Estimation of the Permeability of the Blood–Retinal Barrier in Normal Individuals
Yuichiro Ogura, Yoko Tsukahara, Isao Saito, and Takehisa Kondo

The fluorescein kinetics in the vitreous was simulated with a computer to consider several factors such as permeability of the blood–retinal barrier, outward active transport, plasma fluorescein dynamics, diffusion of fluorescein in the vitreous, and fluorescein leakage from the blood–aqueous barrier. Kinetic vitreous fluorophotometry was performed in normal individuals to estimate the inward and outward permeability of the blood–retinal barrier based on the theory of the simulation model. The results of the simulation studies suggest that the fluorescein concentration in the posterior vitreous after intravenous administration is dependent mainly on the inward permeability and on the plasma concentration and that the outward permeability has little influence on the fluorescein kinetics at the early phase. In the pharmacokinetic analysis of the results of kinetic vitreous fluorophotometry, we obtained average values of $1.8 \times 10^{-5}$ cm/min and $5.6 \times 10^{-4}$ cm/min for the inward permeability and outward permeability coefficients, respectively. The diffusion coefficient of fluorescein in the vitreous was estimated at $7.9 \times 10^{-4}$ cm$^2$/min on the average. The outward permeability of the blood–retinal barrier is approximately 31 times the inward permeability. This suggests that a facilitated process that transports fluorescein outward from the vitreous cavity exists in the blood–retinal barrier of human eyes. Invest Ophthalmol Vis Sci 26:969–976, 1985

Vitreous fluorophotometry has been introduced in the clinical field of ophthalmology and many studies on alterations of the blood–retinal barrier in diseased states have been reported. Penetration of fluorescein into the vitreous cavity is determined not only by permeability of the blood–retinal barrier but also by other factors, such as plasma fluorescein concentration decay, diffusion coefficient in the vitreous and active outward transport of fluorescein from the vitreous. Thus, interpretation of the data of vitreous fluorophotometry is so complicated as to differentiate the contribution of each factor by usual pharmacokinetic analysis. Kinetic vitreous fluorophotometry has been performed to evaluate the outward permeability of the blood–retinal barrier in experimental animals and in human subjects. Although serial measurements give us more information than does single measurement, it is still difficult to distinguish between the inward and outward permeability directly from measured values. Palestine and Brubaker have reported computer simulation of the fluorescein kinetics in the posterior portion of the eye to consider effects of several factors. The present study was undertaken to clarify the influence of some factors on the fluorescein concentration in the vitreous using computer simulation and to estimate the inward and the outward permeability in normal individuals.

Materials and Methods

Computer Simulation

The model that we used in computer simulation of the fluorescein kinetics in the vitreous was similar to that originally devised by Palestine and Brubaker and improved by Zeimer et al. The posterior portion of the globe is assumed to be a hemisphere and the vitreous body is divided into compartments of thin shells. To consider fluorescein leakage from the blood–aqueous barrier, we assumed a similar hemisphere to be present in the anterior portion. Two hemispheres communicate with each other by a central compartment only. The outer wall of the posterior hemisphere represents the blood–retinal barrier and the outermost compartment of the anterior hemisphere represents the posterior chamber (Fig. 1). Assuming that fluorescein in the vitreous moves radially by diffusion only, the fluorescein concentration of the compartment n at time t after intravenous administration is given by the following equations:

\[ n = 1, \quad CV(n, t) = CV(n, t - dt) + [P_{in} \times CP(t) - P_{out} \times CV(n, t - dt)] \times S(n) \times dt/V(n) - [CV(n, t - dt) - CV(n + 1, t - dt)] \times S(n + 1) \times D \times dt/ [dr \times V(n)]; \]

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Fig. 1. Schematic illustration of the simulation model of the vitreous.

