm for placebo, 1.5, 3.0, and 6.0 mg, respectively. Pupil diameter remained somewhat above placebo values throughout the 24-hr observation period across all three atropine doses tested.

Blood pressure. Blood pressure values fluctuated somewhat over time following administration of atropine or placebo, however, statistical analyses did reveal effects related to dose (Table 2). Systolic pressure showed a small but significant decrease as a function of atropine dose level. The 1.5 and 3.0 mg doses, but not the 6 mg dose, decreased systolic pressure significantly below placebo levels. Diastolic pressure showed a similarly small decrease as a function of dose, but this was not significant. However, a significant dose × observation time interaction was found, $F(21,142)=2.1$, $p<0.006$.

Behavioral Performance Measures

Circular Lights. Response rate in the Circular Lights procedure decreased below placebo levels as a function of dose (Fig. 2). Peak effects occurred 1.5 hr postdrug. At that time, average rates were 1.52, 1.51, 1.39, and 1.08 responses per second for the placebo, 1.5, 3.0, and 6.0 mg doses, respectively. Rates were still decreased slightly below placebo levels at 9.0 hr postdrug across all three atropine doses. There was no evidence of a drug effect on this measure at 24 hr postdrug in any of the dose conditions.

Digit Symbol Substitution Test. Response rate on the DSST significantly decreased as a function of dose (Fig. 3, upper panel). Maximal drug effects occurred between 1.5 and 5.0 hr postdrug. At 5.0 hr postdrug, average rates were 1.44, 1.40, 1.34, and 1.06 responses per second for placebo, 1.5, 3.0, and 6.0 mg, respectively. Effects from the 3.0 mg dose dissipated by 9.0 hr postdrug, whereas those from the 6.0 mg dose were still discernible at that time. None of the doses exhibited effects on this measure at 24 hr postdrug.

Percent of DSST trials completed correctly (Fig. 3, lower panel) was not significantly affected as a function of dose, but there was a significant dose × observation time interaction, $F(21,126)=1.9$, $p<0.02$. The interaction was explained by the

TABLE 1

SUMMARY OF EFFECTS OF ATROPINE DOSE

	F Ratios	p Values	Dose (mg/70 kg) Comparisons					
			*Pl-1.5	Pl-3.0	Pl-6.0	1.5-3.0	1.5-6.0	3.0-6.0
Physiological Measures								
Heart rate	11.4	<0.001	Y	Y	Y	Y	Y	N
Pupil diameter	7.6	0.002	Y	Y	Y	N	N	N
Systolic Pressure	3.5	0.04	Y	Y	N	N	N	N
Behavioral Measures								
Circular lights								
response rate	9.6	<0.001	N	Y	Y	N	Y	Y
DSST								
response rate	14.6	<0.001	N	N	Y	N	Y	Y
Logical reasoning								
% correct	5.2	0.006	N	N	Y	N	Y	Y
Rapid arithmetic								
% correct	24.3	<0.001	N	N	Y	N	Y	Y
response latency	14.5	<0.001	N	N	Y	N	Y	Y
trials completed	20.6	<0.001	N	N	Y	N	Y	Y
Digit recall								
% correct	13.4	<0.001	N	N	Y	N	Y	Y
Two-letter search								
% correct	10.7	<0.001	N	N	Y	N	Y	Y
response latency	17.5	<0.001	N	N	Y	N	Y	Y
trials completed	9.2	<0.001	N	N	Y	N	Y	Y
Visual-analog scales								
strength drug effect	30.5	<0.001	N	Y	Y	Y	Y	Y
bad effects	17.9	<0.001	N	Y	Y	Y	Y	N
high	9.2	<0.001	N	Y	Y	Y	Y	N
nauseated	4.5	0.016	N	Y	Y	N	N	N
confused	3.5	0.037	N	Y	Y	N	N	N
blurred vision	33.4	<0.001	N	Y	Y	Y	Y	Y
restless	8.7	0.001	N	Y	Y	N	Y	Y
sleepy	13.3	<0.001	N	Y	Y	Y	Y	N
ARCI scales								
PCAG	9.4	0.001	Y	Y	Y	Y	Y	N
LSD	12.2	<0.001	Y	Y	Y	Y	Y	Y

*Pl: placebo dose condition.

