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A COMPARISON OF SOME ATROPINE-LIKE DRUGS IN MAN, WITH PARTICULAR REFERENCE TO THEIR END-ORGAN SPECIFICITY

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Atropine, methanthelinium, propantheline, oxyphenonium, hyoscine, and hyoscine methylbromide have been compared in man. After graded subcutaneous doses of these drugs simultaneous observations were made on the heart rate, salivary secretion, pupil size, near point of accommodation, micturition, and palmar sweating. This permitted a quantitative assessment of any differential effects of the drugs on the different end-organs.

Small doses which depressed salivary secretion and palmar sweating did not necessarily accelerate the heart or slow micturition. Atropine and hyoscine, which are tertiary amines, had a greater effect than the other (quaternary) drugs on the iris and the ciliary muscle, compared with the effects on the other end-organs studied. This difference may be related to the fact that quaternary compounds penetrate cellular membranes with difficulty.

The time course of the drug effects differed for different end-organs. The changes in heart rate, salivary secretion, and sweating began and ended sooner than those affecting accommodation and the pupil. As the dose of a drug was increased, the peak effect on the heart rate and salivary secretion tended to occur sooner, but the peak effect on the iris and ciliary muscle always occurred later. It is suggested that the aqueous humour may be acting as a reservoir for the drugs. After methanthelinium, all the drug effects began sooner and reached their peak sooner than after the other drugs.

The usefulness of atropine substitutes in man is largely determined by their end-organ specificity. If a drug paralyses all peripheral cholinergic effectors equally, it will inevitably produce more "side effects" than desired effects. To investigate whether drugs differ in the degree to which they affect different end organs, simultaneous observations have been made on several different responses in the same subject, after graded doses of the drugs. The drugs and doses used are shown in Table I.

TABLE I

DRUGS AND DOSES USED

The number of experiments is given in parentheses after each dose.

Drug	Doses in mg./70 kg.			
Atropine sulphate ..		0·5 (7)	1·0 (7)	2·0 (7)
Methanthelinium bromide	7·0 (4)	14·0 (2)	28·0 (5)	56·0 (4)
Propantheline bromide	2·1 (4)	4·2 (2)	8·4 (10)	16·8 (6)
Oxyphenonium bromide	0·5 (3)	1·0 (3)	2·0 (6)	4·0 (7)
Hyoscine methylbromide	0·125 (4)	0·25 (2)	0·5 (6)	1·0 (6)
,, hydrobromide		0·2 (3)	0·4 (4)	0·8 (3)

METHODS

The subjects were 12 normal men, between the ages of 22 and 35 years, and a man aged 50, convalescing from a gastric ulcer.

Each subject received two to four different doses of each of two or more drugs. Doses were related to the body weight of the subject before the first experiment. Successive experiments in the same subject were separated by at least three days. The subjects did not know what drug they were receiving on a particular occasion.

At the start of each experiment, baseline observations were made for ½ to 1 hr. with the subject lying on a couch. After this control period the drug was given by subcutaneous injection into the upper arm and observations were made at frequent intervals until the effects of the drug began to wear off. The subject remained recumbent until the heart rate had returned to within 10 beats/min. of its initial value.

Heart Rate.—Counts for ¼ to 1 min. were made at intervals of about 2 to 6 min. until it began to return to normal; thereafter the rate was counted less frequently. The increase in rate is expressed as % of the initial rate.

Salivary Secretion.—This was measured by a modification of the method of Mushin, Galloon and Lewis-Faning (1953). After the subject had swallowed all resting saliva, 0.2 ml. of 4% citric acid was dropped on the tongue, and held in the mouth for 30 sec. At the end of this time 4 ml. of water was taken into the mouth and kept there for 15 sec., then the contents of the mouth were voided into a measuring cylinder. This can be repeated every 15 to 20 min. The % inhibition of salivary secretion has been calculated from the expression: $100 \times (V_o - V_a)/V_o$, where V_o is the mean volume of saliva obtained before administration of the drug and V_a the volume obtained after giving the drug.

Pupil Diameter.—The diameter of the pupil of one eye was measured by a simple pin-hole pupillometer (Reid, 1955). In this indirect method the intensity of illumination of the eye is low, since the pupillometer keeps out most of the extraneous light. (Unpublished observations made after the completion of the experiments described in this paper have shown that changes in pupil size produced by an atropine-like drug are much more readily apparent when the pupil is measured in bright light.) Measurements to the nearest 0.25 mm. were made in triplicate at intervals of 20 to 30 min. The results have been expressed in terms of the increase in pupil diameter in mm.

Near Point.—The near point of accommodation of one eye was measured with a near point rule every 20 to 30 min.; the results have been expressed in dioptres. Each point represents the mean of three measurements. Subjects who normally wore spectacles wore them for these measurements. In order to make it possible to compare the degrees of paralysis of accommodation obtained in different subjects, the range of accommodation from the near point to the far point was determined for each subject. This was done on an occasion when no drug had been given. When the eye was hypermetropic, a positive lens was placed in front of the eye, such that a distant object was still just in focus. The dioptric power of this lens was added to the range of accommodation between the near point and infinity. In each subject, paralysis of accommodation has been expressed as % of this range: $\frac{D_o - D_m}{D_o + L} \times 100$, where D_o is the near point before the injection, D_m the near point when the action of the drug was at its peak, and L the dioptric power of the lens mentioned.

