# Quantitative study of pupil response to miotic drugs

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*A model by which the time relationship of the miotic effects of three drugs (pilocarpine, eserine, and carbachol) can be described is discussed in a two compartment analysis. The data obtained on six subjects were subjected to a curve-fitting procedure with a computer, from which the parameters of the equation describing the miosis-time curve could be obtained. With these the pertinent characteristics of the responses to the drugs could be compared.*

Certain aspects of the miotic effects of various drugs—such as the latency period between instillation of the drug and the onset of action, the degree of miosis obtained, and the duration of miotic activity —are fairly well known. However, the methods used to measure pupillary diameters during miosis are often inaccurate, the precision depending on the discriminating ability of the examiner. Furthermore, those estimates of the durations of the several phases of action of each miotic drug that have been reported in the literature are not consistent.

This paper is a report of a quantitative study of the pupillary responses to three of the more commonly used miotic drugs; the measurements have been made with a new model of the electronic infra-red pupillograph developed by Lowenstein and Loewenfeld.[1] This instrument is capable of recording almost instantaneous changes in the diameter of the pupil, and it is currently the most accurate instrument available for determining variations in pupillary diameters. The diameters of both pupils are recorded at the same time. This instrument is so well known that it need not be described here. With a suitable recording instrument, such as the Honeywell Visicorder, a permanent record of the variations in pupillary size can be obtained.

## Methods

The drugs used were all of parasympathomimetic action, being: 0.25 per cent physostigmine salicylate (eserine), 1 per cent pilocarpine hydrochloride, and 0.75 per cent carbaminoylcholine chloride (carbachol), each in a methylcellulose solution. A single drop (approximately 0.03 ml.) of the drug was instilled into the lower conjunctival cul-de-sac of one eye. The other eye was left untreated, as a control. In this way, any change in the sympathetic-parasympathetic equilibrium brought about by temporary changes in the subject's alert-

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ness would affect both pupils. Thus, the difference between the two pupils would reflect the intensity of the drug action. The subject was lying on his back during the drug instillation. After instillation he lay with his eyes closed for about 2 minutes, during which time he compressed the appropriate nasolacrimal sac to impede loss of the drug. When carbachol was used, the closed upper lid was massaged for about 10 seconds after instillation. It is recognized that massage of the lid of the closed eye following the instillation of carbachol may introduce potential errors in the action of the drug; for example, it might increase the rate of aqueous flow. However, insofar as possible, the same procedure was followed each time, which should minimize variability.

The subject sat in darkness with his head supported by a suitable head-and-chin rest before the pupillograph. He fixated a small light-green circular spot, projected by a lantern, at a distance of about 1.5 meters and about 25 degrees above the horizontal. Prior to the instillation of the drug, a record was made on the pupillograph to establish the initial sizes of the two pupils with the eyes nearly dark adapted. After the instillation of the drug the measured pupillary diameters were recorded fairly continuously for a period of about 1 hour. During this time the subject remained in darkness. After the first hour, the pupillary diameters were recorded every 30 minutes for another hour, and then at hourly intervals for the next 2 hours. If the pupils were not equal (within the normal variation limit of 0.4 mm.) by then, the recordings were continued at intervals of 2 to 5 hours until pupillary equality was obtained. Prior to these later recordings, the subject was semi-dark adapted by remaining in darkness for 5 minutes before the measurement.

The experiment was repeated at least twice for each subject with each drug (except eserine) with an interval of several days between tests.

Six subjects took part in the study; each subject had normal ocular structures except for refractive errors in two which were fully corrected with spectacles. The diameters of the two pupils of all subjects at the beginning of each experiment were equal within 0.4 mm.

