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Psychoactivity of Atropine in Normal Volunteers[1]

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PENETAR, D M AND J E. HENNINGFIELD *Psychoactivity of atropine in normal volunteers* PHARMACOL BIOCHEM BEHAV 24(4) 1111–1113, 1986.—Subjective effects of atropine sulfate injections were assessed in normal volunteers (n=10), as one portion of a 3-part study (behavioral, subjective and physiologic effects of atropine) Each volunteer was given 0, 2 or 4 mg/70 kg atropine sulfate intramuscularly according to randomized block sequences on different test days. To assess psychoactivity of atropine, the Single Dose Questionnaire (SDQ) and the Addiction Research Center Inventory (ARCI) were given 1 hr before and 1 hr following drug injections Data from the SDQ indicated that atropine produced significant discriminable effects but did not elevate scores on a drug liking scale Data from the ARCI indicated that atropine produced significant sedative-like effects (pentobarbital-chlorpromazine-alcohol scale). Taken together, the data from the psychometric instruments confirms that atropine is a drug of relatively low abuse potential.

Atropine Psychometrics Cholinergic antagonists Human research
Addiction Research Center Inventory Drug abuse Performance assessment battery

ATROPINE sulfate (d,l-hyoscyamine) is a muscarinic cholinergic antagonist that readily crosses the blood brain barrier and produces widespread central and peripheral effects. The physiologic effects of atropine have been studied extensively because of its use in clinical medicine and research [9]. For example, atropine is used in the treatment of accidental pesticide poisonings involving organophosphorus anticholinesterase agents Since military personnel may be "at risk" to such poisons, field kits for certain personnel include atropine-loaded injectors. Such widespread distribution of atropine could have a variety of unintended implications, such as nontherapeutic use (abuse) and adverse influences on mood, cognition, and psychomotor performance. The potential consequences are relevant to the highly demanding duties of today's military forces and to the precise technological tasks required in support of military operations.

The possibility that atropine may be nontherapeutically used is suggested by its use in combination with hallucinogens, and its occasional abuse for its mixed hallucinogenic activity [7]. Consistent with these reports are the data that atropine sulfate and other centrally acting muscarinic antagonists are psychoactive, as witnessed by their potential to produce profound changes in mood and feeling states such as restlessness, disorientation, and hallucinations [9]. Two psychometric instruments of widely accepted utility and validity are routinely used to assess the psychoactivity and abuse liability of drugs: they are the Single Dose Questionnaire (SDQ) and the Addiction Research Center Inventory (ARCI) [8]. Although they are generally used to assess drugs in drug-abusing subjects, they yield consistent results in evaluating nondrug abusing subjects [3,8]. The instruments can characterize the qualitative aspects of subjective effects of drugs, and help to determine whether or not the drug is likely to be abused. Findings using such measures of subjective effects are generally consistent with those obtained in animal studies and epidemiologic findings of patterns of drug abuse [1,2].

We utilized the SDQ and ARCI to characterize the psychoactivity of atropine and to assess its abuse liability in a nondrug abusing population. In the present report, we describe results of our preliminary investigation. Both instruments were sensitive and provided useful information. The results confirmed that, despite some sedative-like effects, atropine does not share the subjective profile of drugs that are widely abused.

METHOD

Subjects

Ten male volunteers with a mean age of 26.1 years (range, 22–31) participated in the study and are described in greater

[1]Human subjects participated in these studies after giving their free and informed voluntary consent Investigators adhered to AR 70-25 and USAMRCD Reg 70-25 on the use of volunteers in research. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense (AR 360-5)

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TABLE 1
AGE, WEIGHT, EDUCATION, AND DRUG USE OF VOLUNTEERS

	Age (year)	Weight (kg)	Education (year)	Beer/Wine Use*	Other Drug Use
1	22	64 5	12	6/month	no history
2	29	68 2	12 5	4/day	marijuana, occasionally
3	31	67 3	16	4/week	marijuana, occasionally
4	26	75 0	12	2/week	marijuana, twice per month
5	30	95 5	17	2/day	no history
6	24	68 2	13	2/week	marijuana, twice per week
7	25	68 2	20	2/day	marijuana daily, previous cocaine use
8	24	75 0	19	2/day	marijuana, occasionally
9	26	81 8	14	2/day	marijuana daily, previous sedative and hallucinogen use
10	24	68 2	18	2/week	marijuana, occasionally