(ii) \( n \geq 2, \ CV(n, t) = CV(n, t - dt) + \frac{([CV(n - 1, t - dt) - CV(n, t - dt) + S(n) - [CV(n, t - dt) - CV(n + 1, t - dt)] + S(n + 1)] \cdot D \cdot dt / [dr \cdot V(n)]}{2}, \)

where \( CV(n, t) \) indicates the fluorescein concentration of the compartment \( n \) at time \( t \); \( CP(t) \), free (unbound) fluorescein concentration in the plasma at time \( t \); \( S(n) \), surface area of the compartment \( n \); \( V(n) \), volume of the compartment \( n \); \( P_{in} \), inward permeability coefficient of the blood–retinal barrier; \( P_{out} \), outward permeability coefficient of the blood–retinal barrier; \( D \), diffusion coefficient of fluorescein in the vitreous; \( dt \), unit time; and \( dr \), thickness of the compartment.

In this study, we used 12 mm as a radius of each hemisphere, 1 mm as \( dr \) and 1 min as \( dt \). The plasma fluorescein concentration after intravenous administration is expressed as a double exponential function of time on the basis of a two-compartment model. Parameters of the plasma concentration decay were determined by computer regression analysis. Since the aqueous fluorescein concentration in the posterior chamber is difficult to determine, it was simulated according to the results of previous reports. That is, parameters were determined so that the concentration of fluorescein in the posterior chamber aqueous might be 7% of that of free fluorescein in the plasma after equilibrium was reached. These conditions were programmed into a computer, then the simulation of the fluorescein kinetics in the vitreous was carried out during the period from \( t = 0 \) to \( t = 300 \) min. The changes in fluorescein concentration were studied when each of those factors had been changed. Thus, the influence of each factor on the fluorescein kinetics was evaluated.

Vitreous Fluorophotometry

Vitreous fluorophotometry was performed in 13 normal individuals who had neither systemic nor ocular disease. None has apparent vitreous abnormalities such as liquefaction, lacuna formation, or posterior vitreous detachment. The subjects ranged in age from 11 to 52 yr (mean, 37.4 yr). All subjects were fully informed of the purpose of the study and their consents were obtained prior to initiation of the study. Sodium fluorescein (Fluorescite, Alcon; Fort Worth, TX), 7 mg/kg of body weight, was injected into the antecubital vein and pupils of each patient were dilated with phenylephrine hydrochloride. Vitreous fluorophotometry was performed on each patient at three time points; preinjection, 2 and 5 hr after fluorescein administration. Measurements were done with an automatic scanning fluorophotometer (Fluorotron Master, Coherent; Palo Alto, CA) without using contact lens. The fluorescence of the chorioretinal peak was only about twice or three times that in the posterior vitreous when we used this dose of fluorescein. It appeared, therefore, that the spread function of the chorioretinal peak was negligible at 3 mm from the retina, so no corrections were made for the spread function. Simultaneously, the total plasma fluorescein concentration was determined at 30 min and 1, 2, 3, and 5 hr after administration and corrected to concentration of free fluorescein, assuming that the percentage of free fluorescein to total fluorescein was 17%. The plasma data were analyzed with a computer as described above.

Estimation of the Diffusion Coefficient of Fluorescein in the Vitreous

The concentration gradient of fluorescein in the posterior vitreous is steep when the diffusion coefficient is low. Conversely, when the diffusion coefficient is high, the concentration gradient is gentle. We calculated concentration gradient in the posterior vitreous against different diffusion coefficients of fluorescein by computer simulation (Fig. 2). The concentration gradient was determined in each patient from a 2-hr scan of vitreous fluorophotometry and, then, the diffusion coefficient of fluorescein in the vitreous was estimated from the concentration gradient.