Sweating.—Sweating on the pad of one middle finger was assessed by an adaptation of the method described by Wada (1950) for the detection of sweating. The skin was painted with 3% iodine in 95% alcohol, and allowed to dry. A thin film of a 1:1 mixture of soluble starch and castor oil was then spread on the area so that each active sweat gland appeared as a discrete black dot. The time in seconds taken for an arbitrary number of black dots to become visible under a lens was taken as an index of sweat gland activity. (If, after a drug had been administered, sweat dots took twice as long to appear, this was taken to indicate 50% inhibition of sweating.)

Micturition.—The time taken to empty the bladder was recorded and the volume of urine measured. The quotient volume/time (ml./sec.), referred to as the "micturition speed" (S_m), has been used as a measure of the effect of the drugs on micturition. To minimize psychological interference, the subject went into a special lavatory, and timed each micturition himself, using a stop-watch. Since it was necessary to leave the couch for this purpose, micturition was only encouraged after the heart rate had passed its peak. In some experiments the subject drank suitable quantities of water beginning about 1 hr. after the drug had been given, in order to enable more frequent observations to be made. This does not affect the volume of saliva secreted (de Wardener and Herxheimer, 1957), nor was there any evidence that it affected the heart rate. Since the S_m varies with the volume passed (Herxheimer, unpublished observations), each S_m obtained under the influence of a drug has been compared with the normal S_m for a similar volume of urine in the same subject. Even when similar volumes are passed on different occasions, however, the speeds may differ considerably, and this limits the accuracy with which it is possible to determine the decrease in S_m attributable to a drug. In the present experiments further errors were introduced, for no observations were made until the heart rate had passed its peak; since the rate of urine flow varied on different occasions, micturition was not always possible at comparable times after injection of the drug. This error due to difficulties in timing affected all the drugs to about the same extent. In many experiments only one or two observations were made in the first 3 hr., so that the peak effect on the bladder is likely to have escaped observation. The % decrease in S_m is given by the expression: $100 \times S_m$ (after drug)/S_m (control). When more than one control observation was available for a given volume, the lowest control S_m was used in the calculation of % decrease.

Other Effects.—These were not specifically looked for, but subjects were asked to report any unusual sensation; direct questions were not asked in this connexion. Obvious changes (such as sleep, flushing of the face) were noted by the observer.

Statistical Procedures.—Log dose/effect regression lines were calculated from the maximum effects of the different doses on the heart rate, salivary secretion, pupil diameter and accommodation. The regressions were tested for linearity and parallelism, and in the absence of a significant departure from parallelism potency ratios were calculated using a common slope. Analyses of variance were carried out to allow for differences between subjects. For this purpose it was necessary to calculate the missing values in each group of observations, and equations of the form described by Finney (1950) were solved by successive approximation. The residual errors obtained from these

analyses of variance were used in testing the significance of differences between any two regression lines.

The results on the time course of the drug effects were examined by analyses of variance, by testing the significance of correlation coefficients, or by t tests. Differences between subjects were not allowed for except in the results on accommodation. The treatment of these results is described below.

The coefficient of precision (λ) was calculated, for each of five responses, from the pooled residual error variance of all the observations used in the calculation of regression lines, and from the common slope.

RESULTS

A typical experiment is illustrated in Fig. 1. The extent of the changes, and their time course, can be seen for each effect investigated.

Dose/Effect Relationships

Heart Rate.—All drugs except hyoscine caused an increase in the heart rate (Fig. 2*a*). Hyoscine either produced a fall or no change and is therefore not shown in Fig. 2*a*. Four of the five log dose/effect lines do not deviate significantly from linearity if doses giving less than a 20% increase in heart rate are excluded. The response to propantheline is linearly related to the log dose except at the highest dose, which has therefore not been used in the calculation of potency ratios. The regression line for atropine is steeper than the lines for the other drugs, but the difference in slope is not significant at the 5% level ($0.1>P>0.05$). A common slope was therefore used to calculate the potency ratios in column (a) of Table II.

