Clinical pharmacokinetics of the eye

Proctor Lecture

Saiichi Mishima

Pharmacokinetics of instilled drugs in the human eye is reviewed. The behavior of drugs in the conjunctival cul-de-sac is discussed, and the loss rates with various vehicles are estimated. Kinetics of intraocular drug penetration follows the same pattern in human and rabbit eyes. From results of rabbit experiments, various pharmacokinetic coefficients are computed, including the permeability of the corneal epithelium. Also, with use of published data in human aqueous, the corneal permeability, apparent absorption, and elimination rate constants are calculated for some drugs in the human eye. From the anesthetic response of the cornea the apparent elimination rate constants of the surface anesthetics are obtained. The pupil response is converted to a response parameter proportional to the biophase drug concentration. The time course of its changes conforms with the kinetics of intraocular drug penetration, and the apparent absorption and elimination rate constants are computed for various drugs. The latter constant becomes smaller with increased ocular pigmentation. Use of the relative bioavailability concept permits comparison of drug absorption efficiency among various vehicles. Pharmacokinetic coefficients are also obtained for the cycloplegic responses. The intraocular pressure response is analyzed, and it is suggested that the reduction ratio in the outflow pressure, outflow resistance, and the aqueous formation rate be used for dose-response studies. The rate of effect disappearance is defined and is given for three beta-adrenergic blocking agents.

Key words: pharmacokinetics, tears, corneal permeability, pupil, accommodation, anesthetics, intraocular pressure, drugs, eye

The purpose of medical treatment is to achieve the desired effects of a given drug and to avoid its untoward side effects. This may be realized by appropriate choice of the therapeutic regimen based on the knowledge of absorption, metabolism, and elimination of the drug, i.e., its pharmacokinetics. On this principle, knowledge of the pharmacokinetics of instilled drugs in the human eye would give a basis for logical use of ophthalmic drugs.

The availability of instilled drugs in the eye is modified principally by three factors: (1) drug kinetics in the conjunctival cul-de-sac, (2) the permeability of the cornea, and (3) the rate at which the drug is eliminated from the eye. The drug kinetics in the conjunctival cul-de-sac of the human subjects has been approached through studies using fluorescein or sodium pertechnetate. Intraocular penetration of instilled drugs takes place mainly through the cornea, and a voluminous literature has accumulated on drug penetration in rabbit eyes. A series of works...
of Robinson and co-workers has greatly elucidated the pharmacokinetics of pilocarpine and fluorometholone in the rabbit eyes, but it is not readily apparent whether these results can be directly extrapolated to the human eye. It is difficult to attempt to study this aspect in the human eye, and the results of a few studies are not enough to achieve a systematic knowledge of its pharmacokinetics. For this reason the intraocular penetration of instilled fluorescein was chosen as a model of drug transfer kinetics from which the basic theory of ocular pharmacokinetics was developed.

There are several ocular responses to drugs that can be quantified with reasonable accuracy so as to make possible investigations on the dose-response relationship and the time course of the response changes. The magnitude of the response at a given time may be considered to be a function of the amount of the drug concurrently present in the biophase of the target tissue, and therefore the time course of the response changes may be analyzed according to the principles of pharmacokinetics. This noninvasive method was found to be fruitful in the pharmacokinetic studies of instilled drugs in the human eye, and the results could be well accounted for by the theory of transcorneal drug transfer; they are also consistent with the chemical analyses made in rabbit eyes. Several pharmacokinetic coefficients computed from the studies of ocular responses may be useful for clinical purposes. An attempt was made in the present article to review these aspects of clinical pharmacokinetics in the human eye, with particular reference to topically applied drugs.

Penetration kinetics of instilled drugs

Behavior of drugs in conjunctival cul-de-sac. An instilled drug penetrates the eye by absorption across the cornea from the precorneal tear film. Thus the mixing and kinetic behavior of drugs in the tears have a direct bearing on the efficiency of drug absorption by the eye.

The conjunctival cul-de-sac normally contains about 7 to 9 μl of tears, with a physiologic turnover rate of 0.1 to 0.15 min⁻¹. The rate of tear flow is about 1 μl min⁻¹. The maximum quantity of fluid that can be contained in the cul-de-sac without overflow is about 30 μl. Since one drop of collyrium dispensed from a conventional ophthalmic bottle is 40 to 50 μl, about 20 μl of the drug is spilled out from the lids at the time of instillation. The increased volume of fluid in the cul-de-sac is quickly delivered into the lacrimal drainage system by the pumping action of the canaliculi associated with the blink movement. The precorneal tear film is a stagnant fluid layer with a thickness of about 7 to 9 μm that is spread over the corneal epithelium by a coacervate of mucin and is stabilized by the superficial oily layer formed by meibomian gland secretion. Therefore its mixing with the marginal tear fluid after drugs are instilled takes place only by blink movements, which at the same time carry the instilled drug away from the cul-de-sac.

Because of the above mechanism, the tear film saturation with the instilled drug is incomplete. After instillation of fluorescein solution, the initial tear concentration, i.e., degree of saturation, increased slightly on increasing the instilled volume from 5 to 20 μl, but further volume increase failed to raise the degree of saturation over a 46% level of the instilled drug concentration. Similarly, in rabbit eyes an increase in the instillation volume was shown to result in a greater loss rate from the tears but not to raise intraocular drug penetration. On this basis, the instillation volume of about 20 μl has been thought to be adequate, and this will be discussed later in relation to the intraocular bioavailability of drugs.

The above phenomena imply that rapidly repeated instillations of a drug do not contribute to the increase of its bioavailability to the eye. Furthermore, when two or three drugs are instilled at short intervals, they mutually dilute each other and reduce the availability of each of them. In addition, the increase in the drainage into the lacrimal sac and the nose lead to an increase in the systemic absorption of the drug, hence the systemic side effects. These systemic effects of
topical ophthalmic drugs are of particular concern in pediatric ophthalmology, and it is important to take measures to reduce systemic drug absorption. It is therefore necessary to dispense appropriate drop size. Maurice suggested the development of a device permitting instillation of precise volumes onto the cornea, which would be useful in clinical practice.

Addition of viscous vehicles (e.g., methylcellulose) could raise the initial tear film saturation when the viscosity increases up to 15 to 20 centistokes. Further increase in the viscosity, however, failed to saturate the tear film any further, the limit being about 80% of the instilled concentration. The higher tear film saturation that follows the addition of viscous vehicles is probably due to slowing the initial drainage of solution and also to the prolonged retention of the thickened tear film, both mechanisms give more time for the drug to mix with the precorneal tear film.

The drug mixed in the tears will then be diluted by tear secretion, and the concentration decrease is related to time by a single exponential, i.e.

$$C_d = C_{d0} e^{-\alpha t}$$

where $C_d$ and $C_{d0}$ are the drug concentrations in the tears at a given time and at time zero, respectively, and $\alpha$ is the rate constant of loss from the tears. The rate constant of loss after instillation of fluorescein solution ranges from 0.05 to 0.3 min$^{-1}$, depending on the degree of lacrimation. When the solution causes stinging, the rate constant can be as high as 1 to 2 min$^{-1}$.

There are numerous papers reporting that the use of viscous vehicles improves the contact of drugs with the cornea, thereby enhancing intraocular penetration and effects. The increased contact of a drug with the cornea may involve either or both of (1) higher initial tear film saturation with the drug and (2) reduction of the rate of loss in the tears. Increase in the tear film saturation was noted above, but the reduction of the loss rate appears to be only slight; with sodium pertechnetate, Tc$^{99m}$, the loss rate was reported to be 0.06 to 0.1 min$^{-1}$ with viscous vehicles. In rabbit eyes the loss rate decreased as the viscosity of the solution increased, but it was stabilized at the level of about 0.1 min$^{-1}$ in the viscosity range of 13 to 15 centistokes, and no further decrease was observed by increasing the viscosity. This is in good agreement with the observation in human eyes.

Ointment is often used as the vehicle and may be classified into two types: the simple base (e.g., castor oil) and the compound base. The compound bases are more often used, and the oil-in-water type emulsion is particularly effective since the drug with low water solubility is contained at a high concentration in the oil phase, from whence it is released into the water phase that becomes continuous with the tears. After instillation these ointments break up into small droplets and remain in the cul-de-.
sac for a long time, acting as a depot of the drug, some may be carried into the lacrimal drainage system and pass into the nose. The loss rate of tetracycline given in castor oil is about 0.01 min\(^{-1}\) and in ointment is about 0.005 to 0.006 min\(^{-1}\).

**Kinetics of intraocular penetration of drugs**

**Drug uptake by the cornea.** No experimental data are available for the corneal uptake of various drugs in the human eye, and we must rely on the results obtained in rabbit eyes. To compare the corneal uptake of various drugs it is necessary to compute tear-cornea drug transfer either in terms of the transfer coefficient or of the permeability of the epithelial barrier. Several papers in the literature have reported the corneal concentration changes shortly after drug instillation, and the permeability of the epithelial barrier may be calculated from their data. The permeability of the rabbit and human corneas will then be compared.