F ratios and p values were determined by repeated measures, two-factor analysis of variance for dose and observation time. Only significant main effects of dose are shown. Yes (Y) and No (N) indicates which doses differed significantly from each other using Duncan's Multiple Range Test.

decreases in this measure at 1.5, 3.0 and 5.0 hr postdrug following the 6.0 mg dose. This effect dissipated by 7.0 hr postdrug. Note that at 24 hr postdrug there was a trend for values across the three atropine doses to be slightly above placebo levels.

Performance Assessment Battery. Figure 4 shows data from each of the PAB tests on response latency (left panels) and percent correct (right panels). For all of the measures, effects began by 1.5 hr postdrug and dissipated by 9.0 hr postdrug for percent correct and 24 hr postdrug for response latency.

On the Logical Reasoning task, percent of trials completed correctly was significantly affected as a function of dose. Response latency on this task was not significantly affected as a function of dose, but there was a significant dose × observation time interaction, $F(21,126) = 1.7$, $p<0.04$. The interaction was due to an increase in latencies from 1.5 hr through 7.0 hr postdrug with the 6.0 mg dose. There was not a significant effect of dose on the number of trials completed (not shown), but there was a

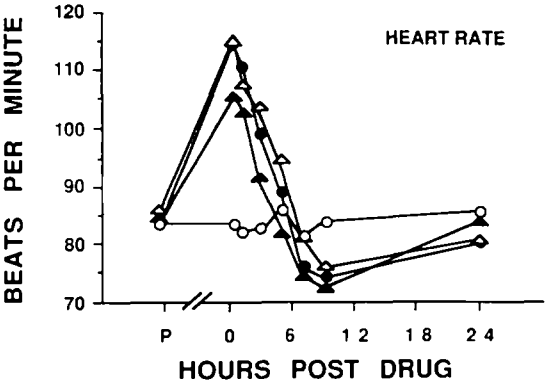

FIG. 1. Mean heart rate in beats per minute is shown as a function of time since drug or placebo was given, and immediately prior to the injections ("P"). Open circles indicate placebo; filled triangles indicate 1.5 mg; filled circles indicate 3.0 mg; open triangles indicate 6.0 mg atropine.

TABLE 2

MEAN VALUES OF PHYSIOLOGICAL MEASURES

Condition	Predrug	Hours Postdrug 0.5	1.5	3.0	5.0	7.0	9.0	24.0
Pupil Diameter (mm):								
Placebo	5.7	5.7	5.8	5.8	5.7	5.7	5.7	6.1
1.5 mg	6.1	6.0	6.2	6.1	6.3	6.0	6.0	6.4
3.0 mg	6.0	6.3	6.2	6.3	6.3	6.2	6.4	6.3
6.0 mg	6.0	6.3	6.5	6.4	6.2	6.4	6.4	6.4
Systolic Pressure (mmHg):								
Placebo	140.1	130.3	134.6	128.4	128.6	131.6	130.6	126.9
1.5 mg	134.4	132.3	125.1	124.4	125.3	125.6	128.0	128.0
3.0 mg	124.9	123.0	132.1	126.9	122.4	121.1	125.1	124.5
6.0 mg	137.6	127.9	126.2	127.9	130.9	124.9	123.1	130.9
Diastolic Pressure (mmHg):								
Placebo	80.6	75.1	78.1	75.4	73.9	71.6	74.5	77.3
1.5 mg	79.2	77.5	75.9	71.3	70.5	71.4	70.7	70.9
3.0 mg	77.4	77.8	78.4	76.4	71.4	67.6	66.6	71.2
6.0 mg	80.6	81.2	71.6	77.9	73.3	72.3	71.1	74.4

significant dose × observation time interaction, $F(21,126) = 1.7$, $p<0.04$. The interaction was due to a decrease in trials completed at 1.5, 3.0, and 5.0 hr postdrug following the 6.0 mg dose.

On the Rapid Arithmetic task, the percent of trials completed correctly, response latency, and the number of trials completed (not shown) were significantly affected by the 6.0 mg dose. Effects were clearly discernible from 1.5 hr through 7.0 hr postdrug.