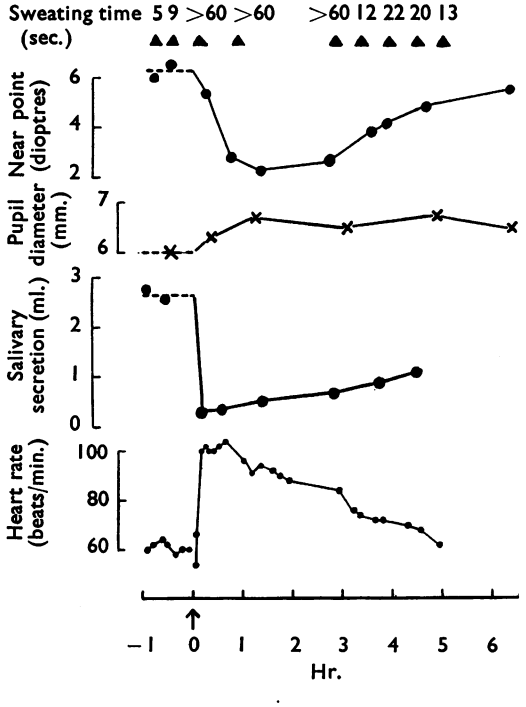

FIG. 1.—The changes observed in one experiment following subcutaneous injection of 56 mg./kg. of methanthelinium bromide at zero time. 2 hr. after the injection the subject voided 93 ml. urine at an average speed of 2 ml./sec.; at 4 hr., 512 ml. at a speed of 9 ml./sec.; and at 6½ hr., 293. ml at a speed of 11 ml./sec

TABLE II

RELATIVE POTENCIES OF ATROPINE-LIKE DRUGS

The potencies have been calculated in terms of mols of the bases. Atropine has been given an arbitrary value of 1.0.

Drug	(a) Acceleration of Heart Rate	(b) Inhibition of Salivary Secretion	(c) Slowing of Micturition	(d) Dilatation of Pupil	(e) Paralysis of Accommodation	(f) Ratio (b)/(e)
Atropine	1·0	1·0	1·0	1·0	1·0	1·0
Methanthelinium ..	0·20	0·22	0·26	0·06	0·11	1·9
Propantheline ..	0·70	0·76	0·59	0·08	0·22	3·5
Oxyphenonium ..	1·4	1·7	0·96	0·29	0·53	3·2
Hyoscine methylbromide	5·6	6·2	2·4	3·2	1·7	3·7
Hyoscine hydrobromide	—	3·7	2·4	5·1	6·5	0·56

Salivary Secretion.—All the drugs strongly inhibited salivary secretion in the doses used (Fig. 2*b*). Only two points for each of four drugs were sufficiently low on the log dose/effect curves to allow the calculation of potency ratios. All the points for methanthelinium and propantheline, and the remaining points for the other drugs, appeared to lie on the upper non-linear portion of the log dose/effect curve. The common slope was therefore calculated from the regression lines for the two lowest points of atropine, hyoscine, hyoscine methylbromide, and oxyphenonium, which are parallel. The potencies of methanthelinium and propantheline in Table II have been estimated on the assumption that log dose/effect lines parallel with the others pass through the lowest point obtained with each drug. The differences in potency shown in Fig. 2(*b*) between oxyphenonium and atropine, and methylhyoscine and hyoscine, are significant at the 5% level.

Pupil Diameter.—Only doses which caused a mean increase in the pupil diameter of more than 0.3 mm. were used in the calculation of the log dose/effect lines (Fig. 3*a*). The relative potencies of the drugs are given in Table II. It is noteworthy that atropine is more potent than oxyphenonium ($P<0.05$), and that hyoscine is about as potent as its methyl derivative.

Accommodation.—The paralysis of accommodation varied greatly between subjects. Two subjects who were myopes showed weak and irregular responses, and were not included. Only doses producing a mean paralysis greater than 7% of the whole range of accommodation were used to calculate log dose/effect lines (Fig. 3*b*). All but the two highest doses of all the drugs except methanthelinium were thus excluded. The three subjects with hypermetropia gave consistently bigger responses than the emmetropes; this probably explains why the standard errors in Fig. 5 are so large. Since each point is the mean of observations on varying numbers of hypermetropes and emmetropes the slope of the log dose/effect lines is falsified unless allowance is made for this heterogeneity. The means have therefore been adjusted so that equal weight is given to the results obtained from hypermetropes and emmetropes. This adjustment was disregarded in computing standard errors and precision coefficients. It appears (Table II, Fig. 3*b*) that hyoscine is more potent than its methyl derivative, and atropine than oxyphenonium, but the differences do not reach the 5% level of significance.

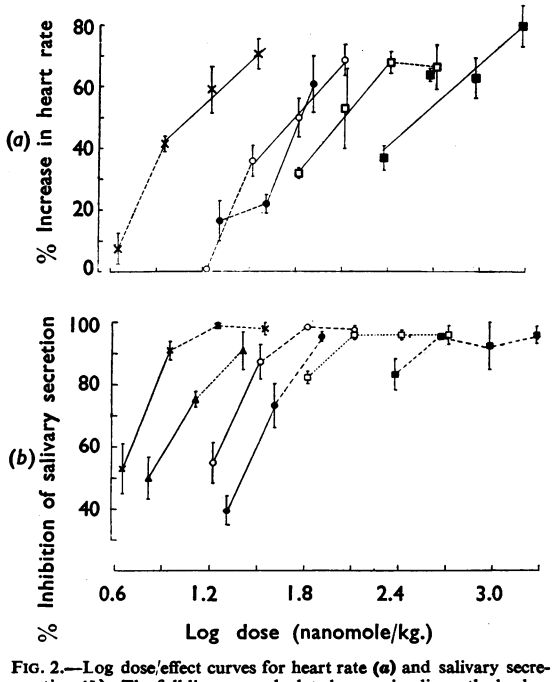

FIG. 2.—Log dose/effect curves for heart rate (*a*) and salivary secretion (*b*). The full lines are calculated regression lines; the broken lines join points lying on the non-linear portions of the dose/effect curves. The standard error of the mean is given for each point. X, hyoscine methylbromide; ▲, hyoscine hydrobromide; O, oxyphenonium; ●, atropine; □, propantheline; ■, methanthelinium.