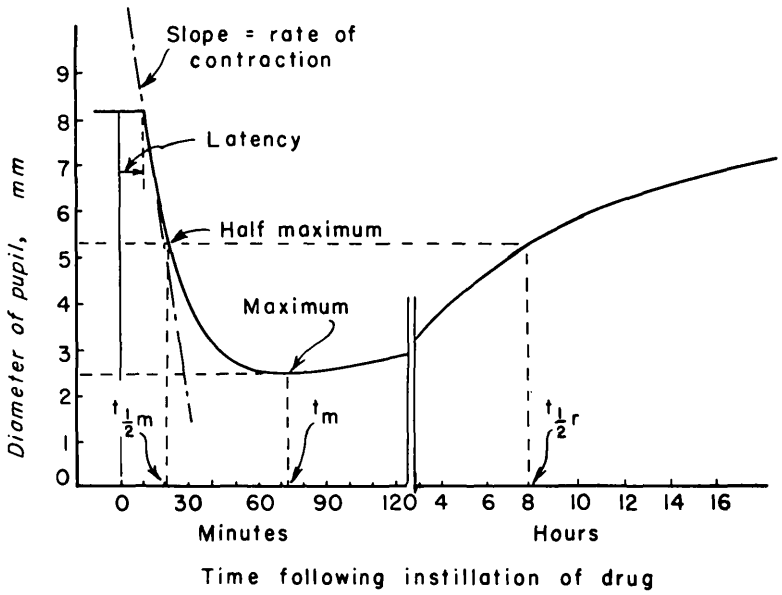


**Fig. 1.** Miosis-time curve, showing important quantities to be derived from it. The single vertical line at 0 minutes represents the moment of drug instillation. The discontinuity in the curve indicates change from minutes to hours on time scale.

**Results and discussion:**
**The miosis-time curves**

The mean diameters of the pupils of each subject at different times beginning at the moment of instillation of the drug into one eye were read from the pupillograph record. These measured diameters when plotted against the elapsed time gave a characteristic miosis-time curve. Fig. 1 illustrates the type of curve obtained and shows the important descriptive quantities to be derived from it. Since the time required for the recovery from miosis is so much longer than the period of contraction, the time scale on the abscissa is shown changed from minutes to hours at the end of 120 minutes (following the scheme of Lowenstein and Loewenfeld),[2] and consequently there is a discontinuity in the graph. Although the descriptive quantities can be estimated from the smooth curve drawn through the data points by inspection, there is a distinct advantage if these can be obtained from a quantitative treatment of the data.

A study of the various sets of miosis-time data obtained showed that a curve defined by an equation of the form

$$y = y_0 + A \exp(-at) - B \exp(-bt)$$

($t$ is measured from the beginning of pupillary constriction) could be fitted to each set of miosis-time data. Such an equation suggests that perhaps a two compartment drug transfer system would be adequate to describe the data. Accordingly, an attempt was made to derive the above equation in terms of such a model.[3]

The particular mechanism involved in the processes whereby a drug is absorbed by the cornea, diffuses into the aqueous humor, and is subsequently absorbed by the iris tissue is no doubt complex. Actually, of course, a three-compartment system must first be considered. In Fig. 2, let Square I be a compartment representing the cornea (and conjunctival cul-de-sac). A specific volume of drug of a specific concentration is instilled into this compartment. The drug immediately begins to be cleared: first, by the washing action of tears and by absorption into the conjunctival blood and lymphatic vessels, and second, through its passage into the aqueous humor. These exchanges are denoted by the arrow directed downward to the unnumbered square and the arrow directed to the square on the right that represents the aqueous humor (Square II). The drug in the aqueous

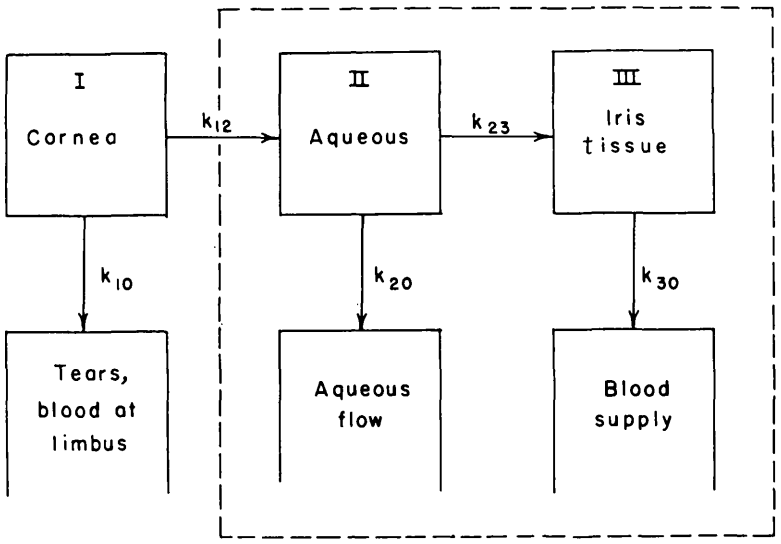


**Fig. 2.** Scheme for representing stages in drug diffusion in a three-compartment analysis. The *k's* are rate constants. The area framed by the broken lines represents a two compartment system.

humor would also be cleared by the aqueous flow (represented by the arrow directed downward) and by its absorption by the iris tissue indicated by the arrow to Square III.

We are interested in the concentration of the drug in the iris tissue because on this concentration will depend the miotic effect. The drug enters Compartment III from Compartment II, but is cleared through the blood supply in the iris and perhaps also by the aqueous humor. This clearance is represented by the arrow directed downward.