*12 oz bottle of beer or 4 oz glass of wine drinks

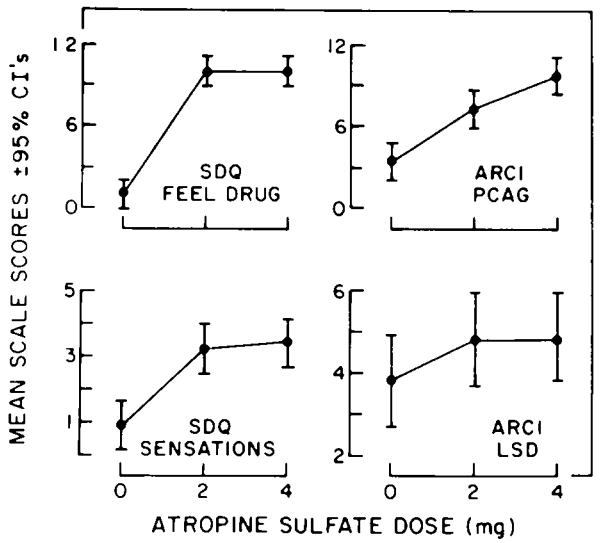

FIG 1 Mean scores on scales of the Single Dose Questionnaire (SDQ) and the Addiction Research Center Inventory (ARCI) are shown as a function of intramuscularly given atropine sulfate Brackets indicate 95% confidence intervals about the points Scores are mean (n=10 subjects) change scores obtained by subtracting pre-drug scale scores from post-drug scale scores

detail in Table 1 None of the participants was a drug abuser or had a history of drug dependence Eight had limited experience in recreational use of drugs other than alcohol None of the participants smoked cigarettes, and all were physically fit and healthy at the time of the study Volunteers were not permitted to drink alcohol the night before or for two days following an experimental session, and were required to remain free of other drugs for the duration of the study Breathalyzer and periodic urinalysis assured compliance Volunteers were particularly cautioned not to take over-the-counter cold medications during the study All volunteers were high school graduates, five had some college, and three were working on advanced degrees Each volunteer gave his informed written consent before participating in the study.

Drug

Atropine sulfate (American Quinine Co , Inc) was purchased in 1 mg/ml ampules. Doses of 2 and 4 mg per 70 kg body weight were given by intramuscular injection to the upper arm in less than a 5-sec bolus. Placebo consisted of 2 ml of bacteriostatic physiological saline given in the same place and manner as the drug All injections were given according to a random block design whereby each subject received each dose and placebo across test days Double-blind procedures were followed Test days were separated by at least 72 hr but each subject completed the three test days within two weeks.

Psychometric Instruments

Two psychometric instruments which have been validated and are widely used in the assessment of centrally mediated drug effects were used in the present study One is the Single Dose Questionnaire (SDQ) which contains four scales the first is a one-line true/false item (Do you feel the medication?) used to determine psychoactivity; the second is a 14-item list of substances from which the subject was asked to choose which the administered compound was most similar to, thereby permitting classification, the third is a 14-item list of "sensations" (including "normal" and "high"), which characterizes and quantifies symptoms, the fourth is a 5-point "Liking" scale which is a measure of euphoria [3,8] The other psychometric instrument is the Addiction Research Center Inventory (ARCI), a true-false questionnaire with empirically derived scales sensitive to various classes of psychoactive substances [3,8] A 40-item version of the ARCI was used, it contained subsets from three scales (1) the Morphine-Benzedrine Group (MBG) scale, which reflects feelings of euphoria and well-being; (2) the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) Scale, which reflects sedation and intoxication, (3) the Lysergic Acid Diethylamide (LSD) scale, which reflects dysphoria and feelings of fear

Procedure

Questionnaires were administered twice on each experimental day, approximately 1 hr before and 1 hr after drug injection. Thirty minutes after an injection a subject was tested in a computerized pursuit tracking task which required about 20 min of vigilant performance After the pursuit tracking task, a number of visual functions were evaluated by an optometrist and measurements of heart rate and blood pressure were made Volunteers then filled out the SDQ and the ARCI, which required about 5 min each time, individually while seated in a laboratory office environment All subjects were told to answer the questions based on how they felt at that moment. As part of the volunteer consent process, subjects were briefed as to range of physiologic and psychologic effects than can be produced by atropine.