On the Digit Recall task, the percent of trials completed correctly was significantly affected as a function of the 3 and 6.0 mg doses. Response latency was not significantly affected in this task. The number of trials completed (not shown) was not significantly affected as a function of dose, but there was a significant dose × observation time interaction, $F(21,126) = 1.9$,

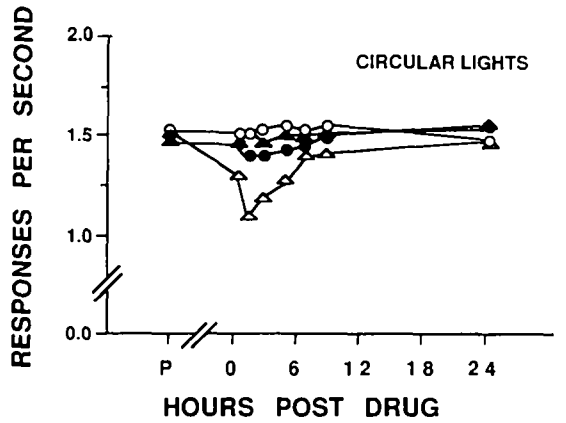

FIG. 2. Mean responses per second while pressing lighted buttons in the Circular Lights procedure is shown as a function of time since drug or placebo was administered and immediately prior to the injection ("P"). Symbols are as in Fig. 1.

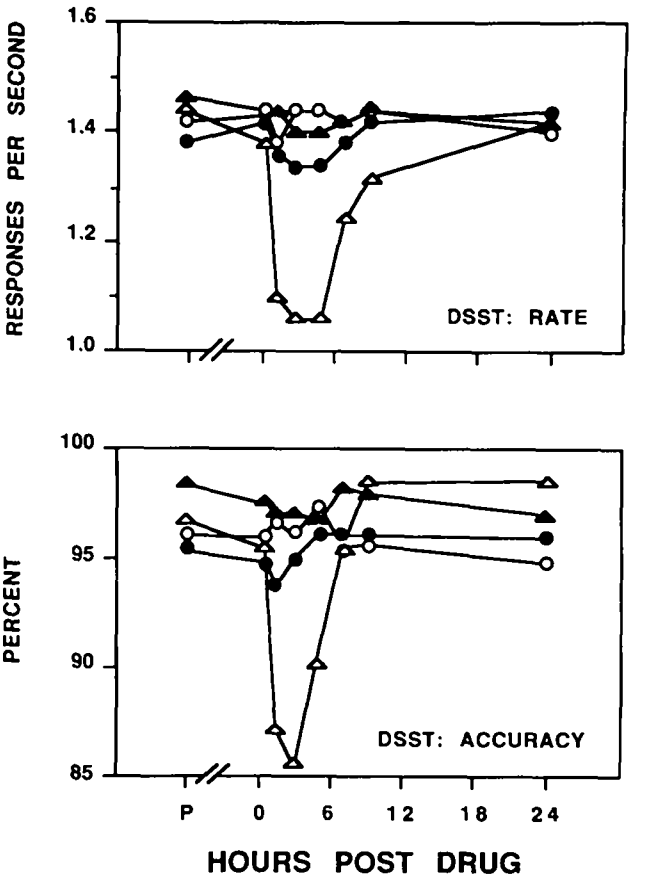

FIG. 3. Mean percent correct (lower panel) and responses per second (upper panel) on the Digit Symbol Substitution Test are shown as a function of time since drug of placebo was given, and immediately prior to the injections ("P"). Symbols are as in Fig. 1.