Estimation of the Inward Permeability of the Blood–Retinal Barrier

We have obtained the following results in the computer simulation study: (1) The outward permeability has little influence on the fluorescein kinetics in the posterior vitreous during the first 2 hr after administration. (2) The leakage from the blood–aqueous barrier does not affect the fluorescein concentration in the posterior vitreous during a few hours. Accordingly, when we consider the fluorescein
kinetics in the posterior vitreous at the early phase, we can ignore contributions of these two factors. Then total fluorescein mass that has penetrated across the blood–retinal barrier until time \( t \) is given in equation 1:

\[
\text{Total fluorescein mass} = \int_0^t S \cdot P_{in} \cdot CP(t) \, dt \quad (1),
\]

where \( S \) is the surface of the blood–retinal barrier. Other symbols are identical to those described above. If the concentrations in all compartments of the vitreous at time \( t \) are known, the equation can be written in the form:

\[
\text{Total fluorescein mass} = \sum_{i=1}^{N} [CV(i, t) \cdot V(i)] \quad (2).
\]

When the diffusion coefficient of fluorescein in the vitreous has already been estimated, we can obtain the fluorescein distribution in the vitreous at any given time by computer simulation. So we can rewrite the right-hand side of equation 2:

\[
\sum_{i=1}^{N} [CV(i, t) \cdot V(i)] = K \cdot \sum_{i=n_1}^{n_2} [CV(i, t) \cdot V(i)]
\]

\[1 < n_1 < n_2 < N \quad (3),\]

where \( K \) is a constant depending on the diffusion coefficient, time, \( n_1 \) and \( n_2 \), and this value is determined by computer simulation. Thus, we can estimate total fluorescein mass from the fluorescein concentrations in some regions of the vitreous at any given time. Combining equation 1, 2, and 3, the following equation can be obtained:

\[
P_{in} = K \cdot \sum_{i=n_1}^{n_2} [CV(i, t) \cdot V(i)] \cdot \int_0^t CP(t) \, dt \quad (4).
\]

Here, we used following values in calculations: \( t = 120 \) min, \( n_1 = 3 \) mm and \( n_2 = 7 \) mm. We estimated the inward permeability by substituting the data of vitreous fluorophotometry for each patient in equation 4.

Estimation of the Outward Permeability Coefficient of the Blood–Retinal Barrier

We obtained the following three major parameters for each patient: (1) plasma concentration decay parameters, (2) the diffusion coefficient of fluorescein in the vitreous, and (3) the inward permeability coefficient of the blood–retinal barrier. Then we input the above data into a computer and the fluorescein kinetics in the vitreous was simulated until 5 hr after administration in each patient. The outward permeability coefficient was estimated empirically so as to fit the calculated concentrations to the measured concentrations in the 5-hr scan of vitreous fluorophotometry.

Results

Computer Simulation

The fluorescein concentrations in the posterior vitreous compartments calculated by computer simulation are shown in Table 1. The values of the parameters used in the simulation were: inward permeability coefficient, \( 1.8 \times 10^{-5} \) cm/min; outward permeability coefficient, \( 5.6 \times 10^{-4} \) cm/min; diffusion coefficient, \( 7.9 \times 10^{-4} \) cm²/min. Those values are the means for normal subjects estimated from the results of kinetic vitreous fluorophotometry, as described.

Table 1. Calculated fluorescein concentrations by computer simulation

<table>
<thead>
<tr>
<th></th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>4 hr</th>
<th>5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV(1)</td>
<td>6.9</td>
<td>6.3</td>
<td>5.6</td>
<td>5.1</td>
<td>4.7</td>
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<tr>
<td>CV(2)</td>
<td>5.4</td>
<td>5.7</td>
<td>5.4</td>
<td>5.1</td>
<td>4.8</td>
</tr>
<tr>
<td>CV(3)</td>
<td>4.0</td>
<td>5.1</td>
<td>5.2</td>
<td>5.1</td>
<td>4.9</td>
</tr>
<tr>
<td>CV(4)</td>
<td>2.7</td>
<td>4.4</td>
<td>4.9</td>
<td>5.0</td>
<td>5.0</td>
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<td>CV(5)</td>
<td>1.8</td>
<td>3.7</td>
<td>4.5</td>
<td>4.9</td>
<td>5.0</td>
</tr>
<tr>
<td>CV(6)</td>
<td>1.1</td>
<td>3.0</td>
<td>4.2</td>
<td>4.8</td>
<td>5.2</td>
</tr>
<tr>
<td>CV(7)</td>
<td>0.7</td>
<td>2.5</td>
<td>3.9</td>
<td>4.8</td>
<td>5.4</td>
</tr>
<tr>
<td>CV(8)</td>
<td>0.4</td>
<td>2.0</td>
<td>3.8</td>
<td>5.0</td>
<td>5.7</td>
</tr>
</tbody>
</table>