During the very early period after instillation the drug is first mixed with the precorneal tear film and is then taken up by the cornea. This process is depicted in Fig. 1, and the transfer equation may be written using equation 1 as

\[
\frac{dC_c}{dt} = k_{c,dc} C_{do} e^{-\alpha t} - k_c C_c
\]

where \(C_c\) is the corneal concentration, \(C_{do}\) is the initial tear concentration, \(\alpha\) is the rate constant of loss from the tears, \(k_{c,dc}\) is the tear-cornea transfer coefficient in reference to the corneal volume, \(k_c\) is the rate constant of loss from the cornea, and \(t\) is the time. Integration of the equation yields

\[
C_c = \frac{k_{c,dc} C_{do}}{\alpha - k_c} \left( e^{-\alpha t} - e^{-kt} \right)
\]

The peak time of the corneal concentration \((T_c)\) is given by

\[
T_c = \frac{\ln \frac{\alpha}{k_c}}{\alpha - k_c}
\]

Since the loss rate in the tears, \(\alpha\), is far greater than that from the cornea, \(k_c\), the peak time occurs shortly after instillation. The peak time, in rabbit eyes ranges from 5 min\(^{22, 43}\) to about 30 min,\(^{47}\) and this must be caused by variation of the loss rate in the tears. It is very difficult to accurately determine the corneal concentrations in a very short time after instillation, and the results of only a few published papers could be analyzed with equation 3. In most published results, the concentration decreases in the cornea after the peak time are shown (Fig. 2); therefore, extrapolation of the curve to time zero is possible to give the value of \([C_c]_0\). Remembering that \(\alpha\) is far greater than \(k_c\), one can write

\[
[C_c]_0 = \frac{k_{c,dc} C_{do}}{\alpha - k_c} = k_{c,dc} C_{do}/\alpha
\]
### Table I. Permeability of the epithelial barrier ($K_{ep}$) of the rabbit cornea to various drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>$K_{ep}$ ($\times 10^{-4} \text{ cm hr}^{-1}$)</th>
<th>Source of data (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine</td>
<td>5.2-7.3</td>
<td>45</td>
</tr>
<tr>
<td>7-19</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>9-18$^a$</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Prednisolone acetate</td>
<td>3.2-5.6</td>
<td>47</td>
</tr>
<tr>
<td>Prednisolone Na phosphate</td>
<td>5.8$^b$</td>
<td>48</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>3.7-5.1</td>
<td>50</td>
</tr>
<tr>
<td>Flurimetholone</td>
<td>2.5-3.4</td>
<td>51</td>
</tr>
<tr>
<td>Timolol</td>
<td>9.6</td>
<td>52</td>
</tr>
<tr>
<td>Befunolol</td>
<td>5.8$^b$</td>
<td>48</td>
</tr>
<tr>
<td>Bupranolol</td>
<td>12</td>
<td>54</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>11</td>
<td>49</td>
</tr>
<tr>
<td>Dipyvalyl-epinephrine</td>
<td>3.7$^b$</td>
<td>48</td>
</tr>
<tr>
<td>Fluorometholone</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>Timolol</td>
<td>5.8$^b$</td>
<td>48</td>
</tr>
<tr>
<td>Bupranolol</td>
<td>13</td>
<td>Takase et al.$^k$</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>4</td>
<td>Uda et al.$^k$</td>
</tr>
<tr>
<td>Dipyvalyl-epinephrine</td>
<td>53</td>
<td>Uda et al.$^k$</td>
</tr>
<tr>
<td>Fluriprofen</td>
<td>26</td>
<td>Takase et al.$^k$</td>
</tr>
<tr>
<td>6-Aminohexanoic acid</td>
<td>12$^c$</td>
<td>59</td>
</tr>
<tr>
<td>Hexurazan</td>
<td>9.6</td>
<td>60</td>
</tr>
<tr>
<td>Sodium</td>
<td>8-24$^a$</td>
<td>61</td>
</tr>
<tr>
<td>Urea</td>
<td>7.5$^c$</td>
<td>62</td>
</tr>
<tr>
<td>D-xylose</td>
<td>1.7$^c$</td>
<td>62</td>
</tr>
<tr>
<td>Sucrose</td>
<td>1.4$^c$</td>
<td>62</td>
</tr>
<tr>
<td>Sodium</td>
<td>8-24$^a$</td>
<td>61</td>
</tr>
<tr>
<td>Urea</td>
<td>7.5$^c$</td>
<td>62</td>
</tr>
<tr>
<td>D-xylose</td>
<td>1.7$^c$</td>
<td>62</td>
</tr>
<tr>
<td>Sucrose</td>
<td>1.4$^c$</td>
<td>62</td>
</tr>
</tbody>
</table>

$^a$Corneal concentration not available; calculation was made from peak aqueous concentration using equation 12.

$^b$Results of in vitro studies for the whole layers of the cornea.

$^c$Results of in vivo studies for the whole layers of the cornea.

$^d$Calculated by the author from in vivo studies.

$^e$Unpublished results.

On the basis of this equation, [C$_{c0}$] can be used to calculate the tear-cornea transfer coefficient, k$_{c,dc}$.

Alternatively, the drug uptake by the cornea in the very early period after instillation may be expressed as follows, since the loss from the cornea during this period is negligible:

$$\frac{dM}{dt} = K_{ep} Q C_{c0} e^{-\alpha t}$$

(6)

where $M$ is the amount of drug transferred, $K_{ep}$ is the permeability of the epithelial barrier, and $Q$ is the area of the cornea. The total amount of the drug absorbed by the cornea, $M_0$, may then be given by integrating the above equation

$$M_0 = K_{ep} Q C_{c0}/\alpha$$

(7)

Denoting the corneal volume as V$_c$, $M_0$ should be given by [C$_{c0}$]V$_c$, and equations 5 and 6 give

$$K_{ep} = \frac{k_{c,dc} V_c}{Q} \frac{[C_{c0}] V_c}{Q C_{c0}}$$

(8)

Thus the values of $K_{ep}$ were calculated from the data published in the literature, assuming that V$_c$ is 0.05 ml, Q is 2 cm$^2$, $\alpha$ is 6 hr$^{-1}$, and $C_{c0}$ is equal to the concentration of the instilled drug. The results are given in Table I. There are many uncertainties in the experimental conditions, which necessitate making assumptions, as above, and the values are therefore only approximate. Nevertheless, the values of $K_{ep}$ for the same drug obtained from different sources appear to be in fair agreement. In addition, it can be seen that the epithelial barrier of the cornea is more permeable to lipid-soluble than to lipid-insoluble drugs.

### Drug transfer into the anterior chamber.

Because of the rapid loss of drugs from the conjunctival cul-de-sac, the uptake by the cornea is practically finished a few minutes after instillation. The drug absorbed by the cornea is then transferred into the anterior chamber, where the drug is carried away by aqueous flow and by diffusion into the blood circulation in the anterior uvea. The transfer kinetics may be represented by a two-compartment open model shown in Fig. 3. The transfer equations applicable to this situation were given by Jones and Maurice$^30$ and are

$$\frac{dC_{c}}{dt} = k_{c,ac} C_a - k_{c,ca} C_c$$

(9)

$$\frac{dC_a}{dt} = k_{a,ca} C_c - k_{a,ac} C_a - k_a C_a$$

(10)

The steady-state distribution ratio, r$_{ca}$, between the cornea and the aqueous may be given by

$$r_{ca} = \frac{k_{c,ac}/k_{c,ca}}$$

(11)

where $k_{c,ac}$ and $k_{c,ca}$ are the aqueous-cornea
and cornea-aqueous transfer coefficients in reference to the corneal volume, \( k_{\text{ac}} \) and \( k_{\text{ca}} \) are the transfer coefficients of the same meaning but in reference to the anterior chamber volume, and \( k_0 \) is the coefficient of loss from the anterior chamber.

A solution of equations 9, 10, and 11 gives

\[
C_a = \frac{M_0 \cdot \frac{M_{\text{ca}}}{V_a} \cdot e^{-A t} - e^{-B t}}{(B - A)} \tag{12}
\]

where \( M_0 \) is the initial amount of drug absorbed by the cornea, \( V_a \) is the distribution volume in the anterior chamber, and \( t \) is the time. The constants \( A \) and \( B \) are given below:

\[
A + B = k_{\text{ca}} + k_{\text{ca}} + k_0 \tag{13}
\]

\[
AB = k_0 \cdot k_{\text{ca}} \tag{14}
\]

An example of the time course of concentration changes in the cornea and the anterior chamber in the albino rabbit after instillation of 1% befunolol solution is illustrated in Fig. 2, and Fig. 4 depicts fluorescein concentration changes in the cornea and the anterior chamber of the human eye after instillation of 10% solution. In both cases the curves are similar, and equation 12 describes the time course of concentration changes in the anterior chamber. The anterior chamber concentration increases initially, reaches a peak, and then decreases in an exponential manner. The slope fitted to the decreasing phase gives \( A \) (Figs. 2 and 4); \( A \) is therefore called
Table II. Pharmacokinetic coefficients in the albino rabbit eye, computed from data in isotope experiments

<table>
<thead>
<tr>
<th>Drug</th>
<th>$K_{c,ca}$ (hr⁻¹)</th>
<th>$k_0$ (hr⁻¹)</th>
<th>$V_a$ (ml)</th>
<th>$A$ (hr⁻¹)</th>
<th>$B$ (hr⁻¹)</th>
<th>Source of data (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine</td>
<td>—</td>
<td>—</td>
<td>1.4</td>
<td>6.3</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Prednisolone acetate</td>
<td>2.9(1.2)*</td>
<td>3(7)*</td>
<td>1.1</td>
<td>8.1</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.6</td>
<td>2.2</td>
<td>0.21</td>
<td>0.6</td>
<td>2.6</td>
<td>49</td>
</tr>
<tr>
<td>Fluorometholone</td>
<td>0.45</td>
<td>2.2</td>
<td>0.18</td>
<td>0.4</td>
<td>2.5</td>
<td>53</td>
</tr>
<tr>
<td>Timolol</td>
<td>0.7</td>
<td>2.5</td>
<td>0.23</td>
<td>0.6</td>
<td>2.8</td>
<td>54</td>
</tr>
<tr>
<td>Befunolol</td>
<td>0.8</td>
<td>3</td>
<td>0.19</td>
<td>0.7</td>
<td>3.5</td>
<td>49</td>
</tr>
<tr>
<td>Bupranolol</td>
<td>0.4</td>
<td>3.5</td>
<td>—</td>
<td>0.4</td>
<td>3.8</td>
<td>55</td>
</tr>
<tr>
<td>Delaminol</td>
<td>0.66</td>
<td>3.5</td>
<td>0.27</td>
<td>0.6</td>
<td>3.8</td>
<td>56</td>
</tr>
</tbody>
</table>

A = apparent elimination rate constant; B = apparent absorption rate constant.
*Numbers in parentheses were calculated for the corneal epithelium.
†Unpublished results.

A = apparent elimination rate constant; B = apparent absorption rate constant.

The values of A and B are a mixed function of the cornea-aqueous transfer coefficient and the loss coefficient in the anterior chamber. However, these coefficients may be computed from the values of A and B. After the peak time has passed, the corneal and aqueous concentrations decrease at a similar rate (Figs. 2 and 4), and the concentration ratio $C_a/C_{ca}$ remains nearly constant during this period; this ratio is denoted as $g_{ca}$. Jones and Maurice showed that the following relationships hold:

$$k_{c,ca} = \frac{A}{(1 - r_{ca}/g_{ca})} \tag{15}$$

$$k_0 = B \frac{1 - r_{ca}/g_{ca}}{1 - r_{ca}/g_{ca}} \tag{16}$$

The steady-state distribution ratio, $r_{ca}$, is about 1.7 for fluorescein in the human eye, but the values for drugs are completely unknown. Therefore they are assumed to be unity.

