Central and Peripheral Effects of Muscarinic Cholinergic Blocking Agents in Man

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The effects of scopolamine, methscopolamine, atropine, and l-hyoscymine were compared in patient-volunteers without premedication, on an equimolar basis on: (1) visually evoked responses (VER), spontaneous EEG activity, and sedation as an index of a central nervous system action; (2) spontaneous heart rate; and (3) dilute citric acid-induced salivary flow. Scopolamine significantly depressed the early components of the VER, which correlated with the state of wakefulness, and caused simultaneous changes in the alpha rhythm of the EEG towards relaxation or sedation. Atropine, l-hyoscymine, and methscopolamine had no significant effect on the VER and EEG in equimolar doses. Methscopolamine caused the greatest increase in heart rate, followed by atropine and scopolamine, each of which increased the heart rate within two minutes. The scopolamine-induced increase lasted only about 10 minutes, whereas the effect of atropine, l-hyoscymine, and methscopolamine continued for 30 minutes or more. Ten to 30 minutes following scopolamine bradycardia was observed. Equimolar doses of l-hyoscymine were more effective than atropine in increasing the heart rate. With regard to blockade of salivary flow the following order of effectiveness was obtained: methscopolamine > scopolamine > l-hyoscymine > atropine. A dose of l-hyoscymine consisting of half the dose of atropine produced about the same effects, indicating the relative ineffectiveness of the d-hyoscymine fraction of atropine.

A great deal of information is available on the antispasmodic and vagal blocking actions of atropine, scopolamine, and related drugs. Edwards and Eger concluded from a review of the literature that the relative potency of atropine and scopolamine varies in their actions on different organ systems. The effect of atropine on the heart appears to be greater than that of scopolamine, but in most other actions the effects of scopolamine equal or exceed those of atropine. An impressive number of clinical studies support the view that scopolamine hydrobromide in dosage equal to atropine sulfate (as a salt) is more effective in blocking salivary secretions and producing sedation. Accurate comparison of potency is complicated by the common practice of giving equal dosage of the salts, and variables such as the relative central actions which alter vagal tone.

In the past few years, we have studied the relative central effects of various drugs on the visual evoked response (VER). We have expanded the scope of these studies to obtain data simultaneously on heart rate as well as antispasmodic effects. We have given equimolar dosage of these drugs on a μg./kg. basis intravenously to patients. In general our findings confirm those reported elsewhere regarding some central and peripheral actions of muscarinic blocking agents.

Methods

Subjects. Seventy otherwise healthy patients scheduled for elective operations served as volunteer subjects. Each subject was brought to the anesthesia induction room two hours before the operation, having received no preanesthetic medication. An intravenous infusion of 5 per cent dextrose in 0.2 per cent saline solution was started and control data obtained. Two dosage schedules for the test drugs were used: the first consisted of a total fixed dose administered intravenously over a 30-second period; in the second the dosage was equal to that of the first, and given in divided doses every five minutes for 15 minutes. One minute after injection, recordings

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of VER were repeated over a period of up to a half-hour. The drugs used, their empirical formulas, molecular weights, and equimolar doses are listed in Table 1. It can be seen that the per cent base for each of the salts varies considerably. From experience we expected that 0.4 mg. of scopolamine hydrobromide would be an effective total dose, one equal to 0.91 μmole, amounting to 5.7 μg./kg. per 70 kg. The equivalent dose of methscopolamine bromide is 5.2, of atropine sulfate 4.6 and 4.7 μg./kg. of l-hyoscyamine sulfate. Inasmuch as these compounds undergo racemization and/or hydrolysis to tropic acid and the corresponding alkaloid, these doses are probably not reached in actual practice. Possible errors in dosage owing to a drug’s being in solution even for a few days may be as large as 15 per cent. We therefore used freshly prepared solutions whenever possible. The schedule of divided dosage was as follows: scopolamine hydrobromide 0.715, 1.43, 2.86, 5.72 μg./kg.; methscopolamine bromide 0.65, 1.30, 2.61, 5.22 μg./kg.; atropine sulfate 1.14, 2.28, 4.55, 9.12 μg./kg.; and l-hyoscyamine sulfate 0.59, 1.18, 2.36, 4.72 μg./kg. Earlier in the study, l-hyoscyamine hydrobromide was used in equimolar amounts and the data combined. The doses given as listed above are total doses. Thus, for scopolamine the first dose was 0.715 μg./kg., the second dose also 0.715 to achieve an accumulative dose of 1.43, the third dose was 1.43 to achieve an accumulative dose of 2.86, and the fourth dose 2.86 to achieve an accumulative dose of 5.72 μg./kg.