\( CV(n) \) represents the fluorescein concentration (ng/ml) in the compartment \( n \) (n mm away from the retina).
Table 2. Effect of the changes in the permeability of the blood-retinal barrier on the fluorescein concentration in the posterior vitreous

<table>
<thead>
<tr>
<th>( P_{in} ) (( \times 10^{-5} ) cm/min)</th>
<th>( P_{out} ) (( \times 10^{-4} ) cm/min)</th>
<th>Fluorescein concentrations (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8</td>
<td>5.6</td>
<td>1 hr</td>
</tr>
<tr>
<td>2.7</td>
<td>5.6</td>
<td>2 hr</td>
</tr>
<tr>
<td>3.6</td>
<td>5.6</td>
<td>3 hr</td>
</tr>
<tr>
<td>1.8</td>
<td>2.8</td>
<td>4 hr</td>
</tr>
<tr>
<td>1.8</td>
<td>0.56</td>
<td>5 hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.7</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>3.6</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>1.8</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>1.8</td>
<td>0.56</td>
<td></td>
</tr>
</tbody>
</table>

\( P_{in} \) and \( P_{out} \) represent the inward and outward permeability coefficients of the blood-retinal barrier, respectively. The fluorescein concentrations are those in the compartment at 4 mm away from the retina.

Table 2 shows the effect of changes in permeability on the fluorescein concentration in the posterior vitreous (4 mm away from the retina). The results show that the change in outward permeability has less influence on the vitreous fluorescein concentration than does that in inward permeability, especially at the early phase. It was considered that the change in plasma fluorescein concentration directly affected the vitreous fluorescein concentration as did the inward permeability.

Estimation of the Diffusion Coefficient of Fluorescein in the Vitreous

The average value (±SD) for the diffusion coefficient estimated from the posterior vitreous concentration gradient in the 2-hr scan was (7.9 ± 2.6) \( \times 10^{-4} \) cm\(^2\)/min. The diffusion coefficient tended to increase with the increasing age of subjects, but no statistically significant correlation was found (Fig. 3).

Estimation of the Inward and the Outward Permeability Coefficients of the Blood–Retinal Barrier

We obtained the average inward permeability coefficient of (1.8 ± 0.5) \( \times 10^{-5} \) cm/min for all the subjects from the posterior vitreous fluorescein concentrations in the 2-hr scan. The mean value of outward permeability coefficient determined by the best-fit method using a computer was (5.6 ± 2.3) \( \times 10^{-4} \) cm/min (Table 3). The outward permeability was about 31 times as high as the inward permeability. There was no correlation between the permeability coefficients and the age or sex of subjects.

Comparison Between the Measured Fluorescein Concentrations and the Calculated Concentrations by Computer Simulation

In Figure 4, broken lines indicate the fluorescein concentrations in the posterior vitreous (1–7 mm away from the retina) as measured by vitreous fluorophotometry. The parameters that were obtained from the 2- and 5-hr profiles are shown in the figure. Using these values, computer simulation of the vitreous fluorescein kinetics was carried out. Unbroken lines indicate the fluorescein concentrations calculated by computer simulation. It is found that the calculated concentrations almost agree with the measured values during the period from 1 to 5 hr.

Discussion

Computer Simulation

To interpret the results of vitreous fluorophotometry, one must consider many factors that influence the vitreous fluorescein kinetics such as permeability of the blood–retinal barrier, plasma fluorescein dy-
Table 3. Diffusion coefficients (D) and permeability coefficients (P_{in} and P_{out}) in normal individuals

