Cardiovascular Effects of Atropine and Neostigmine in Man

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Effects of atropine and neostigmine on heart rate, P-R duration, cardiac output, and total peripheral vascular resistance were studied. In six volunteers neostigmine slowed heart rate, prolonged P-R duration, and shifted the dose–response curve of atropine on heart rate to the right. Atropine sulfate 0.2 mg/70 kg body weight, whether given before or after neostigmine, slowed heart rate but shortened P-R duration significantly. Larger doses of atropine increased heart rate and cardiac output and further decreased P-R duration. In one subject premedicated with 0.8 mg neostigmine methylsulfate/70 kg body weight, 0.2 mg of atropine sulfate produced A-V dissociation.

INTRAVENOUSLY-ADMINISTERED ATROPINE, depending upon dose, can either decrease or increase heart rate, cardiac output, and the P-R duration of the electrocardiogram.[1, 2] In conscious as well as anesthetized dogs, we recently observed that P-R duration may be significantly prolonged at a time when heart rate was accelerated by atropine.[2] In dogs, neostigmine shifted the dose–response curve of atropine on heart rate to the right, but had little effect on the action of atropine on P-R duration. The present study was designed to examine the interaction of atropine and neostigmine on heart rate, P-R duration, and cardiac output in conscious man.

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Methods

Six fit young men without known cardiovascular disease volunteered for the study. The subjects fasted and were studied in the early morning after they had rested for about an hour in the supine position. The radial artery and cephalic vein were cannulated. Arterial blood pressure was recorded on a Grass polygraph using a Statham transducer. Cardiac output was determined by the dye-dilution method with indocyanine green (Cardio-Green §) and a Colson densitometer. Total peripheral resistance was calculated in the conventional way from mean arterial pressure and cardiac output. The mean pressure was assumed to equal the diastolic pressure plus one-third of the pulse pressure. Heart rates were counted for a full minute. Each P-R duration reported is the average of four P-R durations taken from the beginning, the middle and the end of ECG tracings obtained at the indicated times. The P-R duration is defined as the distance from the beginning of the P-wave to the peak of the R-wave. Paper speed of the electrocardiograph was 100 mm/sec when P-R durations were determined.

Commercially-available solutions of atropine sulfate (Burroughs Wellcome) and neostigmine methylsulfate (Prostigmine, Hoffmann–LaRoche) were used. Drug doses are expressed as the weight of the salts per 70 kg body weight. All medications were given into the cephalic vein via a 17-gauge plastic catheter which was flushed with 5 ml of heparinized saline solution after each dose.

Atropine was given in increasing doses of 0.2 (I), 0.4 (II), and 1.2 mg (III), *i.e.*, a

§ Supplied by Hynson, Westcott and Dunning, Inc.