In his study with eserine, Schumacher[4] found that, although the drug persists in the cornea for a number of hours after instillation, little or none of the drug is found in the aqueous humor after 10 to 15 minutes. It remains in the iris tissue, however, for a long time. From polarimetric studies, Müller and co-workers[5] also inferred that the amount of pilocarpine in the aqueous humor after 15 minutes was about one fifth of the amount instilled in the eye. These findings suggest that the corneal endothelial surface may present a kind of barrier to the passage of the drug, such that only when the concentration of the drug in the corneal stroma is above a certain level will the drug pass into the aqueous humor. It is convenient to assume that, from the time of drug instillation until the iris reacts, all of the drug that can will have passed into the aqueous humor. It is, of course, necessary to assume also that, during the time the drug is passing into the aqueous humor, little or none has reached the iris in sufficient concentration to have a miotic effect. We then can consider the problem as a two compartment system—aqueous humor–iris—as suggested in Fig. 2 by the area framed by the broken lines.

The rate of change of the concentration of the drug in Compartment II will depend on the rate at which it is cleared, $k_{23}$ and $k_{20}$; it also will depend on the concentration of the drug in Compartment II, $c_2$, at time t. The model would propose that, in the time interval from the moment of instillation of the drug into the eye until a constriction of the pupil starts ($t_0$ or latency time), most of the drug that will pass into the aqueous humor through the cornea would have done so. Thus, the rate of change of the drug concentration in Compartment II would be given by

$$dc_2/dt = -(k_{20} + k_{23})\ c_2, \qquad (1)$$

in which the rate constants are $k_{20}$ and $k_{23}$.* The solution of this differential equation gives the relationship for the concentration $c_2$ at time t as

$$c_2 = D\ \exp[-(k_{20} + k_{23})t],$$

in which D is a constant. In terms of the time elapsed after constriction of the pupil starts, we define $t' = t - t_0$, and

$$c_2 = D'\ \exp[-(k_{20} + k_{23})t'], \qquad (2)$$

a relationship in which $D' = D \exp[(k_{20} + k_{23})t_0]$.

The rate at which the concentration in Compartment III (corresponding to the iris tissue), $c_3$, is changed will again depend on the rate of absorption of the drug from Compartment II (corresponding to the aqueous humor), $k_{23}$, and on the rate at which the drug is cleared, $k_{30}$, as well as on the concentration, $c_3$, of the drug in Compartment III. All of these rate relationships are assumed to be linear. Thus, the rate of change of the concentration of the drug in Compartment III will be given by

$$dc_3/dt = k_{23}c_2 - k_{30}c_3, \qquad (3)$$

$k_{23}$ and $k_{30}$ being the rate constants of the movement of drug from Compartment II to III and from Compartment III to the blood supply and, perhaps, aqueous humor, respectively. The expression for $c_3$, the concentration of the drug in Compartment III, follows from the solution of this differential

*In the model proposed here, the transport of the drug from the aqueous to the iris musculature was taken as irreversible, hence the single arrow $k_{23}$ in the figure is to the right. If it were reversible there would be another arrow from III to II and labeled $k_{32}$. The differential equations would then be more complicated, but the final solution would still involve only the difference in two exponential functions. However, the meaning of the coefficients in the exponential functions would be different and much more complex in terms of the various rate constants. If the rate constant $k_{32}$, the reversible transport, is very small compared to $k_{23}$—which is reasonable—then the analysis would be substantially the same as that developed in this paper.

equation and is obtained after substituting the value of $c_2$ from (2):

$$c_3 = C\,[\exp(-at') - \exp(-bt')], \qquad (4)$$

in which $C = (k_{23}D')/(k_{20} + k_{23} - k_{30})$, $a = k_{30}$, $b = k_{20} + k_{23}$, and, as before, $t' = t - t_0$.