The data of several previous papers using radioactive compounds to study drug penetration in rabbit eyes allow construction of the time course of drugs in the cornea and aqueous, as shown in Fig. 2. Consequently, analysis by equations 12, 15, and 16 was conducted and the values for $k_{c,ca}$, $k_0$, $V_a$ (anterior chamber distribution volume), A (the apparent elimination rate constant), and B (the apparent absorption rate constant) were calculated. Similar analysis was also performed on our own data, and the results are given in Table II.

The values of $k_{c,ca}$ are in a comparable range for steroids and beta-adrenergic blocking agents, but the value for pilocarpine is large. Pilocarpine was shown to be accumulated at a high concentration in the corneal epithelium, whereas the concentrations in the stroma and aqueous were similar; it was thought that the corneal epithelium acts as a depot of the drug and that the release rate from the epithelium is a limiting factor for aqueous drug kinetics. On the other hand, the concentrations of timolol and befunolol in the corneal epithelium were only about 20% higher than that in the stroma. The stromal concentration was very much higher than the aqueous concentration, indicating that the endothelial barrier is the limiting factor for aqueous kinetics of these beta-adrenergic blocking agents. The discrepancy in values for $k_{c,ca}$ may be attributed to the above difference in the mode of drug release from...
Table III. Pharmacokinetic coefficients in the human eye for various drugs, calculated from actual measurements of aqueous concentrations

<table>
<thead>
<tr>
<th>Drug</th>
<th>A (hr⁻¹)</th>
<th>B (hr⁻¹)</th>
<th>Peak time (hr)</th>
<th>( K_{ep} \times 10^{-4} \text{cm hr}^{-1} )</th>
<th>Source of data (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescein</td>
<td>0.20</td>
<td>1.04</td>
<td>2.2</td>
<td>0.15</td>
<td>4,30</td>
</tr>
<tr>
<td>Tetracycline*</td>
<td>0.7</td>
<td>0.8</td>
<td>1.3</td>
<td>0.1-0.17</td>
<td>25</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>1.4</td>
<td>1.5</td>
<td>0.7</td>
<td>2.5-5</td>
<td>26</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrahydrotriamcinolone</td>
<td>1.4</td>
<td>1.5</td>
<td>0.7</td>
<td>—</td>
<td>23</td>
</tr>
<tr>
<td>Pilocarpine†</td>
<td>0.3-0.48</td>
<td>1.2-2.4</td>
<td>1-1.6</td>
<td>5-7</td>
<td>27,28</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0.5</td>
<td>1.2</td>
<td>1.2</td>
<td>15</td>
<td>24</td>
</tr>
</tbody>
</table>

**A** = apparent elimination rate constant; **B** = apparent absorption rate constant (equation 12 and text).

*For ointment.

†Values determined from the pupil responses; **K_{ep}** (the permeability of the epithelial barrier of the cornea) was calculated from the peak concentration in the anterior chamber.


the cornea to the anterior chamber. The values of **kₙ** are similar for various drugs and they are in good agreement with the values reported in the literature, which were determined with various substances. This is understandable, since the major part of **kₙ** is the rate of substance loss from the anterior chamber by aqueous outflow.

It is of interest that the distribution volume, **Vₐ**, for steroids is similar to the actual volume of the anterior chamber, i.e., 227 to 250 µl, and this may be related to the fact that the albino iris does not accumulate steroids; that is, the concentrations in the aqueous and iris are similar. On the other hand, the distribution volumes for the tested beta-adrenergic blockers are larger than this, indicating that these drugs are bound to the intraocular tissues, and indeed, they are found at a higher concentration in the iris and the ciliary body than that found in the aqueous humor. Conrad and Robinson perfused the anterior chamber of rabbits and determined the distribution volume for pilocarpine to be 575 µl in albino eyes and 760 µl in pigmented eyes. Equation 12 and this large distribution volume of pilocarpine did not fit well to the data shown by Sieg and Robinson; the reason is not clear but it may be related to the special mode of pilocarpine kinetics between the cornea and the aqueous humor.

Figs. 2 and 4 indicate that the transcorneal drug transfer into the anterior chamber follows the basic kinetics of first order. Indeed, in both rabbit and human eyes, the aqueous concentration increases in proportion to the increase in the concentrations of applied drugs. There are several papers reporting intracameral penetration of drugs in the human eyes, and these published data were subjected to the analysis described above. The data scatter in the human experiments is greater than that seen in experiments with rabbit eyes, but the values of the apparent elimination rate constant A and the apparent absorption rate constant B were estimated. On the basis of equation 12, the value of **M₀** was computed from the peak aqueous concentration and the peak time, assuming that **k_{c₁a}** is close to A and **Vₐ** is close to the physical volume of the anterior chamber in man, i.e., 0.175 ml. Once **M₀** is known, the value of **K_{ep}** permeability of the epithelial barrier, may be calculated with equation 7. The results of these calculations are listed in Table III. It is of interest to find that the values of **K_{ep}** for prednisolone and pilocarpine in the human cornea are in the 50% to 70% range of the value for the rabbit cornea. Because the human cornea is thicker than the rabbit cornea, a lower value of **K_{ep}** in the human eye may be expected. In addition, we may say

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that the ocular penetration studies on the rabbit eye and their results are not far from what we can expect for the human eye and that these studies are useful, provided an appropriate conversion of the ocular dimension is made.

Drug binding to tissues and pigments and its pharmacokinetic consequences. Follow-up of the aqueous pilocarpine concentration in the albino rabbit eye for several hours after instillation revealed that the kinetics of aqueous pilocarpine could not be described by equation 12. Pilocarpine is known to be bound to ocular tissues and serum protein, and the drug is probably accumulated in the iris and the ciliary body tissues. The pharmacokinetics of pilocarpine was therefore interpreted on the basis of four-compartment model and the relevant transfer coefficients were calculated. Furthermore, pilocarpine was shown to be metabolized in the ocular tissues but too slowly to affect the intraocular pharmacokinetics of this drug.

Several drugs are known to be bound to melanin, and they are accumulated more readily by pigmented than by albino tissues, which influences their pharmacokinetics in the eye. For example, Fig. 5 illustrates in albino rabbits and Fig. 6 in pigmented rabbits the time course of the concentration changes after the instillation of befunolol. In the albino eyes there is little drug accumulation in the iris and ciliary body, and the steady state of drug distribution is reached rapidly. As a consequence, the concentrations in the aqueous, cornea, and anterior uvea decrease at a similar rate; equation 12 derived from the two-compartment model was applicable. On the other hand, it is evident from Fig. 6 that the anterior uvea of pigmented rabbits accumulates the drug significantly. It is shown that the drugs accumulated in the pigmented uveal tissues are released very slowly. Thus the pigmented tissue acts as a reservoir of drugs, which accounts for long-lasting ef-
effects in the pigmented eye.\textsuperscript{73, 74, 76, 77, 80-82} Indeed, the drug can be found in the pigmented eye even 24 hr after instillation, whereas in the albino eye the drug has disappeared completely. The influence of ocular pigmentation on the pharmacokinetics of the human eye will be discussed in detail later in this article.

**Loss rate of drugs from tears and intraocular pharmacokinetics.** We have considered the pharmacokinetics after instillation of conventional aqueous drug solution, which is lost rapidly from the conjunctival cul-de-sac so that corneal drug absorption is practically complete within a short time. However, when the drug is given in the form of ointment, the loss rate in the tears is significantly reduced, and this influences the pharmacokinetics in the eye. Recently a drug delivery device was made available that controls diffusional drug release from a reservoir by means of special membranes, thereby permitting almost constant drug release.\textsuperscript{83} This device is made in the form of an ocular insert placed in the conjunctival cul-de-sac. Because the drug is released at a constant rate (n per hour), the tear concentration will be maintained at a steady level, that is, \([C_d]\) steady is equal to n/v, where v is the rate of tear flow per hour.

With the pharmacokinetic coefficients for pilocarpine, the intracameral pilocarpine concentrations have been computed for various values of its rate of loss from the tears in the human eye. The results are shown in Fig. 7. Reduction in the loss rate has two effects. First, as indicated by equation 7, the amount of drug absorbed by the cornea is inversely proportional to the loss rate, hence its reduction increases both the amount absorbed and the peak aqueous concentration (Fig. 8). Second, the reduction in the loss rate in the tears retards the peak time (Fig. 9). When the loss rate becomes larger than 0.05 min\(^{-1}\), its change has no significant influence on the peak time. Only when the loss rate is below 0.02 min\(^{-1}\) does the delay in the peak time become evident.

When the loss rate becomes zero, i.e., the tear concentration is maintained at a steady level, the aqueous concentration also reaches a steady state, with a time constant of \(k_0\), the coefficient of loss from the anterior chamber. The steady-state aqueous concentration and tear concentration may then be

\[
[C_a]_s = \frac{K_c Q}{V_a k_0} [C_d]_s
\]

where \(K_c\) is the overall permeability of the corneal layers, \(Q\) is the corneal area, \(V_a\) is the distribution volume in the anterior chamber, \(k_0\) is the coefficient of loss from the anterior chamber, and the suffix \(s\) means steady state. Because the major barrier of the cornea is in the epithelium, it may be assumed that \(K_c\) is almost equal to \(K_{ep}\). By inserting the values for pilocarpine in rabbit eyes, i.e., \(K_{ep} = \ldots\)
Fig. 8. Relationship between the peak aqueous concentration and the loss rate in the tears. Results of computer simulation for pilocarpine as in Fig. 7.

Fig. 9. Relationship between the time of peak aqueous concentration and the loss rate in the tears. Results of computer simulation for pilocarpine as in Fig. 7.
10 × 10⁻⁴ cm hr⁻¹, k₀ = 3 to 7 hr⁻¹ (Tables I and II), and taking Q⁶¹ = 2 cm² and Vₐ⁶⁴ = 0.25 cm³ the relationship between the steady-state pilocarpine concentrations in the tears and the aqueous may be calculated: [Cₘₐₜ]ₚ = 2.3 - 1.1 × 10⁻³ [Cₜₚ].