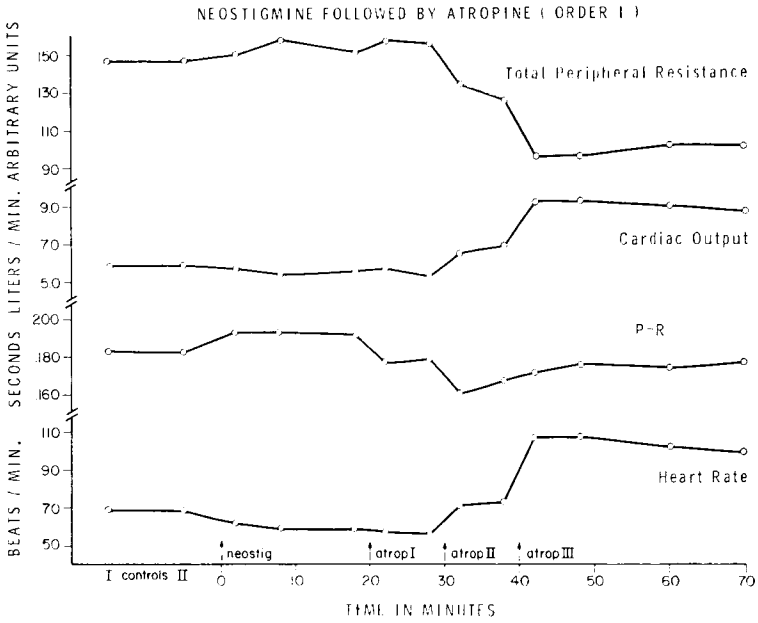

FIG. 1. Six normal volunteers were given intravenously 0.8 mg neostigmine methylsulfate followed by 0.2 (I), 0.4 (II), and 1.2 (III) mg atropine sulfate/70 kg body weight. Mean values of total peripheral resistance, cardiac output, P-R duration and heart rate are shown. The arrows indicate time of drug injection. For statistics see text and table 1.

total of 1.8 mg/70 kg, whereas neostigmine was injected as a single dose of 0.8 mg/70 kg body weight. Each subject was studied under two different conditions: once neostigmine was given before (designated "order I"), once after, the atropine (designated "order II"). Three subjects were studied first with order I, then with order II; in the other three the sequence was reversed. Two weeks were allowed to elapse between drug exposures.

Prior to the injections of drugs, heart rate did not change significantly for ten minutes. At this time, two cardiac output determinations were carried out and pressures were measured. When atropine was given first, doses I, II, and III were injected at ten-minute intervals, and the cardiovascular variables recorded two and eight minutes after each injection. Ten minutes after the last injection, neostigmine was given, and two, eight, 20 and 30 minutes later, the measurements were repeated. When neostigmine was given first, cardiovascular measurements were made two, eight, and 18 minutes after the injection. Then the series of atropine injections was given at ten-minute intervals, 20 minutes after the neostigmine injection.

For statistical analyses, t tests and analyses of variance [3] were computed.

Results

Since blood pressures did not vary significantly, blood pressure data are omitted.

Figure 1 shows the mean effects for the order I (neostigmine before atropine) experiment. Neostigmine 0.8 mg/70 kg caused a significant ($P < 0.01$) prolongation of P-R duration and decrease in heart rate. After the first dose of atropine, injected 20 minutes later, heart rates slowed slightly ($P < 0.05$), but the P-R duration shortened significantly ($P < 0.01$). With the second and third doses of atropine, the expected increases in heart rate occurred concomitantly with an increase in cardiac output and a decrease in calculated total peripheral vascular resistance, as described previously.[1] With dose II of atropine, the P-R duration shortened further, but dose III had no additional significant effect on P-R duration.

Figure 2 shows the same effects for order II where atropine was followed by neostigmine. After dose I of atropine, heart rate decreased significantly ($P < 0.05$) within two minutes after injection and remained below the baseline for eight minutes. The P-R duration shortened within eight minutes after injection ($P < 0.05$). The subsequently-injected dose II and dose III of atropine accelerated heart rate significantly and increased cardiac output,