The precise relationship between the concentration of the drug in the iris tissue and the amount of miosis is, of course, not known, but it may be quite complex. There exists, moreover, a minimal diameter of the pupil, which we can designate as $y_s$, which probably is determined by mechanical factors. Any analytical relationship between pupil constriction and drug concentration in the iris musculature must take this into account. However, it seems inescapable that, for our model and under the conditions of this study (such as constant near-dark adaptation), the diameter of the pupil, y (millimeters), is related to the concentration, $c_3$, of the drug in the iris by

$$(y - y_s) = (y_0 - y_s)\,f(c_3), \qquad (5)$$

in which $y_0$ is the diameter of the pupil with no drugs ($c_3 = 0$) and $f(c_3)$ represents a function of $c_3$, the value of which *decreases* with increase in $c_3$. When $c_3 = 0$, $f(c_3) = 1$ and when $c_3$ is very large, $f(c_3) = 0$. We can expand the function, $f(c_3)$, by Maclaurin's theorem, so that

$$(y - y_s) = (y_0 - y_s)\,[f(0) + c_3f'(0) + \tfrac{1}{2}c_3^2f''(0) + \ldots]. \qquad (6)$$

Assuming that this series converges rapidly, we can, in order to simplify our model, neglect all terms involving $c_3$ above the first degree. Then

$$y = y_0 - pc_3, \qquad (7)$$

in which $p$ would be the constant $(Y_0 - Y_s)\,f'(0)$. The first derivative of this decreasing function would be negative. On substitution of the equivalent of $c_3$ from (4), (7) can be written

$$y = y_0 - A\,[\exp(-at') - \exp(-bt')], \qquad (8)$$

in which $t' = t - t_0$ and $A = (pD'k_{23})/(k_{20} + k_{23} - k_{30})$. This equation would state the relationship between the diameter of the pupil, y, at any time, t, from the moment of instillation of the drug, all on the basis of the assumptions made above.

For each set of data the parameters of (8)—namely A, a, b, and $t_0$—were adjusted, by a systematized guessing technique programmed for the computer, until the sums of the squares of the deviations between each theoretical and experimental point had converged to a minimum. The value of $y_0$ was taken as the measured diameter of the pupil at the moment of instillation of the drug.

Fig. 3 illustrates one set of data with the corresponding calculated curve obtained from (8) conformed to the experimental data points. The deviations between the predicted and experimental points are well within the limits of experimental error. Fig. 4 illustrates similarly the theoretical curve conformed to a set of data reported by Lowenstein and Loewenfeld.[2] The fit is generally excellent. It is possible that some of the curves fail to describe the data points more accurately near the minimal diameter (maximal contraction) because higher powers of the series expansion (6) of $f(c_3)$ were neglected. The greater amount of scatter evident about the curve during the later recovery period is in part due to the moment-to-moment change in the pupil as the result of normal activity. This change would not be effective in the drugged eye during the period of maximal constriction. However, a study of the approximately 40 sets of data and the curves computed to fit each set justifies the conclusion that (8) does adequately describe the miosis-time curve, even if some aspects of the model discussed necessitated oversimplified assumptions. One must also be aware of some of these oversimplified assumptions. For examples: (1) The recovery of the iris from the action of the drug is assumed to be only a function of the drug at the active site; and (2) the drug action is assumed to be independent of pupil size.

In order to study the differences in the miotic responses of different subjects to the same drug under the same experimental

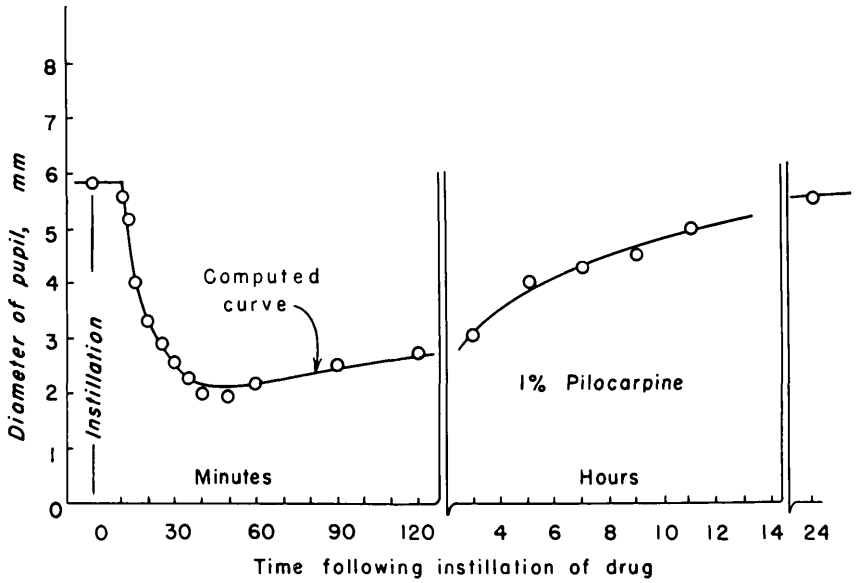


Fig. 3. Theoretical curve based on equation 8 (see text) conformed to the actual miosis-time data taken from the pupillograph record (circles).