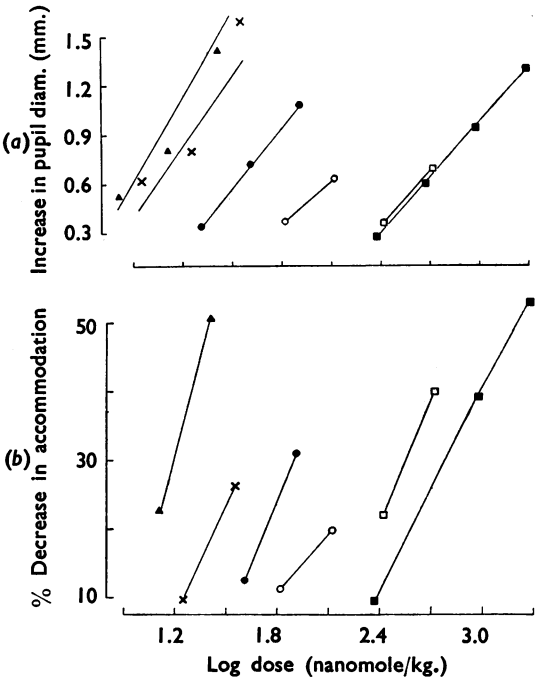

FIG. 3.—(*a*) Calculated log dose/effect regression lines for pupil diameter. (*b*) Log dose/effect lines for accommodation. The points for accommodation are weighted means (see text). The standard errors of the means shown amounted to between 20% and 50% of the means, the average being 35% for the observations on pupil diameter, and 28% for those on accommodation. X, hyoscine methylbromide; ▲, hyoscine hydrobromide; O, oxyphenonium; ●, atropine; □, propantheline; ■, methanthelinium.

Sweating.—Three of the subjects normally showed only minimal sweating on the palms and finger pads, and were therefore excluded. In the others, nearly all the doses inhibited sweating on the finger pad by more than 85%. The lowest dose of atropine (0.5 mg./70 kg.) was the only one that caused less inhibition (mean 65%). It was therefore not possible to estimate potency ratios for this response.

Micturition.—The results are given in Fig. 4. Hyoscine and methylhyoscine were approximately equipotent, and so were atropine and oxyphenonium. The potency ratios in Table II have been calculated from the doses causing a 50% decrease in S_m. These were obtained by graphical interpolation. Methanthelinium is the only drug which appeared to be relatively more potent in its action on micturition than on the other responses.

Other Effects.—All the doses of hyoscine used produced drowsiness, and in many experiments the subjects felt giddy and confused. Drowsiness was also observed after the higher doses of the

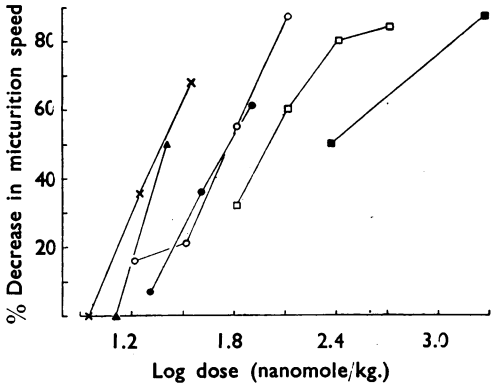

FIG. 4.—Log dose/effect curves for micturition speed. The standard errors of the means for the points, reading from left to right for each drug, are given in parentheses. ✕, hyoscine methylbromide (0, 24, 12); ▲, hyoscine hydrobromide (0, 17); ○, oxyphenonium (9, 12, 28, 5); ●, atropine, (5, 8, 7); □, propantheline (7, 3, 7, 6); ■, methanthelinium (18, 9).

other drugs. The incidence was greatest after methanthelinium and least after atropine (Table III).

Flushing of the face occurred in over half the experiments, and was often accompanied by a sensation of warmth. This effect usually occurred 15 to 20 minutes after the injection.

Uncomfortable dryness of the nose and eyes was noted in a number of experiments. Other symptoms that were occasionally reported included mild headache and epigastric discomfort. Constipation on the following day occurred after three experiments with propantheline and oxyphenonium. In one subject, extra-systoles were observed in 5 experiments, 3 with propantheline and 2 with oxyphenonium.

TABLE III

INCIDENCE OF DROWSINESS

The doses are expressed as multiples of the lowest dose used (see Table I). The proportion of experiments in which the subject was drowsy or fell asleep is given for each dose.