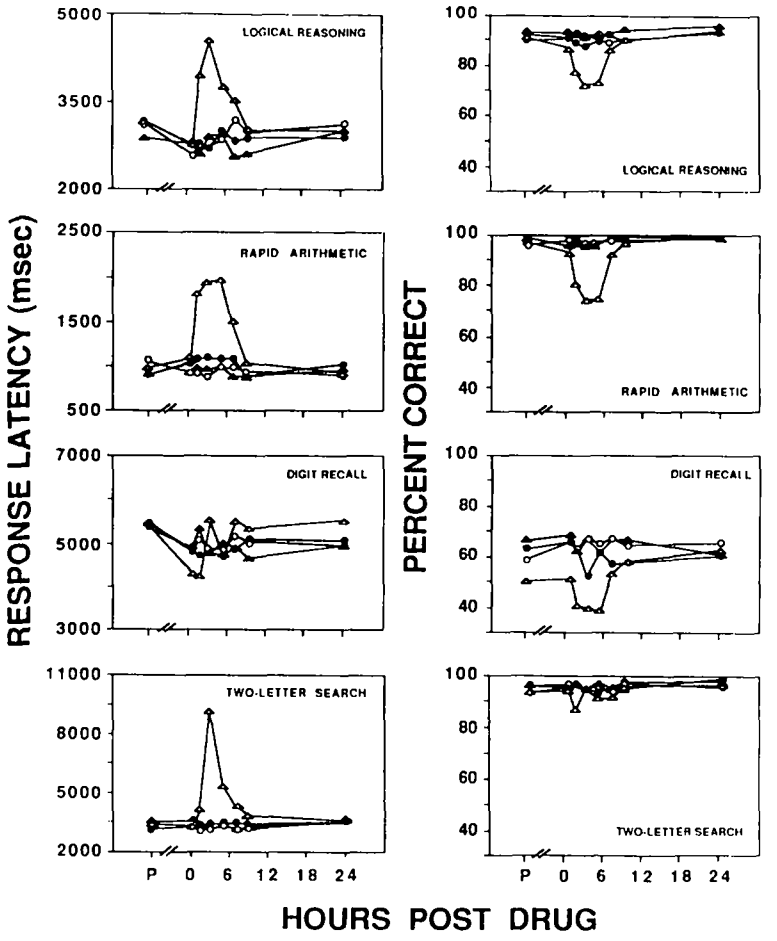

FIG. 4. Mean response latencies (left panels) and percent correct (right panels) from the 4 Performance Assessment Battery tasks are shown as a function of time since drug or placebo was given, and immediately prior to the injections ("P"). Symbols are as in Fig. 1.

$p<0.012$. The number of trials completed increased from predrug levels in all of the dose conditions, but this increase was maintained throughout the seven postdrug observations only in the placebo condition.

On the Two-Letter Search task, the percent of trials completed correctly, response latency and the number of trials completed (not shown) were all significantly affected by the 6.0 mg dose. The time-course of effects were similar to the other PAB measures.

Subject-Rated Measures

Visual-analog scales. Subject ratings on visual-analog scales that assessed global drug effects are shown in Fig. 5. Ratings of the overall "strength" of drug effects and of "bad" drug effects increased significantly as an orderly function of dose. Changes seen after every atropine dose were significantly different from placebo and from each other. On these measures, effects began by 0.5 hr postdrug and continued through 9.0 hr postdrug. These effects generally dissipated by 24 hr postdrug, although two subjects reported a drug effect 24 hr after the 6.0 mg dose. Ratings of "good" effects and drug "liking" were not significantly affected by dose and there were no significant interactions.

Visual-analog ratings of more specific drug-induced symptomatology are shown in Fig. 6. Ratings of drug "high," "nauseated," "confused," "blurred vision," "restlessness" and "sleepiness" increased significantly as an orderly function of dose. The dose-response functions for the nausea and confusion scales were relatively shallow, with the three active doses differing from placebo but not each other. In contrast, the other scales showed a relatively steep and graded dose-response function. For all of these scales, effects began by 0.5 hr postdrug, generally lasted through 9.0 hr postdrug, and had, for the most part, dissipated by 24 hr postdrug.

ARCI scales. Scores from the three subscales of the ARCI short form are shown in Table 3. Scores on the PCAG (Sedation) and LSD (Dysphoria) scales increased as an orderly function of dose. In contrast, scores on the MBG (Euphoria) scale were not significantly affected by drug, although there was a decreasing trend across the active doses.

DISCUSSION

The present report describes the use of a model of motivated and well-trained behavioral performance to assess possible adverse effects of atropine. We found that atropine produced time- and dose-dependent effects on a variety of behavioral measures, physiologic function and subject ratings. In general, the findings