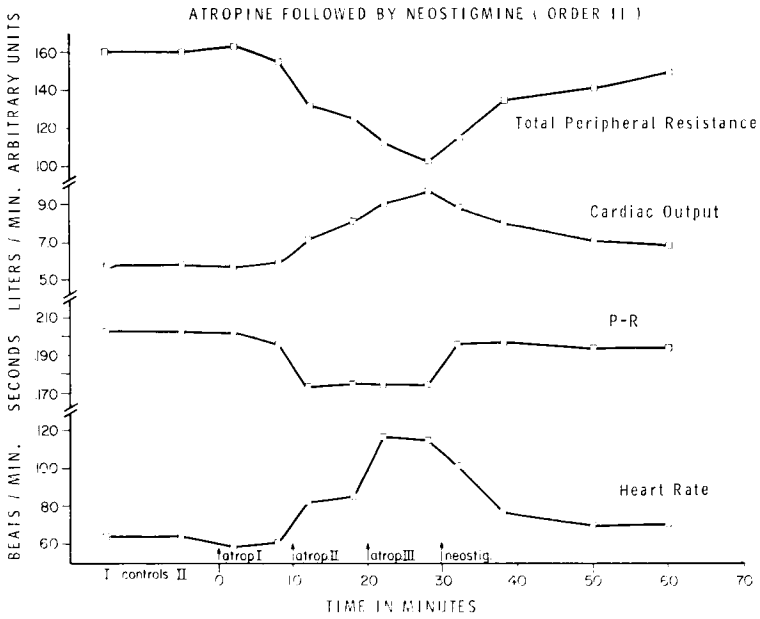

FIG. 2. Six normal volunteers were given intravenously 0.2 (I), 0.4 (II), and 1.2 (III) mg atropine sulfate followed by 0.8 mg neostigmine methylsulfate/70 kg body weight. Mean values of total peripheral resistance, cardiac output, P-R duration and heart rate are shown. The arrows indicate time of drug injection. For statistics see text and table I.

and, since the blood pressure remained unchanged, decreased total peripheral resistance. The P-R durations were shortened further by dose II of atropine, but did not change with dose III. The injection of neostigmine resulted in a significant ($P < 0.05$) prolongation of P-R duration, which once again approached control values.

Some of the data are summarized in table I, showing an analysis of variance in which the effects of the first dose of atropine and the action of neostigmine are examined. The main effects of the drugs, the time, and the order of administration on heart rate and P-R duration were analyzed. The slowing effect of neostigmine was markedly greater in order II than in order I. The table shows that the first dose of atropine decreased heart rate while it shortened (rather than lengthened) P-R duration. This is in contrast to neostigmine, which also decreased heart rate but at the same time (as expected) prolonged P-R duration. While the order affected the degree of response it did not alter the direction of the response. Neostigmine did not measurably affect the action of atropine on cardiac output or calculated total peripheral resistance, but it did alter the atropine effect on heart rate. The acceleration of heart rate by atropine doses II and III was significantly less ($P < 0.05$) in subjects pretreated with neostigmine than in subjects not so pretreated. The slowing of heart rate after atropine dose I was statistically indistinguishable in order I and order II experiments.

In one subject pretreated with neostigmine, a cardiac arrhythmia occurred after the first dose of atropine. P-R durations ranged from 0.175 seconds to 0.430 seconds and P-P intervals varied from 0.80 seconds to 1.0 seconds in an irregular sequence. A-V block appeared for brief periods. The disturbance vanished with the second atropine dose and was not seen in this subject after neostigmine or after atropine dose I when this had not been preceded by neostigmine.

Discussion

The effects of atropine on cardiac output, heart rate and total peripheral resistance will not be further discussed, since they confirm previous reports.[1] In the present study, cardiac output changed parallel with heart rate and blood pressure was not affected; hence, total peripheral resistance changed inversely with cardiac output. Premedication with neostigmine shifted the atropine dose–response curve on heart rate slightly but consistently ($P < 0.05$) to the right. A larger series of

TABLE 1. Analysis of Variance

Comparison of Initial Heart Rate Responses (Mean Drug Effects)				
Order	Atropine		Neostigmine	
	2 min	8 min	2 min	8 min
I	− 2.2	− 2.8	− 6.7	− 9.7
II	− 3.5	− 2.5	− 14.3	− 38.2

Source	Significance
Main effects	
Drug	$P < 0.01$
Time	$P < 0.01$
Order	$P < 0.01$
Interactions—drug:time:order	$P < 0.01$

Comparison of Initial P–R Duration Responses (Mean Drug Effects)				
Order	Atropine		Neostigmine	
	2 min	8 min	2 min	8 min
I	− 0.015	− 0.013	+ 0.010	+ 0.010
II	− 0.001	− 0.006	+ 0.021	+ 0.023

Source	Significance
Main effects	
Drug	$P < 0.01$
Time	N.S.
Order	$P < 0.01$
Interactions—drug:time:order	N.S.

* The effects of 0.2 mg atropine sulfate and 0.8 mg neostigmine methylsulfate on heart rate and P-R duration are analyzed. In order I the neostigmine was given first, followed 20 minutes later by atropine. In order II the drugs were given in reverse sequence (see text).

experiments would probably reveal that neostigmine also affects the response of cardiac output and peripheral resistance to atropine. In our small group the observed neostigmine effects on output and resistance may have arisen by chance.