Drug	Dose			
	1	2	4	8
Atropine	1/7	2/7	0/7	
Methanthelinium	0/4	0/2	2/5	4/4
Propantheline	1/4	0/2	2/10	4/6
Oxyphenonium	0/3	0/3	3/6	2/7
Hyoscine methylbromide ..	2/4	0/2	1/6	2/6
,, hydrobromide ..	3/3	4/4	3/3	

Accuracy of Measurements

In order to obtain an estimate of the precision of the methods used, precision coefficients (λ) were calculated from the results on heart rate, salivary secretion, pupil diameter, accommodation, and micturition. The coefficients were: heart rate, 0.187 (range for individual regressions, 0.131 to 0.212); salivary secretion, 0.073 (range, 0.015 to 0.119); pupil diameter, 0.466 (range, 0.315 to 0.570); accommodation, 0.171 (range, 0.098 to 0.276); micturition speed, 0.214 (range, 0.054 to 0.290). The coefficient is thus greatest for the measurements of the pupil, and smallest for those of salivary secretion.

Time Course of Drug Effects

Information on the time course of drug effects was obtained for all the responses studied, but since the heart rate was recorded at 3 to 6 min. intervals, and the other responses only at intervals of 15 min. or longer, the observations on the heart rate reflect the time course more precisely than do the others. The changes in the less frequently recorded responses can thus be expected to show up only major differences between drugs and between organs.

Heart Rate

Onset of Effect.—The intervals after which the heart rate began to increase are illustrated in Fig. 5. After atropine, methylhyoscine, oxyphenonium, and propantheline, the interval shortened significantly as the dose increased ($P<0.05$); there was no difference in the case of methanthelinium. Fig. 7 can be used to compare the times of onset of the effect following equi-active doses of the drugs. Table IV gives the results of such a comparison for doses causing a 50% increase in the heart rate. These doses have been derived from the individual log dose/effect regression lines, because the slope for atropine differed from the others, so that the use of the common slope might have caused some distortion. The heart rate began to rise much sooner after methanthelinium than after the other drugs.

TABLE IV

MEAN TIMES OF ONSET AND OF PEAK EFFECT, AND DURATION OF EFFECT ON THE HEART RATE AFTER ADMINISTRATION OF EQUI-ACTIVE DOSES CAUSING A 50% INCREASE IN HEART RATE

The equi-active doses have been calculated from the individua regression lines for the drugs; they are expressed in terms of the salts. See text for explanation of duration.

	Dose (mg./ 70 kg.)	Time of Onset (min.)	Time of Peak Effect (min.)	Duration (hr.)
Atropine	1·6	19	37	1·2
Methanthelinium	12·0	4	20	1·5
Propantheline	4·1	14	34	2·3
Oxyphenonium	1·9	16	37	2·4
Hyoscine methylbromide ..	0·36	18	40	2·3

Peak Effect.—Fig. 5 also shows the times at which the maximum effect on the heart rate was observed. In the case of atropine the peak occurred significantly sooner after the higher dose ($P<0.05$); methylhyoscine appeared to behave similarly ($P<0.1$). The times of the peak effects after oxyphenonium, propantheline, and methanthelinium were independent of the doses used. When equi-active doses are compared (Table IV) the peak occurred much sooner after methanthelinium than after the other drugs.

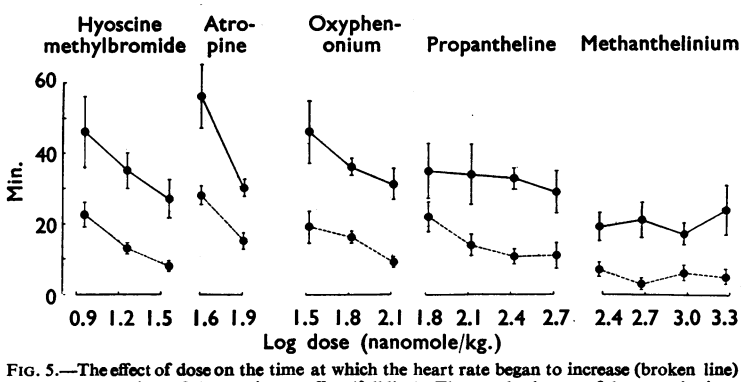

FIG. 5.—The effect of dose on the time at which the heart rate began to increase (broken line) and on the time of the maximum effect (full line). The standard error of the mean is given for each point.

Duration of Effect.—The duration of the effect on the heart rate was arbitrarily taken as the time during which the heart rate exceeded the pre-injection rate by 10 beats/min. or more. Fig 6*a* shows log dose/duration curves for the five drugs. There is no significant deviation from linearity, and the slopes are parallel. The duration of the effect following equi-active doses of the drugs is given in Table IV; it was shorter for atropine and methanthelinium than for the other three drugs.