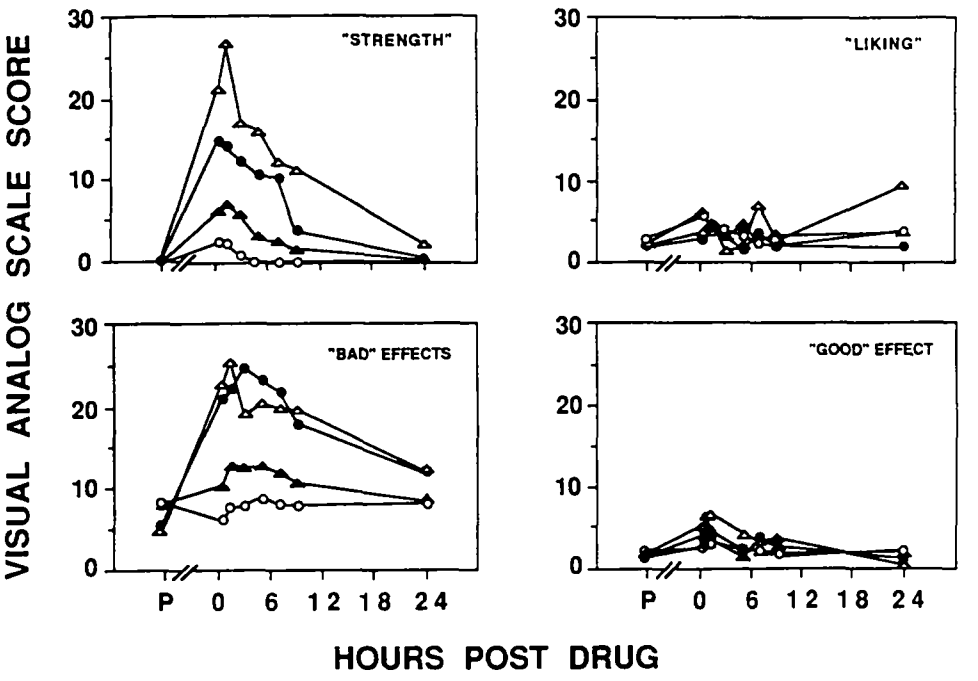

FIG. 5. Mean visual analog scores taken from 0–50 point rating scales are shown for each of the global measures of drug effects on subjective state as a function of time since drug or placebo was given, and immediately prior to the injections ("P"). Symbols are as in Fig. 1.

were consistent with findings from other studies. This study extends the generality of earlier research with atropine by assessing a variety of quantitative measures over time and by manipulating atropine dose (5, 7, 12). Interestingly, although performance in all of the behavioral procedures was impaired by some dose of atropine, these measures were less sensitive to change than physiologic and subject-reported measures. Specifically, changes from baseline required higher doses on behavioral performance measures and lasted for a shorter duration of time than was the case with certain subject-reported and physiologic measures. Such data imply that a simple determination that atropine exposure has occurred does not rule out the possibility that baseline performance levels can be maintained.

The time course of effects obtained in this study are generally consistent with those reported previously, however, the time-action curves include values not previously reported and these have revealed several interesting findings. For example, the atropine-induced heart rate elevations have been well documented, but the subsequent decreases in heart rate, to our knowledge, are not typically reported with atropine (12). Similarly, behavioral performance decrements, which peaked within a few hours and then began to dissipate, were still significant on some measures at 7 to 9 hr postdrug. As also has been reported [e.g., (7)], effects on blood pressure were not robust. Furthermore, the time course of changes obtained in the present study revealed that blood pressure values varied in a complex fashion over time following administration of either atropine or placebo. Such data indicate that conclusions drawn regarding possible effects on blood pressure may be of limited generality depending upon the dose administered and the timing of the measures.

Along with orderly changes in certain physiological systems, subjects exhibited clear evidence of impairment on all of the behavioral procedures. These changes, however, were dose- and time-dependent, which may explain earlier reports of little or no disruption on certain kinds of performance [e.g., (7)]. Specifically, atropine consistently diminished overall rates of responding across all of the tasks when the 6.0 mg dose was administered and often when the 3.0 mg dose was administered. Accuracy of responding was also disrupted, although it sometimes required a larger dose to disrupt accuracy than to suppress response rates. On the DSST task, for example, rates were suppressed by both the 3.0 and 6.0 mg doses, whereas only the latter dose decreased the percent of trials done correctly. The 1.5 mg/kg dose generally did not produce significant effects on the behavioral tasks used in this study. Behavioral performance remained disrupted for 7 to 9 hours following administration of the 3 and 6 mg doses, but was intact the following morning illustrating the absence of a "hangover" effect even with these large doses.

While behavioral performance was not significantly disrupted by the 1.5 mg dose, subjects reported they could detect drug effects. Overall, subjects reported a profile of generally unpleasant effects at all three atropine doses. These effects were dose-dependent increases in "bad" effects, along with increases in "nausea," "confusion," "restlessness," "sleepiness," and "blurred vision." Scores on subject-report scales typically associated with drugs of abuse (drug liking, good effects, and MBG scale of the ARCI) were not significantly increased. These effects are also consistent with earlier findings that atropine is *not* a drug with a high liability for abuse (8). Atropine administration increased scores on the LSD and PCAG scales, which is consistent with previously reported sedating, mildly hallucinogenic, and dysphoric effects (12) as well as findings of an earlier study which included the ARCI (8). As with the measures of behavioral performance, most effects on the self-report scales had dissipated by 24 hours postdrug.