Sendelbeck et al.⁶⁴ placed the ocular pilocarpine insert, delivering 20 μg hr⁻¹, in the conjunctival cul-de-sac of the albino rabbit and found that the steady-state pilocarpine concentration in the iris was about 0.6 μg per gm of tissue. If it is assumed that this is equal to the aqueous concentration, the steady-state tear concentration, [Cₜₚ], can be calculated to be 0.26 to 0.55 × 10⁻³ gm ml⁻¹. This would be achieved if the tear flow rate is 0.6 to 1.3 μl min⁻¹. The normal tear flow rate in the rabbit was reported¹⁵ to be 0.55 μl min⁻¹. The agreement is very good if one considers that the insert may stimulate tear secretion, and this indicates that the permeability of the epithelial barrier of the rabbit cornea to pilocarpine given in Table I is reasonable.

Pharmacokinetics of surface anesthetics

There is probably not a single day that an ophthalmologist can practice without use of surface anesthetics. Applanation tonometry, tonography, minor procedures, and even major surgery are performed with the use of surface anesthetics. These agents can be toxic to the corneal epithelium, where changes of microvilli, cell desquamation, pit formation, etc. are found to occur.⁸⁵, ⁸⁶ To minimize these toxic effects and to promote appropriate use of the surface anesthetics in daily practice, knowledge of the pharmacokinetics of these drugs in the human eye should be useful, and yet there appear to be no reports on this aspect available in the literature. Accordingly, Matsumoto et al.⁸⁷ conducted studies of the surface anesthetics most often utilized in clinical practice.

They prepared lidocaine solutions at six concentrations in the range between 0.2% and 2.0% as well as benoxinate solutions at five concentrations from 0.08% to 0.20%, using commercial vehicles. The pH was 6.6 in the former preparation and 5.5 in the latter. At 1 min intervals after instillation of 20 μl of each solution, the authors determined the sensitivity threshold of the cornea in the temporal intermediate zone with a Cochet-Bonnet esthesiometer⁸⁸ until the corneal sensitivity returned to the predrug level. The sensitivity threshold can be expressed in grams per square millimeter by using the conversion table provided by the authors,⁸⁸ and it is plotted against the time after instillation in Fig. 10 for lidocaine and in Fig. 11 for benoxinate. The peak effect of lidocaine was usually reached 2 to 3 min after instillation, and the peak effect of benoxinate occurred in about 1 to 2 min. Since the peak time was very short, the duration of the effect was calculated as the interval between the time of instillation and the time at which the sensitivity threshold returned to normal level. The logarithm of drug concentrations and the duration of the effect are correlated in Fig. 12 for lidocaine and in Fig. 13 for benoxinate. In both figures a linear correlation is evident. The experiments repeated in six young male volunteers with each drug gave similar results in all cases.

After instillation, the uncharged base of the anesthetics is absorbed by the lipid-
containing corneal epithelium. It is then lost from this tissue by release into the corneal stroma or back into the tears. If the epithelial concentration of an anesthetic is denoted as \( C_e \) and the rate constant of its elimination from the epithelium as \( k_e \), then the changes in epithelial concentration may be given by substituting these symbols for \( C_c \) and \( k_c \) in equation 3. Since the loss rate in the tears, \( \alpha \), is very large, the second term of the equation becomes negligible. This makes the single-compartment model applicable to the present case.

Levy demonstrated that the following equation applies to the pharmacokinetics of a single compartment:

\[
\log C - \log C_{\text{min}} = T k_e/2.3 \tag{18}
\]

that is, a linear relationship is seen between the logarithm of the concentration and the duration of the effect (T). Thus the results in Fig. 12 and 13 may be analyzed on the basis of this equation; the slope of the regression line gives the rate constant of drug loss from the corneal epithelium, and extrapolation of the line gives the \( C_{\text{min}} \), the least effective concentration.

By means of the least-squares method, the regression lines for the relationship were computed for each individual. The elimination rate constant of the drug averaged \( 0.081 \pm 0.011 \) (S.E.) min\(^{-1}\) for lidocaine and...
0.10 ± 0.022 min⁻¹ for benoxinate. The least effective concentration averaged 0.10% ± 0.04% for lidocaine and 0.06% ± 0.007% for benoxinate. With these values for the elimination rate constant and the peak time of the effect, the loss rate of the surface anesthetics in the tears may be calculated on the basis of equation 4, with appropriate symbol changes. It was at least 1 min⁻¹ for lidocaine and 2.5 min⁻¹ for benoxinate. Conrad et al. demonstrated that drug dilution by tearing was the least at physiologic pH and that it increased as the pH deviated toward both acid and alkaline sides. Thus the loss rate in the tears of the above order is not surprising with instillation of surface anesthetics that induce initial stinging reaction. Furthermore, it is possible that the greater loss rate of benoxinate in tears than that of lidocaine is because of the more acidic pH of benoxinate.

Poise et al. reported the average duration of anesthetic effects in man for proparacaine and benoxinate in three concentrations. Similar analysis of their data gave the elimination rate constant from the corneal epithelium of 0.08 min⁻¹ for proparacaine, but data scatter and few data points did not allow exact calculation of the constant for benoxinate. We found three reports in the literature that gave the relationship between the concentrations of surface anesthetics and their effects on animal corneas. The elimination rate constants from the corneal epithelium were computed from their data: 0.08 min⁻¹ for procaine, 0.10 min⁻¹ for butyn pH 5.5, and 0.054 min⁻¹ for butyn pH 7.0 in rabbits; and 0.048 min⁻¹ and 0.052 min⁻¹ for procaine in guinea pigs. These values are in very good agreement with the results in the human cornea.

With a knowledge of the elimination rate constant from the corneal epithelium, the least effective concentration, and the concentration of the drug to be given, the duration of the effect (T) may be calculated by

\[
T = \frac{2.3 \log (C/C_{\text{min}})}{k_e} \quad (19)
\]

Substituting values for benoxinate, one can state that 0.4% benoxinate is effective for 19 min. Similarly, 4% lidocaine is effective for 45 min. The lasting effect of lidocaine is a
Fig. 15. Log-log plot of the response parameter and the drug concentration for the data shown in Fig. 14. For explanation of the response parameter see text. From Ohara K: Jpn J Ophthalmol 21:516, 1977.

result of the high concentration of its available preparation and not of a difference in its elimination rate constant. Poise et al. showed with applanation tonometry that corneal sensation was absent when the corneal sensitivity threshold was about 6.6 gm mm⁻² or higher, and below this level the patients felt the touch of the tonometer. This sensitivity threshold is reached at the peak time after instillation of a 0.18% solution of benoxinate. The presently used 0.4% preparation can maintain the absence of corneal sensation for 8 min during applanation tonometry. These calculations are in agreement with our clinical experience.

Pharmacokinetics of pupil responses

The pupil response is elicited through the contraction and relaxation of two smooth muscles, i.e., the sphincter and the dilator muscles. The sphincter muscles are innervated largely by cholinergic nerves. The dilator muscles are innervated mainly by adrenergic nerves, and the receptors in the muscle are largely alpha-adrenergic. Thus the pupil response is a simple system, from a pharmacologic point of view, which is convenient for drug testing.

A mathematical expression of the time course of the pupil responses after single topical application of drugs has been attempted in human subjects, and a double-exponential equation has been fitted to the time course. The usefulness of the pupil response for pharmacokinetic study of a drug was shown by Levy. He indicated that the decline of the mydriatic response in mice after intravenous administration of an anticholinergic agent allows calculation of the drug elimination rate constant, provided that the appropriate conversion of the response can be made on the basis of the dose-response relationship. Subsequently, Smolen and associates carried out a series of studies on the pupil response in the rabbit. On the basis of the dose-response relationship obtained by intravenous administration of the drug, they developed a function to convert the pupil response into the parameters that indicate the drug concentration in the biophase of the sphincter muscles. Further, they developed a computerized program to estimate the bioavailability of the drug from the pharmacologic data.

The pharmacokinetic study of the pupil response in the human subject was carried out by Yoshida and Mishima using topical pilocarpine and tropicamide. An analysis of the dose-response relationship according to the principle of Wagner permitted calculation of the response parameter (RP) that is proportional to the drug concentration in the biophase of the sphincter muscles. Study of the time course of the RP changes leads to computation of the apparent elimination rate constant and other relevant pharmacokinetic coefficients for these drugs in the human eye. Subsequently, a similar analysis was conducted for various drugs, with use of our own results and data reported in the literature. This section describes conclusions of this type of analysis.

Dose-response relationship in isolated iris.

The iris is a porous structure that allows rapid
access to the vicinity of the sphincter and dilator muscles of solutes even of macromolecular size present in the anterior chamber. Thus a drug in the anterior chamber can reach the biophase of these muscles in a very short time, and their response will correspond to that in the incubation bath of an in vitro system. Accordingly, the interaction of drugs with isolated iris muscles will be considered first.

Fig. 14 shows the dose-response relationship in the sphincter muscle strip of the human eye for carbachol and pilocarpine, determined from the conventional cumulative increase of the drug concentration in the incubation medium. The sphincter muscles have typical muscarinic receptors and pilocarpine and carbachol are directly acting agonists. Since carbachol is considered a full agonist, the intrinsic activity of pilocarpine may be calculated by comparison of the maximum responses. In the human iris this is 0.9, indicating that pilocarpine can be considered also to be a full agonist.

From the maximum response ($R_{\text{max}}$) and the response for a given molar concentration of the drug ($R$), the parameter $R/(R_{\text{max}} - R)$ was calculated and is plotted in Fig. 15 against the molar concentrations of the drug, both on a logarithmic scale. A straight line can be fitted to the relationship, and its slope is close to unity. Thus one can describe the relationship by

$$\frac{R}{R_{\text{max}} - R} = qC$$

where $C$ is the drug concentration and $q$ is the proportionality constant.

Replotting on this principle was carried out for published response relationships: carbachol and the sphincter muscle strip of the cat, relaxation effects of isoproterenol on the bovine and rabbit sphincter strip, atropine and a whole-mount guinea pig iris, adrenaline and acetylcholine and a whole mount of cat iris, and $l$-epinephrine and a whole-mount guinea pig iris. In all cases the logarithmic plot of $R/(R_{\text{max}} - R)$ against...
Fig. 17. Time course of mydriatic response after tropicamide instillation. \( D_c \) and \( D \) are as in Fig. 16. •, \( 1.0 \times 10^{-4} \); ▲, \( 4.0 \times 10^{-4} \); ●, \( 1.0 \times 10^{-3} \); ○, \( 4.0 \times 10^{-3} \) g ml\(^{-1} \). From Yoshida S and Mishima S: Jpn J Ophthalmol 19:121, 1975.