A comparison of dose 4 with that in Table 1 will show that with the exception of atropine, all the other drugs were given in equimolar amounts. The amount of atropine was twice as much. This was done in order to test the hypothesis that most of the activity of atropine (d- and l-hyoscyamine) resided in the l-hyoscyamine portion.

VER Recordings. The summing techniques employed for recording the VER from the human scalp have been described in detail previously. Briefly, EEG recordings were taken from the scalp, the electrodes placed in accordance with the 10-20 system at Fp1, F3, C3, O1 and O2, both ears serving as reference. EEG signals were amplified, displayed on a polygraph and connected to a summing computer. A 500-millisecond analysis with a trigger repeating at 1-second intervals was used. A total of 200 superimposed recordings were written out on an X-Y plotter. A strobe flash unit, enclosed in a sound-damped box, directed a light-flash into the patient’s eyes. Negativity was represented as “up.” Lead 2 of the ECG was recorded at the same time. Usually two to four sets of control VER’s with the subject’s eyes closed were recorded, prior to intravenous medication. When single total doses were administered, the light was flashed
nervous system were used: (a) subjective (patient’s verbal response) and objective evidence of sedation, (b) changes in the spontaneous EEG, and (c) alterations in the VER. Scopolamine proved to be most active among the various muscarinic cholinergic blockers on all three counts. Some of the typical effects of the muscarinic blocking agents on the VER are illustrated in figures 1 and 2. In a dose of 5.7 μg./kg., scopolamine caused a significant decrease in the primary complex or the VER and an increase in latency and decrease in amplitude of wave 3. Both the amplitude and latency of the secondary complex, especially wave 4, were enhanced. The afterdischarge was usually enhanced if the patient relaxed or was depressed if the patient slept. The specific alterations following scopolamine resembled those of natural sleep, and depended upon whether the patient was awake, drowsy or asleep. The EEG showed alterations consistent with a sedative action: (a) increase in alpha rhythm if none or little had been present; (b) low amplitude activity (Stage I) indicative of drowsiness; or, (c) spindles indicative of sleep (Stage II).

In contrast methscopolamine bromide in a total dose of 5.2 μg./kg. and l-hyoscyamine sulfate in a total dose of 4.7 μg./kg. had no significant central effect. No evidence of a central “excitatory” action was noted with any of the latter drugs. The lack of a central action of methscopolamine was especially strik-

Results

Effects on the Central Nervous System. Three criteria for judging effects on the central nervous system were used: (a) subjective (patient’s verbal response) and objective evidence of sedation, (b) changes in the spontaneous EEG, and (c) alterations in the VER. Scopolamine proved to be most active among the various muscarinic cholinergic blockers on all three counts. Some of the typical effects of the muscarinic blocking agents on the VER are illustrated in figures 1 and 2. In a dose of 5.7 μg./kg., scopolamine caused a significant decrease in the primary complex or the VER and an increase in latency and decrease in amplitude of wave 3. Both the amplitude and latency of the secondary complex, especially wave 4, were enhanced. The afterdischarge was usually enhanced if the patient relaxed or was depressed if the patient slept. The specific alterations following scopolamine resembled those of natural sleep, and depended upon whether the patient was awake, drowsy or asleep. The EEG showed alterations consistent with a sedative action: (a) increase in alpha rhythm if none or little had been present; (b) low amplitude activity (Stage I) indicative of drowsiness; or, (c) spindles indicative of sleep (Stage II).

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ing in comparison with the effects of equimolar amounts of scopolamine.

Effects on Salivary Flow. All 4 muscarinic blocking agents in divided doses caused a marked decrease in salivary flow as illustrated in figure 3. The order of dose for each drug is given on the X-axis and the degree of blockade of salivary flow on the Y-axis. Six to 9 patients received each drug in an cumulative dose fashion. Figure 3 shows the antiasialogogue potency as: methscopolamine > scopolamine > L-hyoscyamine > atropine in equimolar amounts. Atropine given in twice molar amounts proved to be only slightly more potent than L-hyoscyamine, indicating that the contribution of d-hyoscyamine to the action of atropine is minimal. L-Hyoscyamine upon standing for 1–2 weeks lost potency. This was discovered when freshly prepared L-hyoscyamine was compared with L-hyoscyamine that had been standing at room temperature, as seen in figure 3. Appropriate tests carried out in the hospital pharmacy indicate that the drug racemizes rapidly upon standing in solution.

