Effect of Intravenous Atropine and Methylatropine on Heart Rate and Secretion of Saliva in Man

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Summary. Intravenous atropine sulphate (0.25, 0.40, 0.75 and 1.50 mg), atropine methylnitrate (0.08, 0.13 and 0.25 mg) and saline were given to 72 healthy medical students. The effects on heart rate and rhythm, systolic and diastolic blood pressure and salivary secretion were studied. Salivation was inhibited by all the doses of the two drugs. There was a clear dose-response relationship and methylatropine was about 3 times as potent as atropine. Heart rate was accelerated by 0.75 and 1.50 mg atropine, and 0.25 mg methylatropine, whereas 0.25 mg atropine and 0.08 and 0.13 mg methylatropine induced bradycardia, which was considered to be due to a peripheral action. It is suggested that the drugs act as partial agonists at muscarinic receptors. No clear effect on blood pressure was seen, except for the highest dose of atropine, after which the diastolic pressure was increased. 20 out of 59 subjects who received anticholinergics developed supra-ventricular arrhythmias; with both drugs periods of nodal rhythm were most common. They appeared shortly after the injection and usually lasted for a few minutes.

Key words: Atropine, methylatropine, heart rate, saliva secretion, arrhythmia.

Large doses of atropine increase the heart rate by blocking vagal effects on the sinus node. However, doses of atropine less than 0.4 - 0.6 mg produce bradycardia in unanaesthetized adult man (Dauchot and Gravenstein, 1970; Eger, 1962; Gravenstein et al., 1964; Gravenstein et al., 1969; Harris, 1921; McGuigan, 1921; Rudolf and Bulmer, 1924). A transient bradycardia may be noticed before the tachycardia when large doses are administered by subcutaneous or intramuscular injection (Cullumbine et al., 1955; Hayes et al., 1971; McGuigan, 1921), or by slow intravenous infusion (Morton and Thomas, 1958; Nalefski and Brown, 1950). It is generally assumed that the bradycardia following small doses of atropine is caused by stimulation of the vagal nuclei in the medulla oblongata (Eger, 1962; Goodman and Gilman, 1970). The purpose of the present study was to test this hypothesis by administering small doses of atropine methylnitrate to human volunteers. This quaternary derivative of atropine is a charged molecule and is believed not to pass the blood-brain barrier to the same extent as atropine (see Discussion).

De Padua and Gravenstein (1969) did not find any significant change in heart rate after small doses of atropine methylbromide given intravenously to pregnant women, whereas large doses caused tachycardia. However, two other quaternary anticholinergic drugs were found to cause transient bradycardia before tachycardia after oral administration to healthy volunteers. Wahlström and Widerlöv (1968), using scopolamine methylnitrate, found a statistically significant bradycardia, while Sundwall et al., (1973) with emepronium observed bradycardia, which was not statistically significant. Further, Hayes and Parr (1970) reported slowing of the heart rate after subcutaneous injection of homatropine methylbromide.

A further purpose of the present investigation was to study the effects of different doses of atropine sulphate and atropine methylnitrate on the secretion of saliva and heart rate in order to compare the relative potency of the two drugs in man.

Material and Methods

The study was designed as a randomized double blind experiment in pharmacology and was performed during three consecutive terms as a student class experiment. The subjects for the experiments were volunteers, healthy male and female medical students. Their ages ranged from 21 to 41 years, with a mode of 22 years. Students with a history of heart disease were excluded. The subjects were examined before the experiment by auscultation of the heart and electrocardiography using leads I-III and V4. A few students were excluded after this examination because of murmurs or some electrocardiographic abnormality. Each subject was used only on one occasion, either with placebo or one dose of one drug. The subjects lay on a bed throughout the experiment. They were not allowed to eat, drink or smoke.

The drugs given were atropine sulphate (AS), in
doses from 0.25 to 1.50 mg, and atropine methyl-nitrate (AMN), in doses from 0.08 to 0.25 mg; the doses are those of the salt. One group also received 0.9 % saline as a placebo control (Table I). The highest AS dose was given as a commercial product (Atropine® 0.5 mg/ml ACO); the other doses were isotonic solutions prepared by the hospital pharmacy. The drugs were given as an intravenous injection of 3.0 ml of solution over 30 seconds, shortly after a venous cannula had been inserted.

Heart rate, systolic and diastolic blood pressure and salivary secretion were studied for one hour. Electrocardiographic recordings were performed during the first 10 minutes, and if arrhythmias occurred the recordings were continued until the electrocardiogram was normal. The electrode positions used were leads II and V4. The subjects were not able to observe their electrocardiograms. Heart Rate was measured every minute from the electrocardiographic recording during the first 10 minutes, and thereafter by manual palpation of the radial or carotid artery every five minutes up to 45 minutes. The last value was recorded at 60 minutes.

Blood Pressure was measured with an ordinary clinical blood pressure cuff by stethoscopic auscultation of the brachial artery. The diastolic pressure was taken as that point at which sounds could no longer be heard. Pressures were recorded every 5 minutes between 5 - 45 minutes and the final value was obtained at 60 minutes.

Secretion of Saliva was measured by a method modified from Herxheimer and Haefeli (1966). The subjects swallowed all the saliva in the mouth and then chewed half a tablet of ascorbic acid (Hybrin® 500 mg, Pharmacia). After 30 seconds of chewing, the saliva and fragments of tablet were collected in a measuring glass. The saliva produced during the following 30 seconds was also collected and the total amount of acid-stimulated secretion during one minute was determined. Salivary secretion was measured four times during the experiment, at 5, 30, 45 and 60 minutes, immediately after the heart rate had been measured.

Pre-Experiment Values. Before the drugs were administered the subjects relaxed on a bed for at least half an hour. They were considered to have stabilized when three consecutive values for heart rate did not differ by more than two beats per minute, and for blood pressure by not more than 5 mm Hg. The means of three consecutive steady-state values recorded at two minute intervals were calculated for heart rate and blood pressure. The mean of two sets of saliva samples collected with an interval of at least five minutes between specimens was also calculated.

The absolute differences between the values of heart rate and blood pressure recorded during the experiment and the pre-experiment values were calculated for each subject. The values of salivary secretion were calculated as a percentage of the pre-experiment value for each subject. The corresponding experiments were then grouped together and the mean and standard error of the mean calculated.

Results

A. Effects of Placebo Administration

Heart Rate. The heart rate remained unchanged throughout the entire experiment with the exception of a small transient decrease after administration of a 0.08 mg dose of AS (Fig. 1).

Fig. 1. Heart rate (beats/minute) after placebo. Mean ± s.e.m. Number of experiments = 13

Table 1. Numbers of experiments with different doses of atropine sulphate, atropine methylnitrate and saline

<table>
<thead>
<tr>
<th>Date of experiments</th>
<th>Atropine sulphate (mg)</th>
<th>Atropine methylnitrate (mg)</th>
<th>Saline</th>
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<td>0.08 0.13 0.25</td>
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<tr>
<td>Total number of experiments</td>
<td>13 5 6 12</td>
<td>13 5 5 13</td>
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More experiments were done with the lowest doses of AS and AMN, since the main purpose was to study the effect of a small dose of the drugs, and with the highest dose of AS, because the study was performed as a class experiment, and the clearcut effects of the high dose were suitable for the demonstration of antimuscarinic effect.