Dose-response relationship of pupil responses. Yoshida and Mishima\(^{31}\) instilled 50 \( \mu l \) of various concentrations of pilocarpine solution in one eye of young subjects after at least 15 min of dark adaptation, and the pupil diameter of both eyes was determined through measurements on infrared photographs taken in a dark room. Similarly, tropicamide experiments were carried out in a room with constant lighting. The pupil response was then expressed in percent response; if the diameter in the control eye is \( D_c \) and the diameter in the experimental eye is \( D \), then the percent response is given by \( [(D_c - D)/D_c] \times 100 \) for pilocarpine and \( [(D - D_c)/D_c] \times 100 \) for tropicamide. The time course of the percent changes is shown in Fig. 16 for pilocarpine and in Fig. 17 for tropicamide. The peak responses were then plotted against logarithm of the drug concentration in Fig. 18 for pilocarpine, and a similar relationship can also be obtained for tropicamide. The relationships appear to be linear.

The iris is an extremely mobile structure, but unrestricted movement occurs only in the range of moderate pupil size; beyond the limit of 3 to 6 mm of the diameter, mechanical restriction hinders iris movement.\(^{118, 119}\) Furthermore, it is impossible for the pupil diameter to become zero or to dilate beyond a certain limit. Thus, with a high concentration of a drug, the response can no longer increase.

logarithm of the drug concentration gave a linear relationship with the slope close to 1. Thus one can conclude that equation 20 describes the dose-response relationship of the sphincter and the dilator muscles. This equation is similar in its form to the theoretical equation derived by Ariëns\(^{117}\) for drug interaction with a one-receptor system. Whatever the theory may be concerning the manifestation of the drug effects, the applicability of the above equation to the in vitro iris preparation indicates that this is also the case for the relationship between the pupil response and the drug concentration in the biophase of the iris muscles of the living eye.
with increase of the drug concentration; that is, a minimum or maximum pupil diameter must exist. Accordingly, the apparent linear relationships shown in Fig. 18 covers only the linear part of the sigmoid dose-response relationship.

The maximum or minimum possible size of the pupil may be determined from the results of Loewenfeld and Newsome. A light reaction was induced after pretreatment with 0.5% phystostigmine, leading to the smallest attainable pupil diameter of 0.92 ± 0.13 mm (S.D.) in six young subjects. Thus 1 mm is a good approximation for the minimum pupil diameter, and this should also apply to pilocarpine, since it is a full agonist for the human iris sphincter muscles. The authors also gave the largest pupil diameter in the dark after topical administration of cyclopentolate or cocaine, which was 7.94 ± 0.96 mm with the former and 8.50 ± 0.71 mm with the latter drug. Yoshida and Mishima also estimated the maximum pupil size to be 8.5 mm from their data, so that both estimates are in agreement.

Using these values for minimum pupil diameter, $D_{\text{min}}$, and the maximum diameter, $D_{\text{max}}$, we can calculate the response parameter, $R/(R_{\text{max}} - R)$, for the pupil response. For this purpose the pupil response, $R$, is redefined as follows. Let us denote the pupil diameter before the drug as $D_0$ and the diameter at time of administration as $D$. We may then write $R = (D_0 - D)$ and $R_{\text{max}} = (D_0 - D_{\text{min}})$ for miotic response, and $R = (D - D_0)$ and $R_{\text{max}} = (D_{\text{max}} - D_0)$ for mydriatic response. By expressing the pupil diameter in millimeters, the response parameter ($RP$) may be written

$$RP = \frac{R}{R_{\text{max}} - R}$$

$$= \frac{D_0 - D}{D - 1} \text{ for miotic response} \quad (21)$$

$$= \frac{D - D_0}{8.5 - D} \text{ for mydriatic response} \quad (22)$$

The response parameter, $RP$, was then calculated from the pupil diameter at peak time and was plotted against the drug concentration, both on a logarithmic scale. Fig. 19 is the example for pilocarpine, and the similar relationship can also be obtained for tropicamide. A linear correlation is seen and the
Fig. 19. Log-log plot of the response parameter and the pilocarpine concentrations from the data shown in Fig. 16. For explanation of the response parameter see text. From Yoshida S and Mishima S: Jpn J Ophthalmol 19:121, 1975.

slope of the regression line is very close to unity. Again one can assume the relationship to be expressed

\[ \text{RP} = \frac{R}{R_{\text{max}} - R} = q' C_{\text{instill}} \]  

(23)

As discussed previously, tear-aqueous drug transfer follows first-order kinetics, and comparison of equations 20 and 23 leads to the conclusion that the RP calculated from the pupil diameter is proportional to the drug concentration in the biophase of the iris muscles.

The mydriatic response of the human eye to norepinephrine\(^{120}\) was analyzed by the log-log plot of the RP against dose. Similarly, the mydriatic response of the rabbit after the intravitreal injection of norepinephrine\(^{121}\) was also analyzed. In both cases a linear correlation was obtained, but the slope was 1.6 to 2. In the isolated iris the slope was 1 for epinephrine, and such deviation of the slope from unity must be characteristic of the in vivo response for this drug. Significant deviation of the slope from unity is attributed to nonlinear deviation of the biophase concentration from the ambient concentration.\(^{117}\)

Because intact sympathetic nerves in the iris actively accumulate exogenously administered norepinephrine,\(^{122}\) it is possible that linear correlation does not hold between the administered amount and the final concentration in the biophase of the dilator muscles. Thus the present analysis using RP is not applicable for the in vivo response to norepinephrine and epinephrine.

**Kinetics of pupil responses.** The RP may be calculated for the pupil diameters at various time intervals after instillation, as shown in Fig. 16, and the results are plotted in Fig. 20. The RP increases in proportion to the increase of the drug concentrations, and the shape of the curves for different drug concentrations are congruent, indicating that the RP is indeed proportional to the biophase drug concentrations. Fig. 21 and 22 show the RP-time curves for pilocarpine and tropicamide, respectively, and the curves are similar. The following equation describes the curves:

\[ \text{RP} = \frac{m AB}{(B - A)} \left[ e^{-A(t - t_0)} - e^{-B(t - t_0)} \right] \]  

(24)

where m, A, and B are constants, and t and t\(_0\) are the time and the lag time required for the response to begin after instillation. This equation is basically the same as equation 12 for intraocular drug penetration; A may be called the apparent elimination rate constant, and B may be called the apparent absorption rate constant. Both A and B are related to the rate of drug release from the cornea into the anterior chamber and to the rate of loss from the anterior chamber.

Similar analysis was made on the results published in the literature. Some authors gave the actual diameter of the pupil in their figures, but others gave only the diameter change either as percentage of the predrug diameter or as the actual difference of the diameter. In the latter case the predrug diameter had to be assumed. One millimeter difference in the predrug diameter did not give significant deviation in the pharmacokinetic coefficients, and therefore it was assumed to be 7.6 mm in the dark (miotic experiments) and 4 mm in the light (mydriatic experiments). The pharmacokinetic coeffi-
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Fig. 20. Time course of the response parameter changes after instillation of pilocarpine solution with various concentrations, calculated from the data shown in Fig. 16. •, 2.5 × 10⁻³; X, 5.0 × 10⁻³; ○, 1.0 × 10⁻²; △, 2.0 × 10⁻² g ml. From Mishima S and Nagataki S: Contact Intraocular Lens Med J 4(3):22, 1978.

Fig. 21. Time course of the response parameter after instillation of 0.5% pilocarpine solution. Two lines for calculation of the absorption and elimination rate constants are shown. From Yoshida S and Mishima S: Jpn J Ophthalmol 19:121, 1975.

coefficients were thus calculated for various drugs and are listed in Table IV.

Duration of effects and drug concentration. The RP of the pupil decreases in a single exponential manner after the peak time has passed. During this period of decay, the second term of equation 24 becomes negligible and the theory of single-compartment would apply to this part of the response. Accordingly, the duration of the effect was defined as the time interval between the time of the peak response and the time of effect termination. The logarithm of pilocarpine concentration and the duration of effect were correlated in Fig. 23, and this was analyzed according to equation 18, which allows calculations of the apparent elimination rate constant and the least effective concentration. This method of calculation may be called the duration method.

The apparent elimination rate constant was 0.34 ± 0.10 hr⁻¹ for pilocarpine (Table IV) and 0.82 ± 0.20 for tropicamide. These values are in good agreement with those obtained by kinetic analysis (Table IV). The pilocarpine miosis time study by Borgmann and Wurster was also analyzed by this method and the results are given in Table IV. The least effective concentration may also be calculated by the dose-response method, i.e., by extrapolation of the relationship, as shown in Fig. 18. The least effective concentration of pilocarpine in five young subjects was 1.0 ± 0.6 × 10⁻³ gm ml⁻¹ by the dose-response method and 1.3 ± 0.6 × 10⁻³ gm ml⁻¹ by the duration method. The least effective concentration of tropicamide in five young subjects was 2.6 ± 1.2 × 10⁻⁵ gm ml⁻¹ by the former and 1.7 ± 0.8 × 10⁻⁵ gm ml⁻¹ by the latter method. The results of both methods are in agreement.

Pharmacokinetic coefficients and ocular pigmentation. We found two sets of data in the literature that allow pilocarpine kinetics in subjects with light-colored and dark irides to be compared. The results reported from England and Germany agree very well, and the apparent elimination rate constant was 0.46 to 0.48 hr⁻¹ in subjects with a lightly
Fig. 22. Time course of the response parameter after instillation of 0.4% tropicamide solution. Two lines for calculation of the absorption and elimination rate constants are shown. From Yoshida S and Mishima S: Jpn J Ophthalmol 19:121, 1975.

pigmented iris and 0.36 to 0.37 hr⁻¹ in subjects with a dark iris (Table IV). The former value is close to the rate constant of 0.44 hr⁻¹, computed from the results given in two reports from the United States. Although these did not state the iris color of the subjects, it is quite possible that the majority had lightly pigmented irides. The rate constant in European subjects with dark irides is similar to the value computed for Japanese subjects (Table IV). Recently, Dr. J. W. Shell* at the School of Pharmacy of the University of California in San Francisco gave us preliminary results of his experiments, in which he found that the half-life of pilocarpine effect decay averaged 4.7 hr in four heavily pigmented subjects and 2 hr in three lightly pigmented subjects. These values correspond to the apparent elimination rate constants of 0.15 hr⁻¹ and 0.33 hr⁻¹. The apparent elimination rate constant of homatropine was calculated from the average time course reported by Gambill et al.⁹⁹; it was 0.19 hr⁻¹ and 0.31 hr⁻¹ for subjects with dark and light eyes, respectively. We may conclude that the apparent elimination rate constant for these drugs decreases with increasing ocular pigmentation.