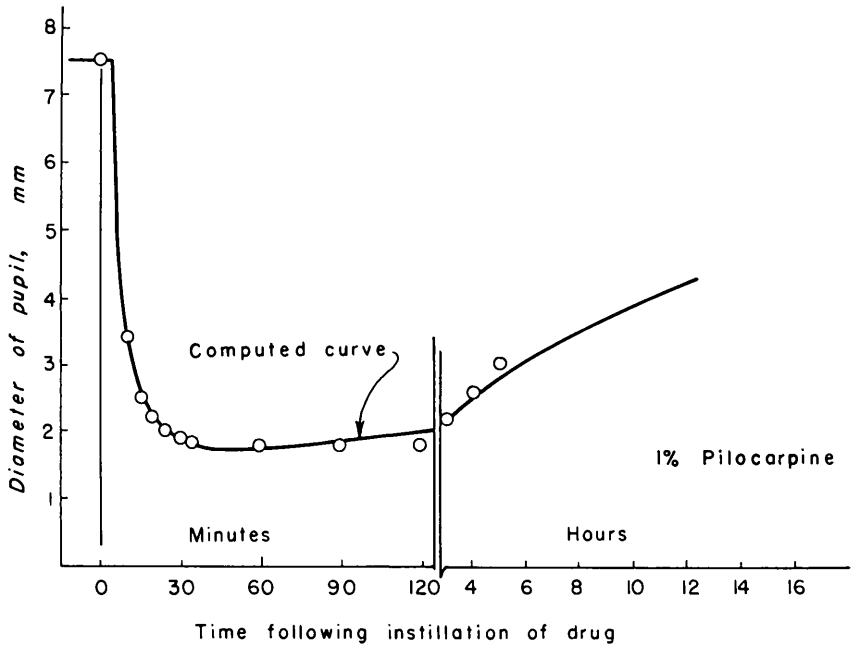


Fig. 4. Theoretical curve based on equation 8 (see text) conformed to a set of miosis-time data obtained for subject A by Lowenstein and Loewenfeld.[2]

conditions and of the same subjects to different drugs and different concentrations, a comparison of the rate constants in our model—namely, $k_{23}$ (absorption) and $k_{30}$ (clearance)—might be helpful. The clearance rate constant, $k_{30}$, can be found directly from the calculation because $a = k_{30}$. Unfortunately, it is not possible to resolve $b = k_{20} + k_{23}$ into its parts because we have data pertaining only to the iris compartment. Independent data concerning the same system or information on the concen-

tration-time relationship of other compartments of the proposed model are necessary. However, if it is assumed that $k_{20}$ (clearance from aqueous humor) does not change in such a way as to mask any correlation in the variation between $k_{23}$ and $k_{30}$, it may be instructive to study the ratio b/a (approximately, absorption/clearance rates). This ratio may tend to minimize the unwanted effects of variations between subjects. Perhaps also important is the rate of change of pupillary diameter at the beginning of the miosis. This rate, given by $R_0 = -A(b - a)$ which is derived by differentiating (8) with respect to t', evaluated for the time $t' = 0$, was added to the computations.

From the parameters found by computation in the model equation, we also can easily find the curve indicating the rate of change of pupillary size with elapsed time. Fig. 5 illustrates an example for one subject, together with the primary miosis-time curve. This rate (or derivative) curve dramatizes the very rapid—almost precipitous—rate of constriction in the first minute of the miotic effect. The processes of recovery are active at once, the rate also being greatest at the beginning when the drug concentration in the iris would be greatest. The elapsed time at maximal rate of recovery will be at $t_z$ indicated in the figure. This elapsed time from the beginning of the miosis should be twice the elapsed time for maximal constriction of the pupil. By obtaining the values for the parameters for the miosis-time data from the computer fitting-procedure, one can readily find the following pertinent quantities:

$t_0$ = latency period (minutes);
$t_{\frac{1}{2}m}$ = the time (minutes) for the pupil to reach half of maximal constriction;
$t_m$ = the time (minutes) for the pupil to reach maximal constriction;
$t_{\frac{1}{2}r}$ = the time (minutes) for the pupil to recover to half of maximal constriction;
$y_m$ = diameter of pupil at maximal constriction (millimeters);
$R_0$ = rate of change in pupillary diameter at beginning of the miosis-time curve (millimeters/minute);
b/a = approximate ratio of rate (absorption and clearance) constants, $(k_{20} + k_{23})/k_{30}$.