Effects on Heart Rate. With cumulative doses a progressive increase in heart rate was recorded (fig. 4). After atropine an initial slight bradycardia was observed only after the first dose. The order of effectiveness in producing tachycardia was: methscopolamine > L-hyoscyamine > atropine > scopolamine. A twice equimolar dose of atropine was only slightly more effective than L-hyoscyamine.

The duration of effect of a single maximal dose of these agents is illustrated in figure 5. The maximum increase in heart rate from single-dose administration resulted in a somewhat greater response than that following the same dose in increments. This suggests that the accumulative dose technique is not completely accurate, probably because of metabolic breakdown and/or redistribution of the drug. Nevertheless, the relative potencies of the various muscarinic blockers appeared to be similar. In some patients the increase in heart rate following methscopolamine was unusually marked. The similarity of action of L-hyoscyamine to twice as much atropine again suggests that the active portion of atropine is L-hyoscyamine. Scopolamine produced an initial increase in heart rate as large as that produced by L-hyoscyamine, soon followed either by a return to control levels or by bradycardia. Within 15 to 30 minutes after the scopolamine the heart rate returned to or almost to control levels. This finding probably accounts for the seeming lack of vagal-blocking properties of scopolamine which has repeatedly been reported. Patients given saline generally showed a slight decrease in heart rate (fig. 5).
Fig. 5. Duration of action of single equimolar doses of muscarinic blocking agents on the heart rate. The mean percentage change in heart rate of groups of 9–16 patients is plotted for a 30 minute period. All drugs were given in single equimolar amounts except atropine which was given in twice the amount. The order of effectiveness in increasing heart rate was methscopolamine > atropine and \( l \)-hyoscymine > scopolamine. At 2 and 5 minutes after injection the increase in heart rate after scopolamine was similar to \( l \)-hyoscymine. However, after 10 minutes the mean heart rate after scopolamine rapidly returned toward control levels. In some patients a secondary bradycardia was observed.

Discussion

The data obtained in this investigation are in agreement with those from previous clinical and experimental studies demonstrating the superior effectiveness of scopolamine over atropine as an antisialogogue. Most anesthesiologists have compared 0.4 mg. of scopolamine hydrobromide with 0.4 mg. of atropine sulfate in adults. As noted in table 1, such a dose of atropine is somewhat larger than it should be (0.32) for an equimolar comparison. Despite the use of slightly more (0.08 mg.) atropine, such studies clearly indicate that it is less effective as an antisialogogue.

There is much evidence to support the hypothesis that \( l \)-hyoscymine is the active form in atropine.\(^{16,17}\) The contribution of \( d \)-hyoscymine to the effects of atropine appears negligible. Our data support this view. A dose of atropine containing twice as many molecules (1 N \( l \)- and 1 N \( d \)-hyoscymine) as \( l \)-hyoscymine (1 N) was essentially of similar effectiveness, both as an antisialogogue and as a vagal blocker. Although \( l \)-hyoscymine is the active portion of atropine it is not of practical value to use \( l \)-hyoscymine per se, since it readily racemizes to atropine. In the present study, as well as that of Trotti and Adriani,\(^{11}\) methscopolamine possessed outstanding antisialogogue activity.

Methscopolamine was also the most effective in increasing heart rate. \( l \)-Hyoscymine was next while scopolamine and atropine were least effective. This was particularly evident in the case of scopolamine. Although scopolamine produced an initial tachycardia almost as marked as that noted with atropine, it was of short duration. These findings support those of Gravenstein et al., in their more elegant cardiovascular studies.\(^{5}\) The most marked tachycardia was that produced by methscopolamine; in some cases almost alarming. This would prevent this drug from being used widely for preanesthetic medication in equimolar amounts to atropine and scopolamine. In cases where the most effective vagal blockade free of central effects is desired, however, methscopolamine would be of greater value than atropine.

All three indexes of central action, including alteration of the VER, spontaneous EEG, and evidence of sedation, clearly support the general impression that scopolamine has a central sedative action not present with atropine. However, it is known that large doses of atropine have a similar sedative action.\(^{18}\) In our studies no evidence was obtained for a central stimulant action of atropine. In fact, neither atropine, \( l \)-hyoscymine, nor methscopolamine in the equimolar doses used had significant central actions.