Chen and Poth¹²⁸ pointed out that the mydriatic action of cocaine, euphthalmine, and ephedrine is less effective in black subjects than in white subjects, and the effect in Chinese is intermediate. This is comparable to what we have seen in the apparent elimination rate constant of pilocarpine. Similarly, numerous reports agree that the effects of various miotics and mydriatics are less intense in more heavily pigmented subjects.¹²⁹–¹³¹ Less marked effects with increasing pigmentation are also reported for hypotensive effects of pilocarpine and epinephrine.¹³²,¹³³ Since these drugs are bound to the pigments of the anterior uvea, the decrease in the effects may be attributed to reduction in the biophase drug concentration. In rabbits and guinea pigs the mydriatic effects of various drugs were shown to decay at a slower rate in pigmented strains than that in albino strains, and this was attributed to the depot effect of the pigments, which release bound drugs slowly.¹³⁰–¹³² A difference in the pharmacokinetics of drugs between the pigmented and albino rabbits is shown in Figs. 5 and 6, and this difference supports the above explanation.

Relative bioavailability and form of drug delivery. Rapid loss of instilled drug solution from the conjunctival cul-de-sac makes only a small fraction of a given drug available to the eye. However, the use of various vehicles has been reported to increase the availability of the drug, thereby increasing its effect.¹⁸,²⁰,²¹,¹³⁴–¹⁴⁰ Efficiency of various methods of drug delivery in increasing drug penetration may be studied by the use of the concept of bioavailability. A comparison of the bioavailability of a drug between different forms of delivery may be made by means of the area under the concentration-time curve.

There is only one report in the literature that gives an estimate of the area under concentration-time curve of a drug, prednisolone, in the anterior chamber of the human eye after topical application, and on this basis the pharmacokinetic coefficients of prednisolone.

*Personal communication.
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Fig. 23. Relationship between the duration of miotic effect and logarithm of pilocarpine concentrations. For definition of the effect duration see text. From Yoshida S and Mishima S. Jpn J Ophthalmol 19:121, 1975.

Table IV. Kinetic coefficients of the pupil responses

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of cases</th>
<th>$A$ (hr$^{-1}$)</th>
<th>$B$ (hr$^{-1}$)</th>
<th>Lag time ($t_0$, hr)</th>
<th>Peak time (hr)</th>
<th>Source of data (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine</td>
<td>$5^A$</td>
<td>$0.34 \pm 0.10^9$</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>$5^B$</td>
<td>$0.27 \pm 0.05$</td>
<td>$1.84 \pm 0.40^9$</td>
<td>—</td>
<td>1.6</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>$5^C$</td>
<td>$0.35 \pm 0.12$</td>
<td>$1.20 \pm 0.29$</td>
<td>$0.13 \pm 0.075^9$</td>
<td>0.6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>$6^C$</td>
<td>$0.44 \pm 0.14$</td>
<td>$2.44 \pm 0.44$</td>
<td>$0.15 \pm 0.08$</td>
<td>1.0</td>
<td>3 cases (Fig. 1 of 123), 3 cases (Figs. 1, 3, 5 of 98)</td>
</tr>
<tr>
<td>Tropicamide</td>
<td>$5^B$</td>
<td>$0.84 \pm 0.14^9$</td>
<td>$2.22 \pm 0.26^9$</td>
<td>—</td>
<td>31</td>
<td>Fig. 2 of 124</td>
</tr>
<tr>
<td></td>
<td>$3^C$</td>
<td>0.68</td>
<td>1.5</td>
<td>0.16</td>
<td>1.0</td>
<td>Unpublished data</td>
</tr>
<tr>
<td></td>
<td>$1^B$</td>
<td>0.60</td>
<td>4.0</td>
<td>0.10</td>
<td>0.56</td>
<td>126</td>
</tr>
<tr>
<td></td>
<td>$1^C$</td>
<td>0.64</td>
<td>4.5</td>
<td>0.12</td>
<td>0.63</td>
<td>Fig. 5</td>
</tr>
<tr>
<td>Homatropine</td>
<td>All$^C$</td>
<td>0.23</td>
<td>2.55</td>
<td>0.24</td>
<td>1.2</td>
<td>Fig. 4</td>
</tr>
<tr>
<td></td>
<td>Dark iris$^C$</td>
<td>0.19</td>
<td>2.46</td>
<td>0.25</td>
<td>1.37</td>
<td>Fig. 6 of 99</td>
</tr>
<tr>
<td></td>
<td>Light iris$^C$</td>
<td>0.31</td>
<td>2.07</td>
<td>0.25</td>
<td>1.33</td>
<td>Fig. 6</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>$1^C$</td>
<td>0.63</td>
<td>2.05</td>
<td>0.34</td>
<td>1.73</td>
<td>Fig. 2</td>
</tr>
<tr>
<td>Hydrosyam-</td>
<td>$1^C$</td>
<td>0.47</td>
<td>2.53</td>
<td>0.34</td>
<td>1.16</td>
<td>Fig. 3</td>
</tr>
<tr>
<td>phenetamine</td>
<td>$1^B$</td>
<td>0.025</td>
<td>—</td>
<td>—</td>
<td>31</td>
<td>Fig. 6 of 127</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>1</td>
<td>0.017</td>
<td>—</td>
<td>—</td>
<td>125</td>
<td>Fig. 5 of 127</td>
</tr>
</tbody>
</table>

$A = $ apparent elimination rate constant; $B = $ apparent absorption rate constant; $D_0 = $ predrug pupil diameter (assumed as indicated).

$^A$ Calculated from the relationship between the duration and logarithm of concentration.

$^B$ Calculated by peeling method.

$^C$ Calculated by a computer.

$^D$ Numbers are mean ± S.D.
lone in the human eye given in Table III were computed. However, it is extremely difficult to construct the complete time course of concentration changes by human experiments of this type. On the other hand, pupil changes can be followed easily for a long time without any strain to the subjects, and the RP that is proportional to the biophase concentration can be obtained by simple calculation. Thus the study of the bioavailability in the human eye may be carried out with the area under the RP-time curve. Integration of equation 24 from time to infinity gives

$$\int_{t = t_0}^{t = \infty} RP \, dt = m$$  \hspace{1cm} (25)

If a drug with a given concentration is applied in different forms, the bioavailabilities of these preparations can be compared by means of the values of m, hence it may be called the coefficient of the relative bioavailability.

**Drop size and bioavailability.** The effects of the volume of instillation on the bioavailability were studied by Sugaya and Nagataki. They prepared 0.5% pilocarpine solution at physiologic pH and instilled 5, 10, 20, and 50 μl to young normal subjects. The coefficient of relative bioavailability was calculated from the RP-time curve by computer and is plotted in Fig. 24 against the volume of instillation. The probable range of the mean was also computed and is given in the Fig. 24. The coefficient of relative bioavailability increases slightly with the drop-size increase from 5 to 20 μl, but no further augmentation can be seen by increasing the drop size. These results may be accounted for by the behavior of drugs in the conjunctival cul-de-sac, i.e., rapid drainage of instilled volume and poor tear film saturation with the drug. Clinical implication of this phenomenon has been discussed in the preceding section, and the volume of 20 μl was thought to be practical for clinical use.

**Viscous vehicles and bioavailability.** The effects of viscous vehicles on the bioavailabil-
ity were studied on the same principle with the RP-time curve. Pilocarpine solution of 0.5% was prepared at physiologic pH and osmolarity, with addition of various concentrations of hydroxypropylmethylcellulose (HPMC). After instillation of 20 µl, the RP was calculated and is plotted in Fig. 25, where the results with 0.5% pilocarpine aqueous solution are also shown for comparison. The vehicle with 0.5% HPMC significantly increases the RP, hence the intraocular pilocarpine concentration. The coefficient of relative bioavailability with the vehicle was greater than that with aqueous solution, and the ratio averaged 3.1 ± 1.9 (S.D.) in five normal subjects.

The relative bioavailability and the viscosity of the solution are plotted in Fig. 26; the probable range of the mean is also shown. The bioavailability increases with increasing viscosity of the vehicle, but no further rise can be seen above the viscosity of 10 to 20 centistokes. Thus the viscosity of 10 to 20 centistokes is thought to be adequate for ophthalmic preparation.

From equation 12 it is evident that the bioavailability is proportional to the amount of the drug initially absorbed by the cornea and is proportional to the degree of tear film saturation. The degree of tear film saturation was calculated for drop size and viscosity studies on the basis of tear flow data with fluorescein, and the relative bioavailability is plotted in Fig. 27 against the degree of tear film saturation of pilocarpine. This shows that the above theory is indeed applicable to human eyes.

Ointment and bioavailability. A typical RP-time curve after application of 100 mg of 0.5% pilocarpine ointment is shown in Fig. 25. As compared to aqueous solution, the bioavailability increased more than twice. Inspection of the RP-time curve with the ointment reveals two interesting aspects: (1) the RP increase occurs with a delay and (2) the time of peak RP takes place with a significant delay, as compared with that for aqueous solution and HPMC solution.

The lag time, $t_0$, given by equation 24 was computed to be $7.7 \pm 3.4$ min (S.D.; $n = 20$) with aqueous pilocarpine solutions and $6.8 \pm 1.8$ min ($n = 20$) with HPMC solution, but the apparent lag time with ointment was $12.7 \pm 2.5$ min ($n = 12$). A significant delay occurs with ointment in the intraocular penetration of the drug. The delay of the peak time is evident in Fig. 25; the peak time with aqueous solution is less than 1.5 hr but with ointment it is about 2.5 hr. It has already been shown that the delay of the peak time is caused by a reduction in the loss rate from the tears to less than 0.01 min$^{-1}$, and this is the case with ointment. The delay in the intraocular drug penetration may be attributed to the mode of drug release from the ointment, as discussed above.