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Examined eye</th>
<th>D ( (\times 10^{-4} \text{ cm}^2/\text{min}) )</th>
<th>P_{in} ( (\times 10^{-5} \text{ cm/min}) )</th>
<th>P_{out} ( (\times 10^{-4} \text{ cm/min}) )</th>
<th>( \int_0^{120} \text{CP}(t) , dt ) ( (\times 10^{3} \text{ g/ml} \cdot \text{min}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>F</td>
<td>OS</td>
<td>3.9</td>
<td>1.6</td>
<td>4.5</td>
<td>161</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>M</td>
<td>OD</td>
<td>9.1</td>
<td>1.5</td>
<td>8.5</td>
<td>119</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>F</td>
<td>OS</td>
<td>5.4</td>
<td>1.9</td>
<td>10.7</td>
<td>210</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>M</td>
<td>OD</td>
<td>11.6</td>
<td>1.5</td>
<td>5.0</td>
<td>133</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>OS</td>
<td>7.5</td>
<td>2.1</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>M</td>
<td>OS</td>
<td>6.5</td>
<td>2.9</td>
<td>5.5</td>
<td>97</td>
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<tr>
<td>7</td>
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<tr>
<td>8</td>
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<tr>
<td>9</td>
<td>44</td>
<td>F</td>
<td>OD</td>
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<td>6.0</td>
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<td>10</td>
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<td>OD</td>
<td>9.1</td>
<td>1.6</td>
<td>2.5</td>
<td>80</td>
</tr>
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</table>

Mean ± SD 37 ± 14 7.9 ± 2.6 1.8 ± 0.5 5.6 ± 2.3 152 ± 59

\( \int_0^{120} \text{CP}(t) \, dt \) represents the integral of the plasma concentration of free fluorescein up to 120 min. Patient 4 was examined in both eyes.

**Fig. 4.** The comparison between the measured fluorescein concentrations and the calculated concentrations in the posterior vitreous of normal individual.
the vitreous body. Palestine and Brubaker\(^1\) have reported the pharmacokinetics of fluorescein in the vitreous of humans by the compartment analysis using computer simulation. However, their model was a hemisphere that represented only the posterior half of the eye and they did not consider a contribution of leakage from the blood–aqueous barrier. Moreover, their fluorophotometer had low resolution, so they failed to fit the calculated fluorescein profiles to the measured concentrations. Zeimer et al\(^1\) have improved this model by combining a similar hemisphere in the anterior portion with a posterior hemisphere. In the present study, we added the fluorescein kinetics in the posterior chamber to the simulation model to consider the effect of the leakage from the blood–aqueous barrier.

The results of the computer simulation have shown that the changes in the inward permeability of the blood–retinal barrier directly affect the fluorescein concentration in the posterior vitreous. On the other hand, the fluorescein kinetics in the vitreous for a period of several hours after administration is less affected by the outward permeability, especially at the early phase. When the computer simulation was carried out with 90% decrease of the outward permeability coefficient, the calculated concentration at 2 hr increased by only about 14%. It has also been shown that the plasma fluorescein concentration has a direct influence on the vitreous fluorescein kinetics in the simulation. In our study, the fluorescein concentration in the plasma was expressed as a double exponential function based on the pharmacokinetic theory of a two-compartment model. The regression curve almost fits the measured concentrations until 5 hr. Zeimer et al\(^1\) have recommended regression analysis by means of a three-exponential function. Recent studies\(^2\) have reported that fluorescein is rapidly glucuronized in the liver after intravenous administration and that this metabolite of fluorescein, fluorescein monoglucuronide, has weak fluorescence in the plasma. But little experimental data have been available on the kinetics of fluorescein monoglucuronide in the eye. In the present study, we presented the data obtained in the early phase after intravenous administration and neglected the effects of metabolites of fluorescein. More experimental data about the fluorescein metabolism is required to analyze the fluorescein kinetics in the plasma.

Changes in the diffusion coefficient of fluorescein result in differences in the concentration gradient of fluorescein in the vitreous. When we consider a total mass of fluorescein in the vitreous, the diffusion coefficient has little influence on the fluorescein kinetics. However, if there is posterior vitreous detachment or partial vitreous liquefaction, it is expected that the result might be different. In such a pathologic vitreous, fluorescein moves more rapidly with mechanical motion of the vitreous gel and the direction of fluorescein movement is not yet assumed to be radial only. We are now performing a further study of the vitreous simulation model in pathologic states.