Salivary Secretion

The time of onset of the effect on salivary secretion was not determined precisely, but the times between which inhibition began are known. In 30 out of the 36 experiments with methanthelinium and propantheline, inhibition was observed within 9 min. of the injection. (In the other 6 experiments salivary secretion was not tested in the first 10 to 20 min.) In most of the experiments with the other drugs inhibition had not begun 5 min. after the injection, and was only detected after 20 to 30 min., when the second observation on salivary secretion was made. Table V gives the approximate time of onset of inhibition after equi-active doses of the drugs. These were derived from the regression lines using the common slope.

The times at which the inhibition was maximal are shown in Fig. 7. In the experiments with atropine, hyoscine, hyoscine methylbromide, and oxyphenonium the peak occurred earlier as the dose was increased ($P<0.02$). After propantheline and methanthelinium the time of the peak effect was not related to the dose. In the experiments with methanthelinium the peak was reached much more rapidly than after any of the other drugs. This is exemplified in Table V.

The time during which salivary secretion was inhibited more than 50% was linearly related to the log dose for all the drugs (Fig. 6*b*). The log

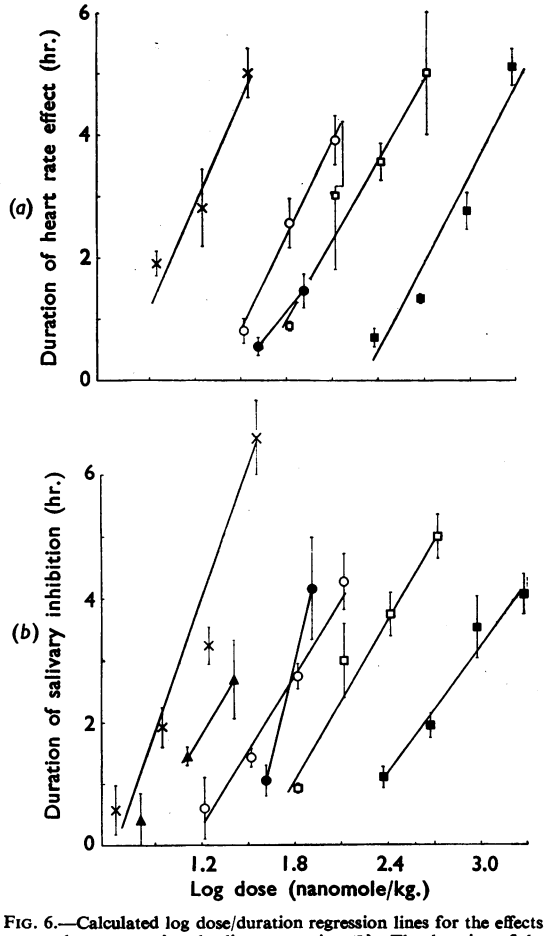

FIG. 6.—Calculated log dose/duration regression lines for the effects on heart rate (*a*) and salivary secretion (*b*). The duration of the effect on the heart rate has been arbitrarily taken to be the period during which it exceeded the resting level by 10 or more beats/min. The duration of the effect on salivary secretion was the period during which it was inhibited by 50% or more. The standard error of the mean is given for each point. ✕, hyoscine methylbromide; ▲, hyoscine hydrobromide; ○, oxyphenonium; ●, atropine; □, propantheline; ■, methanthelinium.

TABLE V

MEAN TIMES OF ONSET AND OF PEAK EFFECT, AND MEAN DURATION OF EFFECT ON SALIVARY SECRETION AFTER ADMINISTRATION OF EQUI-ACTIVE DOSES CAUSING 85% INHIBITION OF SALIVARY SECRETION

Doses are expressed in terms of the salts.

Drug	Dose (mg./70 kg.)	Time of Onset (min.)	Time of Peak Effect (min.)	Duration (hr.)
Atropine	1·2	>7	37	2·1
Methanthelinium	7·1	<4	14	1·1
Propantheline	2·2	<5	25	1·2
Oxyphenonium	0·95	>6	34	1·6
Hyoscine methylbromide ..	0·23	>9	54	1·9
,, hydrobromide ..	0·52	>7	39	1·9

dose/duration lines for atropine and methylhyoscine are steeper than those for the other drugs ($P<0.01$).

Pupil Diameter

The effect on the pupil began later than that on the heart rate and salivary secretion, and took much longer to reach its peak. The peak effect occurred later after high doses than after low ones (Table VI).

TABLE VI

MEAN TIME OF MAXIMUM EFFECT ON PUPIL

These means are not strictly comparable with those shown in Fig. 3 (*a*) since experiments in which the pupil was not affected could not contribute to the means in this table. Single observations are marked with an asterisk. The doses refer to the weights of the salts.

Drug	Dose (mg./70 kg.)	Mean Time of Maximum Effect on Pupil Hr. After Injection ± Standard Error of Mean
Atropine	0·5	1·5±0·5
	1·0	4·1±1·2
	2·0	3·3±0·6
Methanthelinium	14·0	1·1*
	28·0	2·5±0·6
	56·0	2·4±0·4
Propantheline	8·4	1·8±0·1
	16·8	5·2±1·4
Oxyphenonium	2·0	1·5±0·2
	4·0	5·5±2·7
Hyoscine methylbromide ..	0·25	0·6*
	0·5	2·5±0·8
	1·0	4·1±0·8
,, hydrobromide ..	0·2	1·8±0·1
	0·4	1·6±0·4
	0·8	7·5±1·5

The duration of the effect was taken to be the time during which the pupil diameter exceeded the control diameter by 0.5 mm. or more. On several occasions, after high doses had been given, the pupil was still enlarged at the end of the experiment; in these cases "mean duration" was a minimum rather than a true mean (Table VII).