It would appear that if an average adult patient requires both antisialogogue and some vagal blocking action, he should be given doses of approximately 0.6 mg. of atropine. If a central sedative and antisialogogue effect is desired, 0.4 mg. doses of scopolamine are highly suitable. On the other hand, if a potent antisialogogue and vagal blocking action but no central effect is desired, methscopolamine should be considered. The differential advantages of atropine and scopolamine are supported by this study.

Summary and Conclusions

Scopolamine, methscopolamine, atropine, and \( l \)-hyoscymine were compared on an equimolar basis as to their effect on: (1) visually evoked
responses (VER), spontaneous EEG activity, and sedation as an index of a central nervous system action; (2) spontaneous heart rate; and (3) dilute citric acid-induced salivary flow. The study was carried out before operation in patient-volunteers who fasted and had not received medication during the previous 12 hours.

Scopolamine altered the VER by significantly depressing its early components, and causing simultaneous changes in the alpha rhythm of the EEG in the direction of relaxation or sedation. These VER changes correlated with the state of wakefulness. Atropine, l-hyoscyamine, and methscopolamine had no significant effect on the VER and EEG in equimolar doses.

Methscopolamine caused the greatest increase in heart rate, followed by atropine and scopolamine, each of which increased the heart rate within two minutes. However, the scopolamine-induced increase lasted only about 10 minutes, whereas the effect of atropine, l-hyoscyamine, and methscopolamine continued for 30 minutes or more. Ten to 30 minutes following scopolamine bradycardia was observed. Equimolar doses of l-hyoscyamine were more effective than atropine in increasing the heart rate.

With regard to blockade of salivary flow the following order of effectiveness was obtained: methscopolamine > scopolamine > l-hyoscyamine > atropine. A dose of l-hyoscyamine consisting of half the dose of atropine produced about the same effects, indicating the relative ineffectiveness of the d-hyoscyamine fraction of atropine.

It is concluded that scopolamine is the most potent centrally acting drug, and the second most potent peripherally. Its vagal blocking effects are transient, compared to atropine, l-hyoscyamine or methscopolamine. Methscopolamine has no central action but has marked peripheral muscarinic cholinergic blocking effects. Equimolar doses of atropine and l-hyoscyamine lack significant central, but have definite peripheral effects. These quantitative and qualitative differences in drug action offer the anesthesiologist the opportunity to choose a specific muscarinic cholinergic blocking agent, depending upon the patient's needs.

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References
Anesthesia

DIFFUSION THROUGH RUBBER Ether, nitrous oxide, halothane, and cyclopropane diffuse through silicone rubber. General anesthesia can be produced in dogs by passing the vapors of any of these anesthetic agents through a coil of silicone rubber tubing, each end of which is placed in an artery and vein. Potential applications include a new method for general anesthesia and a simple accurate vaporizer for halothane. (Folkman, J., Long, D. M., Jr., and Rosenbaum, R.: Silicone Rubber: A New Diffusion Property Useful for General Anesthesia, Science 154: 148 (Oct.) 1966.)

PROFOUND HYPOTHERMIA Severe metabolic acidosis usually follows the termination of profound hypothermia by blood stream cooling. Without treatment this was fatal in the majority of the experimental animals. Tissue hypoxia during cooling was suspected as the cause of the severe acidosis. Inadequate oxygen delivery rather than inadequate oxygen transport was held to be the immediate cause of death as the result of the shift to the left of the oxyhemoglobin dissociation curve, i.e., Bohr effect. During pervascular cooling the blood is much colder than the tissues whose oxygen demand is higher than can be dissociated from oxyhemoglobin of cold blood. A small arterio-venous oxygen difference is not an indicator of decreased oxygen demand of the tissues, but reflects inadequate release of oxygen from hemoglobin. Maintenance of a normal P$_{CO_2}$ of 40 to 50 mm. of mercury during profound (11° C.) blood stream cooling is inadequate to prevent metabolic acidosis. Appearance of such acidosis in the face of full oxygen saturation and a normal P$_{CO_2}$ points to the existence of tissue hypoxia. Addition of very high concentrations of CO$_2$ seems to be of great benefit in terms of making more oxygen available to the tissues during pervascular cooling. (Aleksic, A., and Tanaka, T.: The Influence of Carbon Dioxide Tensions of the Blood on the Arterio-Venous Oxygen Difference during Profound Pervascular Hypothermia, Z. Exp. Med. 141: 230 (Oct.) 1966.)