**Estimation of the Diffusion Coefficient of Fluorescein in the Vitreous**

The estimated values of the diffusion coefficient ranged from \(3.9 \times 10^{-4}\) cm\(^2\)/min to \(12.8 \times 10^{-4}\) cm\(^2\)/min (mean, \(7.9 \times 10^{-4}\) cm\(^2\)/min). The values for the diffusion coefficient of fluorescein have been determined in the water,\(^2,28\) in the cornea\(^27,29\) and in the lens.\(^28\) The values estimated in the present study were relatively higher than those values found in vitro, but the mean value coincided closely with the value estimated by Zeimer et al\(^1\) by means of computer simulation. They suggested that the discrepancy between in vitro and in vivo diffusion coefficients might be due to factors, other than diffusion, affecting the movement of fluorescein in the vitreous in vivo. Mechanical mixing of the vitreous gel with the eye motion is supposed to be a main factor among them. Therefore the values estimated by this method include the effects of some factors other than diffusion, so it would be appropriate that the term “dispersion coefficient” is used instead of “diffusion coefficient.”

Anyway, at present, this is the only method by which one can estimate the diffusion coefficient in the vitreous in vivo. We believe that new knowledge of physiologic nature of the vitreous will be obtained by the analysis of more clinical data using this method.

**Estimation of the Permeability Coefficient of the Blood–Retinal Barrier**

Blair et al\(^10\) have reported the method for estimating the ratio of the inward permeability to the outward permeability in human subjects. Their method is to find a time when the fluorescein concentration in the vitreous is maximum and to calculate the ratio between the vitreous fluorescein concentration and the plasma concentration at that time. This method needs frequent measurements and blood samplings to find the peak time and gives us only the ratio between the inward permeability and the outward permeability. Zeimer et al\(^1,31,32\) have described the method for calculating the inward permeability coefficient from a single scan of vitreous fluorophotometry. In the present study, we also estimated the outward permeability coefficient to fit the calculated concentrations to the measured concentrations in the 5-hr scan by computer simulation.
We found that the outward permeability coefficient was about 31 times as high as the inward permeability coefficient. This value is consistent with the values reported in other studies (Table 4). 17,18,30-33 This result suggests that the outward movement of fluorescein across the blood–retinal barrier is a facilitated process other than simple diffusion. It has been reported by Cunha-Vaz and Maurice 34 that fluorescein is actively transported across the blood–retinal barrier outward from the vitreous cavity in rabbits. They also suggested that this transport might be an energy-dependent process that could be inhibited by metabolic inhibitors. Stone and Wilson 35 have found that a similar active outward transport of fluorescein exists in the anterior uvea of rabbits. From our results and previous reports, it is strongly suggested that the active outward transport of fluorescein also exists in the blood–retinal barrier of human eyes. However, Cantril and Pederson 36 have recently reported that the posteriorly directed fluid flow contributes to the loss of fluorescein in the vitreous in cynomolgus monkeys. There might be such a bulk flow that affects the fluorescein kinetics in the human vitreous, but to date no evidence has been found. The fluid dynamics in the vitreous body will be clarified in the near future by further study of fluorescein kinetics in the vitreous using vitreous fluorophotometry.

**Key words:** vitreous fluorophotometry, simulation, blood–retinal barrier, permeability, diffusion

**References**


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**Table 4. Inward (P_in) and outward (P_out) permeability of the blood–retinal barrier**

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Subjects</th>
<th>P_in (cm/min)</th>
<th>P_out (cm/min)</th>
<th>Ratio of P_out/P_in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunha-Vaz and Maurice</td>
<td>Rabbit</td>
<td>9.1 x 10^-5</td>
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<td>Palestine and Brubaker</td>
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<td>Human</td>
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<td>Blair et al</td>
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<td>31</td>
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<td>Miyake</td>
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<tr>
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* This value was assigned based on data obtained in rabbits by Cunha-Vaz and Maurice. 34