Accommodation

Changes in the near point began at variable times after injection of the drug. The delay was greatest with atropine, and least with methanthelinium. The timing of the peak effect was significantly related to the dose, in the experiments with atropine, propantheline and methanthelinium ($P<0.05$): the higher the dose, the longer the interval between the injection and the peak effect (Fig. 7). A similar trend was apparent with the other drugs. The duration of the effect was taken to be the time during which the near point of accommodation was decreased by 0.5 dioptre or more. A weighted mean duration was calculated as described above for each dose, so that observations from emmetropes and hypermetropes contributed equally. The results are given in Table VII.

TABLE VII

MEAN DURATION OF EFFECTS ON THE EYE

The duration of the effect on accommodation was taken to be the time during which voluntary accommodation was diminished by 0·5 dioptres or more. The means have been weighted as described in the text. The duration of the effect on the pupil was taken to be the time during which the pupil diameter exceeded the control diameter by 0·5 mm. or more. Each mean is followed by its standard error. The value marked with an asterisk was based on a single observation. Doses are expressed in terms of the salts.

Drug	Dose (mg./70 kg.)	Mean Duration of Effect hr. (±Standard Error of Mean)	
		Accommodation	Pupil
Atropine	0·5	0·4 (±0·2)	0·1 (±0·1)
	1·0	2·6 (±1·2)	3·8 (±1·7)
	2·0	8·8 (±3·4)	7·3 (±1·5)
Methanthelinium	7·0	0·6 (±0·4)	0
	14·0	2·1*	1·5 (±1·5)
	28·0	6·5 (±2·2)	4·6 (±2·2)
	56·0	8·5 (±0·3)	7·1 (±1·0)
Propantheline..	8·4	5·0 (±1·2)	0·3 (±0·3)
	16·8	13·9 (±2·4)	2·2 (±2·2)
Oxyphenonium	2·0	2·0 (±1·4)	0·4 (±0·3)
	4·0	3·8 (±1·7)	1·4 (±1·3)
Hyoscine methylbromide ..	0·5	0·6 (±0·2)	0·7 (±0·3)
	1·0	11·8 (±3·0)	4·8 (±2·2)
,, hydrobromide ..	0·2	0·1 (±0·1)	1·2 (±0·9)
	0·4	3·2 (±1·1)	2·8 (±1·2)
	0·8	10·2 (±1·2)	4·7 (±2·6)

Sweating

In most experiments sweating began to diminish within 30 min. of the injection, and the peak effect usually occurred between 30 and 60 min. after the injection. After methanthelinium, the onset was more rapid than after the other drugs (mean, 13 min.), and the peak came sooner (mean, 17 min.). There was no consistent relation between the time of the peak effect and the dose.

The duration of 50% inhibition of palmar sweating, estimated by interpolation, was of the same order as the duration of 50% inhibition of salivary secretion. The slopes of the log dose/duration lines were similar to those shown for salivary secretion in Fig. 6*b*, except in the case of hyoscine. The two lowest doses of this drug

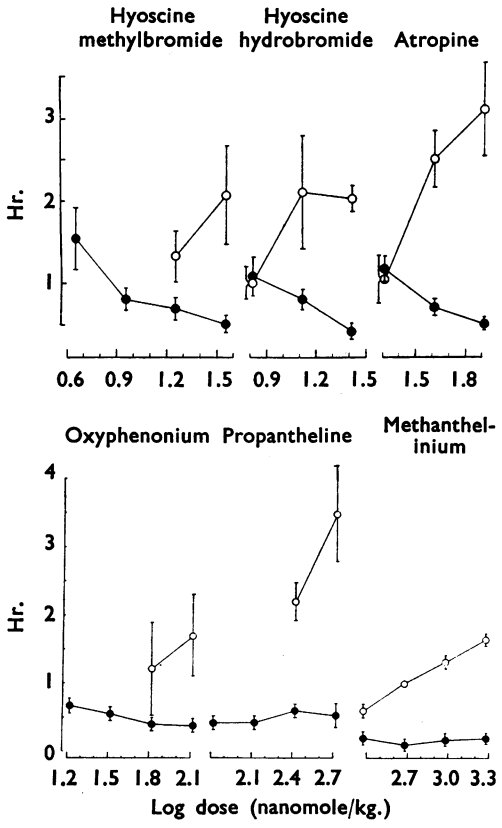

FIG. 7.—Effect of dose on the time of occurrence of the maximum effect on salivary secretion (●) and on accommodation (○). The standard error of the mean is given for each point.

inhibited sweating for rather longer than they inhibited salivary secretion, so that the slope was less steep.