Hydrophilic soft contact lens and bioavailability. The use of soft contact lenses pre-
Fig. 26. Relationship between the relative bioavailability and the viscosity of the HPMC solution containing 0.5% pilocarpine. Solid lines, Probable range of the mean. For definition of the relative bioavailability see text. From Sugaya M and Nagataki S: Jpn J Ophthalmol 22:127, 1978.

Soaked in a drug solution has been reported to enhance the drug effects.\(^1\)\(^4\)\(^5\) Fig. 28 shows the RP-time curve after the 1 hr wear of a soft contact lens presoaked in 0.02% pilocarpine solution for 25 min. The RP-time curves for 0.5% pilocarpine in aqueous solution and in 0.5% HPMC solution are also shown for comparison. The bioavailability is greatly augmented by the soft contact lens, but the peak time shows no significant delay compared with that with aqueous solution. The pupil response with pilocarpine in two of the published papers\(^1\)\(^4\)\(^5\) also indicates practically no delay in the time of peak response. This shows that the loss rate of drugs from the tears with this modality is not much different from that with viscous vehicles. The soft contact lens absorbs various drugs at a high concentration and releases them rapidly into the surrounding medium. The release rate was estimated to be about 0.03 to 0.04 \(\text{min}^{-1}\) from published data,\(^1\)\(^4\)\(^5\) and this is in support of the above conclusion. Thus the increase in the bioavailability with soft contact lens use is mainly caused by a burst of drug from the absorbed sites of the lens into the tear film. The tear film concentration can be very high, depending on the amount of drug absorbed by the soft contact lens, and this can be dangerous.

Drugs may often be instilled with the soft contact lens present in the eye. A set of the RP-time curves for pilocarpine instilled with and without the soft contact lens in the eye are shown in Fig. 29. In the case of Fig. 29, left panel, the RP is higher in the presence of the lens than without it, but in Fig. 29, right panel, the result is reversed. In the latter case, it seems that the soft contact lens is acting as a barrier to the access of drugs to the cornea. However, when instillation is carried out carefully to bring the drug under the soft contact lens, one can increase the bioavailability of the drug. The fact that careless instillation can greatly reduce the bioavailability in the presence of the soft contact lens is of clinical importance, and this is worthwhile warning.
Clinical pharmacokinetics of the eye

Drug delivery device. A drug delivery device in the form of an ocular insert was made available, and the inserts of pilocarpine and corticosteroid were reported to be useful clinically. Fig. 30, top, shows the change in the release rate of pilocarpine insert over 1 week. During the steady state, this type of insert, Pilo-20, releases pilocarpine at a rate of 20 μg/hr, hence the tear film concentration must also be at a steady state. Horie et al. tried this insert in 16 subjects, and the average change in the pupil diameter was converted to the RP. The RP-time curve is shown in Fig. 30, bottom. The RP-time curve is seen to conform very well with the curve of the rate of pilocarpine release from the insert. The horizontal line in Fig. 30, bottom, is the RP value at the peak time after single instillation of 1% pilocarpine solution in the same group of subjects. Comparison with the Pilo-20 points after the second day leads to the conclusion that this method of administration maintains a level equivalent to the peak concentration after instillation of 0.4% to 0.5% pilocarpine solution.

Pharmacokinetics of cycloplegic responses

Several reports are available that show the time course of the cycloplegic response to various drugs. These data may be analyzed on the basis of the principles expounded here so as to derive the pharmacokinetic coefficients of these responses.

The dose-response relationship. Lommatzsch reported measurement of the response of isolated ciliary muscles to pilocarpine, and his results can be interpreted according to equation 20. In living monkey eyes, Törnquist studied the dose-response relationship of pilocarpine-induced refractive

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Fig. 27. Relative bioavailability and the degree of tear film saturation. The initial tear film concentrations were estimated from drop size studies (○) and viscosity studies (●) of the tear flow with fluorescein. The relative bioavailability is obtained through similar studies with 0.5% pilocarpine. From Sugaya M and Nagataki S: Jpn J Ophthalmol 22:127, 1978.

Fig. 28. Time course of the response parameter after instillation of 0.5% pilocarpine solution (●), instillation of 0.5% pilocarpine in 0.5% HPMC solution (○), and after 1 hr wear of the soft contact lens (▲) presoaked in 0.02% pilocarpine solution for 25 min.
changes determining, in addition, the maximum possible refractive change with high doses of the drug. These results were analyzed and it was found that equation 20 or equation 23 is adaptable to pilocarpine-induced refractive changes. In cycloplegic responses the maximum response must be the state of zero amplitude of accommodation, and the RP may be given by

$$\text{RP} = \frac{\Delta_0 - \Delta}{\Delta}$$  \hspace{1cm} (26)$$

where $\Delta_0$ is the amplitude of accommodation before the drug and $\Delta$ is the amplitude of accommodation after drug. From the peak response after instillation of various concentrations of tropicamide, Yoshida\textsuperscript{152} calculated RP and plotted it against the instilled concentration of tropicamide, both on logarithmic scales. She found a linear relationship, and the slope of the regression line in five subjects averaged $0.91 \pm 0.21$ (S.D.). Thus equation 23 is applicable to the cycloplegic response. A similar confirmation was also obtained with the results of Smith.\textsuperscript{153}

Pharmacokinetic coefficients of cycloplegic response. An example of the RP-time curve for the cycloplegic response to tropicamide is shown in Fig. 31. Again, we can see that equation 24 can describe the RP-time curve of the cycloplegic response. Accordingly, the apparent elimination rate constant, the apparent absorption rate constant, the lag time, and the peak time were calculated. A similar analysis was carried out on the data published in the literature, and these results are listed in Table V.

The elimination rate constant of tropicamide is larger than that found for the mydriatic response. Likewise the elimination rate constant of homatropine may be slightly larger than that seen for the mydriatic response, but for scopolamine and atropine the two types of responses have similar rate constants. It is
interesting that the lag time and the peak time for cycloplegia are similar to the values obtained for the pupil responses. This probably indicates that the time required for the drug to reach the ciliary muscles is similar to the time needed for access to the sphincter muscles. The rapid access of cycloplegic drugs to the ciliary muscles may be accounted for by the outflow of the aqueous humor through the uveoscleral route, which would carry the drug with the aqueous

**Pharmacokinetics of intraocular pressure responses**

The intraocular pressure (IOP) can be determined accurately, and its response to antiglaucomatous drugs has been studied by many investigators. In addition, various methods are available to study the aqueous humor dynamics in the human eye, and the mechanism by which the drug-induced hypotensive reaction becomes manifest has been the central subject of many investigations. The IOP does not respond directly to the drugs as in the pupil reaction, but it is the final result of complex mechanisms interacting with each other. Therefore the pharma-
Fig. 32. Relationship between the reduction in the IOP and the baseline IOP 2 hr after instillation of 1% bupranolol solution. The correlation coefficient is 0.84. The regression equation is \( \Delta P_1 = 0.46(P - 10.9) \). (Takase et al: unpublished results.)

### Table V. Pharmacokinetic coefficients of cycloplegic responses

<table>
<thead>
<tr>
<th>Drug</th>
<th>A (hr(^{-1}))</th>
<th>B (hr(^{-1}))</th>
<th>Lag time (hr)</th>
<th>Peak time (hr)</th>
<th>Source of data (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropicamide</td>
<td>1.54 ± 0.56</td>
<td>3.25 ± 1.52</td>
<td>0.1 ± 0.23</td>
<td>0.6</td>
<td>Computer fitting to data of 152</td>
</tr>
<tr>
<td>Cyclometolate</td>
<td>0.44</td>
<td>2.3</td>
<td>0.15</td>
<td>1.05</td>
<td>Averaged curve from Fig. 1 of 154</td>
</tr>
<tr>
<td>Homatropine</td>
<td>0.35</td>
<td>1.3</td>
<td>0.2</td>
<td>1.6</td>
<td>Fig. 3 of 155</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>0.022</td>
<td>2.9</td>
<td>0.1</td>
<td>1.8</td>
<td>Fig. 6 of 127</td>
</tr>
<tr>
<td>Atropine</td>
<td>0.012</td>
<td>1.44</td>
<td>0.1</td>
<td>3.4</td>
<td>Fig. 5 of 127</td>
</tr>
</tbody>
</table>

A = apparent elimination rate constant; B = apparent absorption rate constant (equation 24).

The pharmacokinetics of responses is the dose-response relationship, but this aspect of the IOP response has been reported infrequently. This may be because of various difficulties inherent to defining the drug-induced IOP response, besides the necessity for careful subject selection. Without medication the IOP is subject to diurnal variation, which presents a difficulty in determining the baseline IOP to which the drug-induced IOP changes are compared. Furthermore, the amplitude of the diurnal variation is not insignificant compared with the drug effects, particularly in glaucoma patients.

In normal subjects, both eyes behave in a...
Table VI. Correlation between IOP reduction in mm Hg and control level of IOP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regression equation (ΔP)</th>
<th>No. of eyes</th>
<th>r*</th>
<th>Source of data (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>0.358 (P - 6.29)</td>
<td>19</td>
<td>0.82</td>
<td>168</td>
</tr>
<tr>
<td>2%</td>
<td>0.338 (P - 7.92)</td>
<td>44</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>4%</td>
<td>0.77 (P - 15.65)</td>
<td>16</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>L-Epinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>0.768 (P - 14.30)</td>
<td>22</td>
<td>0.85</td>
<td>170</td>
</tr>
<tr>
<td>Timolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25%</td>
<td>0.33 (P - 0.90)</td>
<td>52</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>0.5%</td>
<td>0.37 (P - 4.23)</td>
<td>42</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>1.0%</td>
<td>0.44 (P - 2.34)</td>
<td>11</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>0.697 (P - 9.91)</td>
<td>15</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>4%</td>
<td>0.60 (P - 8.06)</td>
<td>14</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Carteolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5%</td>
<td>0.25 (P - 1.24)</td>
<td>23</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>0.54 (P - 8.87)</td>
<td>47</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Befunolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.125%</td>
<td>0.351 (P - 15.1)</td>
<td>60</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>0.25%</td>
<td>0.395 (P - 11.59)</td>
<td>60</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>0.5%</td>
<td>0.443 (P - 8.04)</td>
<td>60</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>0.697 (P - 13.17)</td>
<td>60</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Bupranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2%</td>
<td>0.15 (P - 12.6)</td>
<td>30</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>0.5%</td>
<td>0.31 (P - 11.3)</td>
<td>30</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>0.46 (P - 10.9)</td>
<td>30</td>
<td>0.84</td>
<td></td>
</tr>
</tbody>
</table>

*Correlation coefficient.
† Unpublished data.