In the dog, 0.006 to 0.01 mg atropine sulfate/kg body weight given intravenously prolonged the P-R duration, while higher doses (up to 1.0 mg/kg) shortened it.[2] This observation was remarkable because prolongation of the P-R duration occurred in dogs when heart rate was accelerated by atropine. In these dogs the P-R duration shortened only with the higher atropine doses, when tachycardia was pronounced. This suggested that the anticipated relationship between heart rate and P-R duration, *i.e.*, prolongation of P-R duration with slowing of heart rate and shortening of P-R duration with acceleration of heart rate, did not exist when atropine produced changes in heart rate. In the present study in man we again have evidence that atropine may affect heart rate and P-R duration in opposite directions. Here, unlike our observations in the dog, even the smallest dose of atropine shortened the P-R duration, although this same dose slowed the heart rate.

The P-R duration as here defined encompasses the P-wave, the P-R segment (end of P-wave to beginning of R-wave) and the upstroke of the R-wave. Changes in P-R duration therefore could be caused by changes in any of these. After conclusion of the study here reported we have employed better recording equipment and have measured, in man, P duration, P-R segment, and R duration separately. On the basis of these so-far-unpublished observations we can state that the R duration is not affected by atropine in this dose range and that much of the change in P-R duration is brought about by an effect on the P-wave. These unpublished studies confirm that atropine may shorten P-R duration while slowing heart rate.

Neostigmine slowed heart rate and prolonged P-R duration according to the classic concepts of cholinergic effects on cardiac rate and conduction. It thus serves well as a contrast to atropine and its bradycardic effects. It is interesting that heart rate was slowed much more profoundly by neostigmine when this cholinesterase inhibitor was given as the second drug (table 1). We probably should not simply assume that neostigmine could exert a greater effect in subjects with high heart rates (after atropine) than in subjects with average normal heart rates. In an earlier study,[4] neostigmine lowered heart rate in subjects tachycardic from an injection of ephedrine about as much as neostigmine lowered heart rate in unmedicated volunteers. In subjects rendered tachycardic by atropine, however, neostigmine seemed to be much more

effective in slowing rate. We assume that a waning atropine effect, a shift of the dose–response curve of atropine to the right, and an unmasking of the bradycardic effects of small atropine doses all contributed to this effect.

The results of this study provide no definite explanation but raise several important points that must be pondered every time atropine is used clinically, particularly in combination with agents such as neostigmine, which also affect the heart via an interaction with acetylcholine. We can identify three different effects of atropine:

1) In low doses atropine lowers heart rate. It may therefore enhance rather than counteract a bradycardia produced by neostigmine.

2) In high doses atropine increases heart rate. It may therefore counteract the bradycardic effects of neostigmine.

3) Apparently unrelated or at least not in parallel with either slowing or the quickening effects of atropine on heart rate, this drug affects conduction through the atria, as measured by the P-R duration.

In this present study neostigmine served primarily as a drug that can also decrease heart rate, but in contradistinction to atropine it always prolonged P-R duration when slowing rates. Arrythmias seen with atropine should therefore be examined to see whether atropine's divergent effect on rate, on the one hand, and on conduction, on the other hand, may have been responsible for or contributed to the development of arrythmia. Theoretically we worry about giving a drug that can decrease rate and at the same time shorten rather than facilitate conduction, or that will increase rate and simultaneously lengthen rather than shorten conduction through the atria.

The occurrence of cardiac arrhythmias following the administration of atropine in a subject pretreated with neostigmine may serve as a reminder that cardiac arrhythmias are not uncommon and that fatal cardiac arrest has been reported in patients under anesthesia who were given atropine and neostigmine in the reversal of curarization.[5] Under which circumstances arrhythmias can occur, and what interaction of atropine and neostigmine on conduction and on rate are required, as well as the role of anesthesia in this interplay of drug effects, remain to be described. We need data on the actions of atropine on the membranes of pacemaker and conduction tissue in the heart. We must learn what atropine does to rate of depolarization, threshold potential, resting membrane potential and refractory period. Our studies and much other evidence suggests that it does more than simply mimic and then counteract the effects of acetylcholine on the heart.

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