Micturition

The micturition speed frequently remained below 50% of normal for over 5 hr. after the highest doses of the drugs. The results were insufficient for a detailed examination of the duration of this effect.

Initial Stimulant Effects

In a proportion of experiments various paradoxical stimulant effects occurred before the customary inhibition began. Cardiac slowing frequently preceded acceleration, salivary secretion was often increased when tested within 8 min. of the injection, in some experiments there was a transient increase in the power of accommodation, and in a few pupillary constriction preceded dilatation. These paradoxical results will be reported in detail elsewhere.

DISCUSSION

Some of the effects of the drugs on the heart rate were surprising. Hyoscine slowed the heart in most experiments, and never caused acceleration. Anaesthetists should therefore not rely on hyoscine if they wish to block the vagus. When the other drugs were given, acceleration of the heart was frequently preceded by slowing, indicating that these drugs have a dual action on the heart rate, and the dose/response relationship presumably results from the interaction of these two opposing effects. Compared with the quaternary drugs, atropine seems to produce relatively more slowing than acceleration, and it is possible that differences of this kind also exist between the various quaternary drugs. Such considerations might explain the difference in slope between the line for atropine and those for other drugs, and also the anomalous response to the highest dose of propantheline (Fig. 2*a*). Another, but perhaps less plausible, explanation for this response which is much smaller than one would expect might be steric hindrance at the receptors.

All the drugs had a much greater effect on salivary secretion than on the heart rate; this has long been known to be so in the case of atropine (Henderson, 1923). Palmar sweating also appeared to be very sensitive to all the drugs. Therapeutic doses of atropine-like drugs only infrequently cause overt disturbances of micturition, but the results show that they produce definite slowing in normal subjects. This suggests that post-operative retention of urine may on occasion be due to the premedication.

The potency ratios in Table II show a remarkably consistent pattern. The ratios for the effect on the heart rate and salivary secretion run parallel for each drug, and the same is true for the effects on the pupil and on accommodation. When the effect on salivary secretion is compared with those on accommodation and the pupil, however, a striking difference is found. The ratios given in column (f) of Table II are much lower for hyoscine and atropine, the tertiary amines, than for the quaternary compounds, indicating that the tertiary compounds gain access to the ciliary muscle and iris more easily than the quaternary ones; the order is hyoscine, atropine, methanthelinium, and then the other three drugs. This order resembles that of the relative potencies of the drugs in causing drowsiness in the present experiments. Hyoscine was much more active than the quaternary drugs, and of these methanthelinium appeared to be a little more potent than the others. Atropine was least active, presum-

ably because it causes central stimulation rather than depression.

The relative potencies of the drugs in slowing micturition were not strikingly different from the figures for salivary secretion and heart rate, despite the possibility that an effect on the bladder may in part be due to the presence of drug in the urine. Levine and Clark (1955) have shown that, after intravenous infusion of methanthelinium in the dog, nearly 30% of the drug is excreted in the urine within 2 hr. If this also occurs in man, it might explain why methanthelinium is relatively more potent in its effect on micturition than in its action on salivary secretion and heart rate.

The time course of the drug effects shows a number of interesting features. With one exception there was little difference between drugs in the length of the latent period before the onset of the various effects. The exception was methanthelinium, whose actions became manifest much earlier than those of the other drugs. This suggests that it may be more rapidly absorbed from the site of injection than the other drugs, but this finding could also be explained in other ways.

The time course was not the same for the different effects studied; paralysis of accommodation and dilatation of the pupil mostly began later and lasted longer than the effects on the heart rate and salivary secretion. The maximum effects on accommodation and pupil also occurred later than those on the heart rate and salivary secretion. The higher the dose of a particular drug, the later did the peak effects on the eye occur (Fig. 7). The peak effects on the heart rate and salivary secretion behaved quite differently: they tended to occur earlier as the dose was increased. All these findings imply that the effects of the drug on the eye were still increasing although the concentration of the drug at other sites had been falling for some time. This suggests the existence of some reservoir which accumulates the drug while its concentration in the extracellular fluid is high, and then slowly gives it off to the iris and ciliary muscle. The aqueous humour might plausibly act as such a reservoir, although it seems at first sight surprising that the ciliary muscle and iris, which are well supplied with vessels, should take up much greater amounts of all the drugs from the aqueous humour than from the blood.

Involvement of the aqueous in the passage of drug from the blood to the iris and ciliary muscle could also explain why the quaternary compounds are less potent in their actions on the eye than the tertiary amines atropine and hyoscine. The blood-aqueous humour barrier has many features in common with the blood-cerebrospinal fluid barrier (Davson, 1956), and there is evidence that quaternary ammonium compounds pass into the cerebrospinal fluid much less readily than do tertiary amines (Paton and Zaimis, 1952; Bhattacharya and Feldberg, 1958). It has also been noted that many quaternary ammonium compounds are much less potent in their action on the central nervous system than closely related tertiary compounds (Nyman, 1943; Ing, Dawes, and Wajda, 1945).

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