Table VII. Reduction ratio in outflow pressure and outflow resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>ΔP*/P, - 9</th>
<th>ΔR*/Rapp*</th>
<th>No. of eyes</th>
<th>Source of data (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine (2%)</td>
<td>0.43 ± 0.20†</td>
<td>0.27 ± 0.13</td>
<td>19</td>
<td>168</td>
</tr>
<tr>
<td>Pilocarpine (4%)</td>
<td>0.48</td>
<td>0.49 ± 0.07</td>
<td>12</td>
<td>169</td>
</tr>
<tr>
<td>Physostigmine (1%)</td>
<td>0.47</td>
<td>0.47 ± 0.10</td>
<td>8</td>
<td>169</td>
</tr>
<tr>
<td>L-Epinephrine (2%)</td>
<td>0.50 ± 0.10</td>
<td>0.52 ± 0.07</td>
<td>22</td>
<td>170</td>
</tr>
<tr>
<td>Acetazolamide (500 mg)</td>
<td>0.19 ± 0.12</td>
<td>0.07 ± 0.16</td>
<td>17</td>
<td>181</td>
</tr>
<tr>
<td>Timolol (0.5%)</td>
<td>0.42 ± 0.20</td>
<td>0.09 ± 0.38</td>
<td>16</td>
<td>183</td>
</tr>
</tbody>
</table>

*P becomes episcleral venous pressure.*
† Unpublished data.

similar way, allowing drug testing in one eye and use of the fellow eye as the control. This appears to be possible also in selected groups of glaucoma patients. This is, however, not necessarily the case, and the IOP values of the same eye before and after administration of the drug have to be compared. Some drugs, when instilled in one eye, do not affect the contralateral eye, which allows both sides to be compared. Others significantly affect the fellow eye and complicate this comparison in an individual subject. Whatever control is adopted, the error will be large, and this may be reduced by averaging repeated determinations.

In correlating the IOP response with the drug concentration, the response has been expressed in various ways: percentage reduction in reference to the control IOP, reduction of the IOP in mm Hg, and reduction ratio or the percentage reduction in the outflow pressure. Such diversity does not permit direct comparison of various reports, and it is desirable to establish a method that will enable us to compare the results of various studies on a common basis.
The relationship between the drug-induced IOP reduction and the control level of the IOP will first be considered. An example of this relationship is illustrated in Fig. 32, where a linear correlation is significant: the higher the IOP, the larger the IOP reduction with the same drug. This was first shown by Goodwin and was later recognized by Krill and Newell and Kronfeld. Table VI gives the regression equations for the relationship from our own results and also from published data. Although the data scatter is not small, the linear correlation is statistically significant in all cases. The intercept of the regression line with the IOP axis averaged 9.0 ± 4.5 mm Hg (S.D.), which is in agreement with the episcleral venous pressure reported by various investigators. In addition, it is noted in Table VI that the slope of the relationship increases with increasing concentration of the drug without significantly altering the intercept. This is in keeping with the report that the episcleral venous pressure does not change significantly with drugs such as pilocarpine, acetazolamide, epinephrine, and beta-adrenergic antagonists. On this basis, the relationship between the IOP reduction (ΔP) and the IOP (P) may be represented by

\[ \frac{ΔP}{P - 9} = X \]  

and the value X is varied by changes in the drug concentration. This can therefore be used to express the drug effects on the IOP, i.e., the ratio of the outflow pressure reduction.

Goldmann gave an equation relating the rate of aqueous flow (F), the IOP (P), the episcleral venous pressure (P_e), and the resistance of outflow in the conventional outflow route (R_r). Subsequently, the uveoscleral route of aqueous bulk flow became known, and this flow is insensitive to IOP changes. Incorporating these aspects and denoting the rate of uveoscleral flow as U, one may write

\[ F = \frac{1}{R_r} (P - P_e) + U \]  

The uveoscleral flow in the human eye comprises 4% to 12% of the total flow. Although it was shown to change in response to drugs in monkey eyes, we have currently no clinical method of estimating it in the human eye. It is therefore disregarded in the following discussion for simplicity of analysis. When small changes occur in the outflow resistance and the rate of aqueous formation, and the IOP is reduced to a new steady-state level, the following relationship may be derived from the above equation to express these changes:

\[ \frac{ΔP}{P - 9} = \frac{ΔR_r}{R_r} + \frac{ΔF}{F} \]  

The dose-response studies may be carried out for the IOP changes, for the outflow resistance, and also for the aqueous humor formation. This equation should relate the results of these studies.

The outflow resistance is the reciprocal of the outflow facility of the outflow channel, which differs from the conventional tonographic outflow facility, since the latter includes the pseudofacility, i.e., the suppressibility of aqueous humor formation by elevating the IOP. The reciprocal of the tonographic outflow facility is therefore denoted as R_app, which is about 16% smaller than R_r, and the difference is probably 20% at the most. Since the error of the tonography can be larger than this, one may substitute R_app for R_r as an approximation. Consequently, the reduction ratios of the outflow pressure and of the R_app were calculated from the published data, with the assumption that the episcleral venous pressure is 9 mm Hg. The results are given in Table VII. It is of interest to note that the reduction ratio in the outflow pressure is close to the reduction ratio of R_app with pilocarpine and epinephrine, but they differ markedly with acetazolamide and timolol. This is in accordance with the understanding that the former group of drugs influences mainly the outflow resistance, and the latter group affects largely the rate of aqueous humor formation.

On the basis of the above theory, the use of the reduction ratio of the outflow pressure is thought to be more logical than...
other formulations of the IOP response, since it allows direct correlation with the changes in other parameters, i.e., the changes in the outflow resistance and the rate of aqueous humor formation. With the use of this expression of the IOP response, the results of Harris and Galin163 and Drance and Nash165 on pilocarpine effect are found to be almost identical. Similarly, the dose-response relationship for the IOP effect of epinephrine166 and its effect on the outflow resistance160 are very similar. An extrapolation of the relationships gave the least effective concentration of about 0.1% to 0.15% for pilocarpine and 0.1% to 0.2% for epinephrine. In addition, a survey of various published results suggests that the maximum drug effects on the outflow pressure reduction ratio would be around 0.6 to 0.7.

When we study the drug effects on the IOP of normal subjects, the initial outflow pressure is low and a slight fluctuation of the episcleral venous pressure can occur177. In these cases, the assumption of a fixed value of the episcleral venous pressure would render a great error in the outflow pressure calculations. Even if the episcleral venous pressure is measured individually, it is difficult to apply the present method of calculation to the results with a few normal subjects. In fact, very low IOP is occasionally encountered in normal subjects after instillation of drugs (e.g., timolol), indicating a possibility that the episcleral venous pressure reduction actually occurs in these cases. Thus the present method of analysis shown in Table VII is applicable only in glaucoma and ocular hypertension cases, where the outflow pressure is high enough to allow disregard of small fluctuation of the episcleral venous pressure. It must also be pointed out that the method should be used on statistical basis for a large number of cases and that the judgment should be made with due consideration on the error range of the techniques of examination.
**Duration of hypotensive effects and drug concentration.** In analogy to the pupil response, the duration of the hypotensive effect of an antiglaucomatous drug may be defined as the interval between the time of peak response and the time when the effect terminates. In the case of a long-acting antiglaucomatous drug, the termination time may be obtained by extrapolation of the time course of the IOP changes. The duration of the effect may then be correlated with the drug concentration, but because of marked IOP fluctuation in an individual, such a correlation could be seen only with use of the average duration. An example of the correlation is shown in Fig. 33, where the average duration of the hypotensive effects in eight normal subjects is plotted against the logarithm of concentration of befunolol solution applied topically. The correlation is seen to be linear, and this may be analyzed by equation 18. Since the relationship between the intraocular drug concentration and the IOP response is unknown, the slope of the regression line was called the rate of effect disappearance instead of the elimination rate constant of the drug. Extrapolation of the line gives the least effective concentration, and this value agrees well with the least effective concentration calculated by extrapolation of the dose-response relationship. The least effective concentration was 0.13% to 0.16% for bupranolol, about 0.08% with bafenolol, and about 0.045% for timolol. A similar linear correlation between the duration of hypotensive effect and the logarithm of the dose is also seen in published data on the hypotensive effect of colchicine in rabbit eyes.

The least effective concentration and the rate of effect disappearance permit estimation of the effect duration of a given concentration of a hypotensive drug. For example, the least effective concentration of pilocarpine may be assumed to be about 0.1% and the rate of effect disappearance about 0.35 hr⁻¹, a value corresponding to the apparent elimination rate constant of this drug in the iris. The effect duration of 8% pilocarpine was estimated with equation 18 to be about 15 hr. Taking the peak time of about 2 hr into account, this drug is effective even 15 hr after instillation, the result being consistent with the report of Drance et al. Thus the knowledge of these two pharmacokinetic coefficients is useful in determining the concentration of the therapeutic preparation and the frequency of its application.

**Concluding remarks**

The noninvasive method of analyzing the response in relation to the dose of the drug enables us to estimate the rates at which some instilled drugs are absorbed and eliminated in the anterior segment of the human eye. Knowing these pharmacokinetic coefficients, it is possible to construct curves of the intraocular drug concentration with various modalities of drug application, e.g., single or multiple drop instillation at certain intervals, application of ointment, or a constant-rate drug delivery device. This should be useful in planning the therapeutic regimen according to the patient's need. However, drug therapy in practice is very complicated and many factors must be taken into consideration, such as slow development of effects or individual differences in drug sensitivity because of age, heredity, progress of pathologic processes, or development of drug tolerance. Thus the pharmacokinetic coefficients obtained by the present analysis on the basis of a simple model may give only a rough estimate of the dynamic state of drug behavior in an actual clinical situation. It is hoped, however, that such pharmacokinetic results in the human eye will give us additional confidence in clinical practice.

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