TABLE 2

FREQUENCY OF SELF-REPORTED SYMPTOMS AS A FUNCTION OF DRUG CONDITION*

	Normal	Relaxed	Nodding	Sleepy	High	Total†
Placebo	7	4	0	0	1	5
2 mg	2	5	3	5	7	20
4 mg	0	6	7	7	8	28

*Occasional positive responses on the following additional SDQ items were not related to dose drive, other, coasting, pleasant sick, nervous, and turning stomach

†Not including "normal" responses

RESULTS

Both the SDQ and the ARCI were sensitive to atropine administration. Specifically, when analyzed according to a one-way analysis of variance, the data indicated that participants discriminated reliably both doses from placebo, as assessed by the first scale on the SDQ ($p<0.001$). Total number of self-reported symptoms, as assessed by the third scale on the SDQ, were also significantly elevated by atropine ($p<0.01$) Liking scale scores were not significantly changed by atropine, however Liking scores by Subjects 1, 2, 4 and 5 were mildly elevated by atropine as compared to placebo. On the second scale of the SDQ, subjects identified the injections as "blank" following 90% of placebo injection, after 2 mg 20% of the volunteers responded "blank," and after the 4 mg injection 10% responded "blank " After 2 mg of the drug, 20% indicated "downers," and after 4 mg, 30% indicated "downers."

The most frequently reported sensations produced by atropine injections were "relaxed," "nodding," "sleepy," and "high" (Table 2). The frequency of occurrence of these sensations, either separately or as a group, was directly related to atropine dose level, and always exceeded placebo. Conversely, self-reported "normal" was inversely related to dose level

Consistent with occasional identifications of "downers" on the SDQ, scores on the PCAG ("Sedative") scale of the ARCI were significantly increased in direct response to atropine dose ($p<0.001$) As shown in Fig 1, LSD ("Dysphoria") scale scores were slightly, but nonsignificantly increased A somewhat stronger, but also nonsignificant, trend was for MBG ("Euphoria") scale scores to decrease. Despite the absence of increased mean scores on the MBG and Liking scale score, four volunteers showed increased Liking and two volunteers showed increases in MBG scale scores One of these had also shown an increase in his Liking score.

Significant elevations in diastolic blood pressure (but not systolic) and pulse rate were observed for both doses tested. Dose-related changes in pursuit tracking performance and visual functions (e.g , pupil size, accommodation, visual acuity) were orderly and will be reported in subsequent papers

DISCUSSION

Both of the Addiction Research Center instruments provided useful information regarding the subjective effects of atropine in this nondrug abusing population. The effects on these instruments were consistent with effects obtained on other instruments used in the study. Data from the Single Dose Questionnaire indicated that both doses of atropine were psychoactive and produced reliably discriminated symptomatic effects The Addiction Research Center Inventory confirmed that the psychopharmacologic profile of interoceptive effects produced by atropine was predominantly sedative-like. Scores on either, or both, the euphoriant scales (Liking scale of the SDQ and MBG scale of the ARCI) were elevated in certain individuals but not in the group results. This profile of subjective effects is consistent with clinical descriptions of the effects of atropine [9].

Previous research has shown that scores from the MBG scale generally covary with "Liking" scale scores, supporting the notion that this scale reflects euphoric drug effects [8]. Dose-related increases in "Liking" and MBG scale scores are the hallmark subjective effects of abused drugs and define a drug as a euphoriant. Atropine did not produce the striking dose-related increases in scores on the euphoria scales that are produced by most dependence-producing drugs in known drug abusers or of psychomotor stimulants in normal and drug-abusing volunteers [8]. Therefore, this study confirms that atropine has limited abuse potential. However, sedatives such as alcohol, and possibly other psychoactive drugs, may selectively produce elevations in euphoria scales among persons with histories of sedative abuse or alcoholism [3–6]. Whereas such individuals were not used in the present study, it is plausible that persons with histories of sedative abuse or alcoholism would be vulnerable to abuse of a drug with some sedative-like interoceptive effects.

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