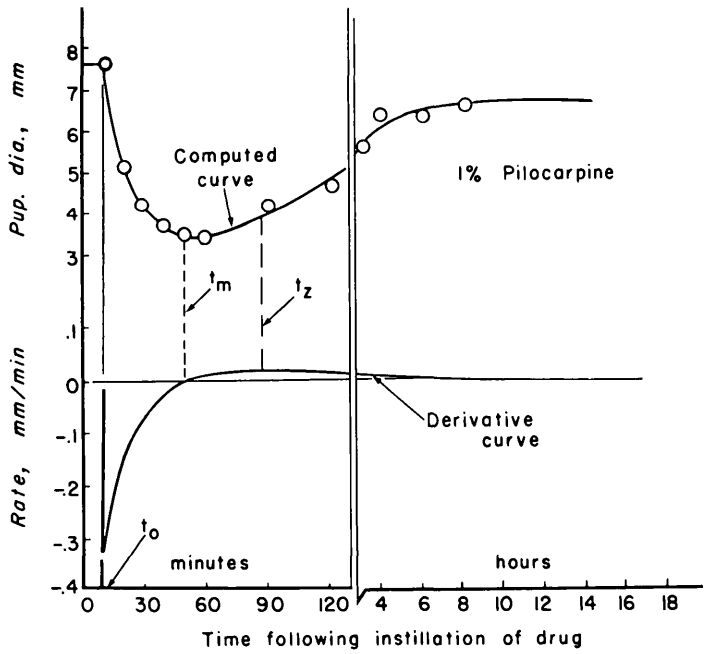


**Fig. 5.** Curves for one subject. Top: Usual miosis-time data. Bottom: Corresponding calculated rate of change (derivative) of pupillary diameter with elapsed time.

Tables I, II, and III summarize these results as well as the parameters for the equation. These tables include the results on the greater part of all sets of data pertaining to the miosis-time curves with the three drugs used.

Because the number of subjects used in this study is small, definitive conclusions probably should not be drawn from the results. However, it is of interest to note certain aspects that may be of value in that at least they illustrate the method proposed here.

**Latency period.** The mean latency period

**Table I.** Characteristic quantities and parameters for miosis-time curves with 0.25 per cent eserine

| *Subject, age (yr.), status* | $y_0$ *(mm.)* | $t_0$ *(min.)* | $t_{½m}$ *(min.)* | $t_m$ *(min.)* | $t_{½r}$ *(min.)* | $y_m$ *(mm.)* | $R_0$ *(mm./min.)* | *A* | *a* | *b* | *b/a* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A, 28, emmetrope | 7.60 | 15.5 | 22.7 | 66.7 | 403 | 5.07 | −0.271 | 7.20 | 0.004 | 0.042 | 10.5 |
| B, 45, presbyope and myope | 7.80 | 13.5 | 22.1 | 54.0 | 449 | 5.30 | −0.332 | 6.21 | 0.002 | 0.055 | 27.5 |
| C, 28, emmetrope | 8.30 | 14.9 | 28.3 | 89.8 | 430 | 5.91 | −0.163 | 9.35 | 0.003 | 0.020 | 6.6 |
| D, 36, emmetrope | 6.80 | 13.1 | 23.0 | 58.3 | 338 | 4.07 | −0.270 | 7.78 | 0.009 | 0.044 | 4.9 |
| E, 61, presbyope | 6.00 | 13.6 | 23.1 | 42.0 | 533 | 3.48 | −0.542 | 3.69 | 0.002 | 0.148 | 74.0 |
| F, 29, high myope | 7.20 | 13.1 | 19.4 | 48.8 | 582 | 5.91 | −0.603 | 6.37 | 0.001 | 0.096 | 96.0 |
| Mean | | 13.9 | 23.1 | 60.0 | 456 | 4.96 | −0.364 | | | | |
| S.D. | | 1.0 | 2.9 | 16.9 | 28.0 | 0.99 | 0.182 | | | | |

Abbreviations: $y_0$, initial diameter of pupil; $t_0$, latency time; $t_{½m}$, time for pupil to have reached half of maximal constriction; $t_m$, time for pupil to reach maximal constriction; $t_{½r}$, time for pupil to have recovered to half maximal constriction; $y_m$, diameter of pupil at maximal constriction; $R_0$, rate of change in pupillary diameter at beginning of miosis-time curve; A, a, and b, parameters found for equation 8; b/a, ratio of rate constants.