Overall, the results from the present study show that atropine administration produces orderly and generally dose-dependent physiological and behavioral changes. The specific time course of

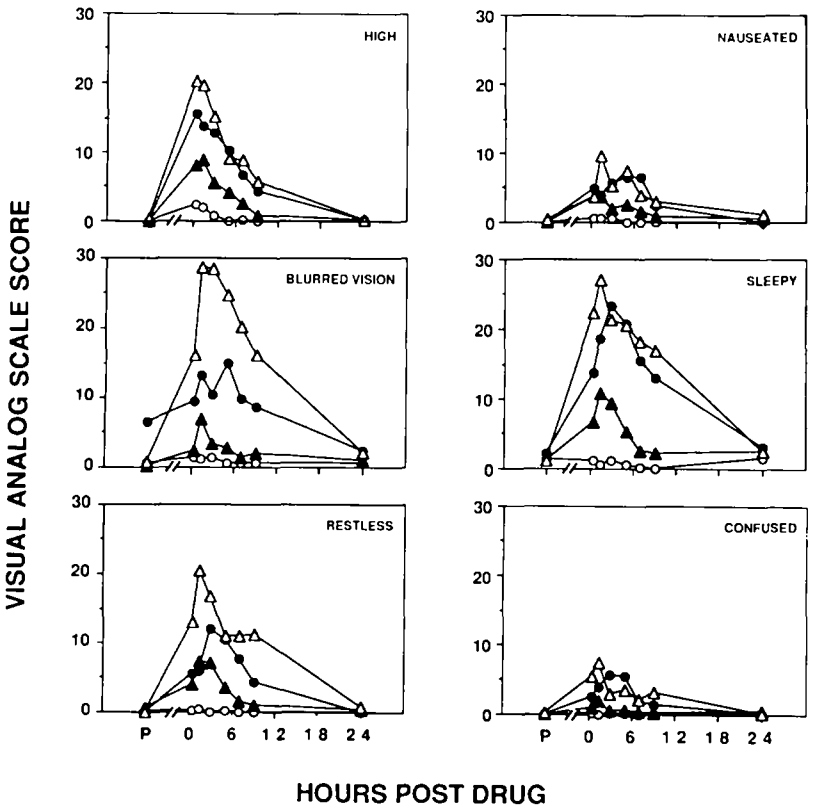

FIG. 6. Mean visual analog scores taken from 0–50 point rating scales are shown for each of the specific symptomatic measures of drug effects as a function of time since drug or placebo was given, and immediately prior to the injections ("P"). Symbols are as in Fig. 1.

effects and dose sensitivity depend upon the measure used, however. Therefore, precise predictions of behavioral decrements cannot be made simply on the basis of verification of exposure. In fact, exposure data based simply upon self reports and physiologic changes may overestimate the degree of performance impairment expected. In general, physiologic and subject-rated effects began by 30 min postdrug, peaked within 60 minutes postdrug, and then began to dissipate very slowly over the next 24 hours. In contrast, with measures of behavioral performance, disruption often did not peak until 3 to 5 hours after drug administration, and then subsided to baseline values within a few hours more. Although these performance measures revealed significant behavioral impairment, subjects remained generally verbally coherent and physically coordinated.

TABLE 3

MEAN VALUES OF SCORES FROM THE ADDICTION RESEARCH CENTER INVENTORY

	Drug Condition			
Scale	Placebo	1.5 mg	3.0 mg	6.0 mg
LSD	4.3	5.4	7.8	8.3
PCAG	2.9	3.8	4.7	6.3
MBG	2.7	1.7	0.8	1.0

Regarding the mechanism of action of the effects of atropine on behavioral performance, it should be noted that the present study provides little basis for determining the degree to which the effects observed involved the central nervous system and/or changes in visual function. Specifically, independent measures of visual acuity and accommodative amplitude were not assessed, although earlier findings, that atropine does impair such functions suggests that at least part of the behavioral performance disruption was secondary to visual system impairments (7). The involvement of changes in central nervous system function should be at least partially revealed in the pending analysis of the electrophysiologic data from this study.

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