**Table II.** Characteristic quantities and parameters for miosis-time curves with 1 per cent pilocarpine

| *Subject, age (yr.), status* | *Set* | $y_0$ *(mm.)* | $t_0$ *(min.)* | $t_{½m}$ *(min.)* | $t_m$ *(min.)* | $t_{½r}$ *(min.)* | $y_m$ *(mm.)* | $R_0$ *(mm./min.)* | *A* | *a* | *b* | *b/a* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A, 28, emmetrope | 1 | 7.43 | 9.4 | 17.5 | 52.4 | 208 | 4.97 | −0.399 | 6.65 | 0.005 | 0.065 | 13.0 |
| | 2 | 8.00 | 11.0 | 20.5 | 59.5 | 217 | 5.26 | −0.364 | 7.43 | 0.005 | 0.054 | 10.8 |
| B, 45, presbyope and myope | 1 | 7.80 | 8.7 | 16.5 | 50.4 | 216 | 4.03 | −0.340 | 5.23 | 0.005 | 0.070 | 14.0 |
| | 2 | 7.60 | 8.5 | 15.6 | 46.3 | 195 | 3.86 | −0.358 | 5.04 | 0.005 | 0.076 | 15.2 |
| C, 28, emmetrope | 1 | 8.58 | 9.5 | 21.1 | 69.8 | 313 | 4.23 | −0.250 | 5.43 | 0.003 | 0.049 | 16.3 |
| | 2 | 8.10 | 10.4 | 18.9 | 56.0 | 251 | 5.14 | −0.404 | 6.51 | 0.004 | 0.066 | 16.5 |
| D, 36, emmetrope | 1 | 7.32 | 11.2 | 19.5 | 49.1 | 126 | 3.51 | −0.271 | 7.96 | 0.013 | 0.047 | 3.6 |
| | 2 | 7.00 | 10.3 | 16.6 | 45.3 | 209 | 4.46 | −0.431 | 5.53 | 0.005 | 0.083 | 16.6 |
| E, 61, presbyope | 1 | 5.82 | 9.6 | 15.8 | 49.3 | 344 | 3.65 | −0.386 | 4.11 | 0.002 | 0.096 | 48.0 |
| | 2 | 6.10 | 9.1 | 14.7 | 42.0 | 255 | 3.29 | −0.399 | 3.80 | 0.003 | 0.108 | 36.0 |
| F, 29, high myope | 1 | 7.15 | 10.4 | 17.2 | 56.4 | 542 | 6.37 | −0.617 | 6.93 | 0.002 | 0.091 | 45.5 |
| | 2 | 6.89 | 9.6 | 16.0 | 49.0 | 371 | 5.86 | −0.630 | 6.56 | 0.002 | 0.098 | 49.0 |
| Mean | | | 9.8 | 17.5 | 52.1 | 271 | 4.55 | −0.404 | | | | |
| S.D. | | | 0.8 | 2.0 | 7.5 | 109 | 0.97 | 0.115 | | | | |
| Average diff.: 1st and 2nd runs | | 0.3 | 0.8 | 1.9 | 7.2 | 72 | 0.5 | 0.066 | 0.86 | | | |

Abbreviations: $y_0$, initial diameter of pupil; $t_0$, latency time; $t_{½m}$, time for pupil to have reached half of maximal constriction; $t_m$, time for pupil to reach maximal constriction; $t_{½r}$, time for pupil to have recovered to half maximal constriction; $y_m$, diameter of pupil at maximal constriction; $R_0$, rate of change in pupillary diameter at beginning of miosis-time curve; A, a, and b, parameters found for equation 8; b/a, ratio of rate constants.

**Table III.** Characteristic quantities and parameters for miosis-time curves with 0.75 per cent

| *Subject, age (yr.), status* | *Set* | $y_0$ *(mm.)* | $t_0$ *(min.)* | $t_{½m}$ *(min.)* | $t_m$ *(min.)* |
|---|---|---|---|---|---|
| A, 28, emmetrope | 1 | 7.90 | 12.0 | 18.3 | 55.7 |
| | 2 | 7.85 | 12.1 | 23.3 | 57.1 |
| B, 45, presbyope and myope | 1 | 7.10 | 17.3 | 28.5 | 72.3 |
| | 2 | 7.75 | 15.8 | 25.0 | 58.3 |
| C, 28, emmetrope | 1 | 8.20 | 17.1 | 25.2 | 47.6 |
| | 2 | 7.90 | 14.0 | 24.0 | 56.6 |
| D, 36, emmetrope | 1 | 7.60 | 15.4 | 25.0 | 48.2 |
| | 2 | 7.20 | 12.0 | 22.5 | 50.1 |
| E, 61, presbyope | 1 | 5.85 | 12.1 | 19.0 | 65.3 |
| | 2 | 6.25 | 13.3 | 20.5 | 76.5 |
| F, 29, high myope | 1 | 7.00 | 11.0 | 21.6 | 69.7 |
| | 2 | 6.80 | 12.2 | 20.6 | 64.4 |
| Mean | | | 13.7 | 22.9 | 60.2 |
| S.D. | | | 2.2 | 3.0 | 30.1 |
| Average diff: 1st and 2nd runs | | 0.3 | 1.7 | 2.5 | 7.1 |

Abbreviations: $y_0$, initial diameter of pupil; $t_0$, latency time; $t_{½m}$, time for pupil to have reached half of maximal constriction; ameter of pupil at maximal constriction; $R_0$, rate of change in pupillary diameter at beginning of miosis-time curve; A, a,

($t_0$) with 1 per cent pilocarpine was 9.8 minutes with a standard deviation between subjects of 0.9 minute, while that with 0.25 per cent eserine and 0.75 per cent carbachol was 13.9 (S.D. = 1.0) and 13.7 (S.D. = 2.2) minutes, respectively. Because of the larger variability of data when carbachol was used, it is uncertain whether the difference in latency times between pilocarpine and carbachol is significant. The difference between these times for eserine and pilocarpine, on the other hand, is significant (by the "t" test) at the 1 per cent level.

**Rate of miosis.** The rates at which the pupil constricted at the beginning of the miosis ($R_0$) with pilocarpine and with eserine were about equal, while that with carbachol was significantly less. This is to say, the action of this latter drug (in the concentration used) is less powerful. Also to be noted is the fact that the maximal constriction is less than that with the other two drugs.

**Time to maximal constriction.** The tables show that the time from instillation of the drug to maximal constriction ($t_m$) was essentially the same for all three drugs in the concentrations used.

**Time to half recovery.** The elapsed time ($t_{½r}$) from instillation of drug to the moment when the pupil recovered to half of the maximal constriction differed between drugs and between subjects, being longest for eserine (456 minutes) and shortest for carbachol (164 minutes). Whether these differences are due to the particular concentrations used or whether they indicate a property of the drug itself cannot be ascertained from this study.

**The ratio b/a.** The ratio of the exponential coefficients *b* and *a*, which may be an approximate indication of the ratio of the rates of absorption and clearance of the drug in the iris tissue (or at least an indication of its miotic effect), appeared to be of the same order of magnitude for three of the subjects but it was considerably greater for two. The larger values might suggest a lower rate of clearance from the aqueous humor or an increased rate of absorption of the drug. In addition to a lack

carbachol

| $t_{½r}$ (min.) | $y_m$ (mm.) | $R_0$ (mm./min.) | A | a | b | b/a |
|---|---|---|---|---|---|---|
| 188 | 3.23 | −0.219 | 5.06 | 0.006 | 0.050 | 6.3 |
| 173 | 2.85 | −0.167 | 4.34 | 0.005 | 0.044 | 8.8 |
| 100 | 1.07 | −0.063 | 2.03 | 0.008 | 0.039 | 4.9 |
| 96 | 2.38 | −0.084 | 250.62 (?) | 0.047 (?) | 0.048 | 1.0 |
| 156 | 1.85 | −0.152 | 2.77 | 0.007 | 0.062 | 8.7 |
| 135 | 2.10 | −0.152 | 2.83 | 0.005 | 0.058 | 11.6 |
| 121 | 1.71 | −0.077 | 3.22 | 0.006 | 0.030 | 5.0 |
| 140 | 0.95 | −0.066 | 2.13 | 0.012 | 0.042 | 3.5 |
| 190 | 1.47 | −0.076 | 2.51 | 0.006 | 0.036 | 6.0 |
| 220 | 2.20 | −0.053 | 18.97 (?) | 0.008 | 0.010 | 1.3 |
| 210 | 2.57 | −0.151 | 3.30 | 0.003 | 0.049 | 16.0 |
| 240 | 3.20 | −0.146 | 5.40 | 0.005 | 0.032 | 6.4 |
| 164 | 2.13 | −0.117 | | | | |
| 46 | 0.75 | 0.053 | | | | |
| 20 | 0.7 | 0.019 | 0.99 | | | |

$t_m$, time for pupil to reach maximal constriction; $t_{½r}$, time for pupil to have recovered to half maximal constriction; $y_m$, di- and b, parameters found for equation 8; b/a, ratio of rate constants.

of ancillary data, there are too few subjects in the present study to allow elaboration on this point.

These results must be interpreted only in terms of the type of drugs used, their concentrations, the method of instillation in the eye, and the ages of the subjects. However, this discussion has pointed out a method for studying more fully the miotic effects of drugs from a quantitative point of view, based upon a particular model in a compartment analysis.

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