Use of hydrophilic contact lenses to increase ocular penetration of topical drugs

Stephen R. Waltman* and Herbert E. Kaufman**

Hydrophilic contact lenses take up and release fluorescein from solution in a measurable manner. This is more rapid with Bionite than with the Soflens lenses. Bionite lenses, either untreated or pretreated with fluorescein, markedly increase the concentration of this drug in the anterior segment of the eye. This suggests that these lenses may be useful adjuncts in attaining and maintaining high drug concentrations in the eye without the use of frequent topical medication. The drug concentration attained with these lenses is higher than that possible with frequent topical medication alone.

Key words: corneal contact lens, hydrophilic properties, contact lens variables, hydroxyethyl methacrylate, methyl metacrylate, fluorescein, concentration, cornea, anterior chamber, aqueous humor, contact lens solutions, topical drug administration, rabbits, human, hydrophilic contact lens, fluorophotometer, ocular drug penetration.

When standard collyria are used with hydrophilic contact lenses the corneal epithelium can be damaged. Previous work suggests that the preservatives, which are metabolic poisons, are concentrated and thereby damage the cornea, but that nontoxic medication without preservatives can be used. This raises the question of the ability of these lenses to concentrate and provide prolonged contact with substances, and whether they can be used to deliver high concentrations of drugs to the anterior segment of the eye. The dynamics of the uptake and release of fluorescein by these lenses in vitro and in vivo, in man and rabbits, was studied as a model for other agents.

Methods and materials

Bionite hydrophilic lenses from Griffin Laboratories and Soflens lenses from Bausch and Lomb were studied. Some of the Bionite lenses were specifically designed for rabbit corneas. Both types of lenses are made of cross-linked hydrophilic polymers of 2-hydroxyethyl methacrylate (Hema). When Hema is polymerized in the presence of a bifunctional monomer such as ethylene glycol dimethacrylate chains cross linked by diester molecules, approximately one link

From the Department of Ophthalmology, University of Florida College of Medicine, Gainesville, Fla.

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*Present address: Department of Ophthalmology, Washington University School of Medicine, St. Louis, Mo. 63110.

**Address requests for reprints to Dr. Kaufman, Department of Ophthalmology, University of Florida, Gainesville, Fla. 32601.
every 200 monomer units is formed. This basic building block is used in both types of hydrophilic lenses, but the length of the chains, cross linking, and degree of water binding differ. The finished lenses also are fabricated differently, in form and thickness. These lenses are described in greater detail by Gasset and Kaufman.  

Individual vials of sterile 2 per cent fluorescein solution were used for human experiments. Otherwise, disodium fluorescein was made up in various concentrations in 0.1 M phosphate buffered saline with a pH of 7.4.

An objective slit lamp fluorophotometer was used to measure fluorescein concentration in the lenses, in the anterior segment of the eye, and in the solutions being studied. The construction of this instrument will be described in greater detail elsewhere. Essentially it consists of a light sensing device built into the eyepiece of a conventional slit lamp and involves no manipulation of the tissues being studied. It is capable of measuring the fluorescein concentration of an area 0.08 mm. across. The response of the instrument is linear between $5 \times 10^{-6}$ and $5 \times 10^{-2}$ mg. per milliliter and is accurate to within $\pm 2$ per cent. In all instances the unknown is compared to a fresh stable standard fluorescein solution.

Results

In vitro studies—fully hydrated

Uptake. Fully hydrated lenses were placed in solutions of various fluorescein concentrations. At the specified time these lenses were rinsed briefly in saline and mounted on the end of a glass test tube. The fluorescein concentration in the lens was then measured and the lens returned to its solution.

The lenses themselves absorb less than 3 per cent of the exciting or emitted light, and therefore do not interfere with the study of fluorescein concentration. Because the volume of the soaking solution was so large in comparison to the volume of the lenses, no changes could be detected in the fluorescein concentration of the solution.

When the lenses were viewed with the slit lamp the Bionite lenses fluoresced uniformly after 90 seconds of soaking. It was possible to make out 3 distinct zones in the Soflens lenses for 30 minutes as the fluorescein penetrated to the interior of the lenses more slowly. The rate of uptake of fluorescein, from a $5 \times 10^{-3}$ mg. per milliliter solution, is shown in Fig. 1. The concentration in the lenses is expressed as a percentage of the soaking solution. The Bionite lenses take up fluorescein much more rapidly and uptake is essentially complete after 2 hours. The Soflens lenses take up the fluorescein more slowly and continue to do so for over 24 hours. The final concentration in the Soflens lenses is approximately 2.3 times greater than that in the Bionite lenses.

Elution studies. After the lenses had been presoaked for at least 24 hours in $5 \times 10^{-3}$ mg. per milliliter of fluorescein solution, they were placed in 4 c.c. of buffered saline and the time rate of change of fluorescein concentration in the lenses and the eluting solutions was measured. The rate of change of the fluorescein concentration in the eluting solutions is shown in Fig. 2. At the end of one hour the Bionite lenses had released 70 per cent of the fluorescein into solution while the Soflens lenses released 25 per cent. Only after 8 hours did the Soflens lenses release 90 per cent of the bound fluorescein.

After all fluorescein had been eluted from each type of lens it was determined that the Soflens lenses took up twice as much fluorescein as did the Bionite lenses on a weight basis.

Bionite lenses were soaked in various concentrations of fluorescein between $5 \times 10^{-2}$ and 20 mg. per milliliter and the fluorescein taken up by them was then eluted. The total uptake of fluorescein was linearly related to the concentration of the soaking solution over this 4,000-fold concentration range. Bionite lenses were air dried and then placed in fluorescein solution. The uptake by the dried lenses was almost identical to that of the fully hydrated lenses.

In vivo studies. Bionite lenses were pre-soaked in a solution of either 0.1 per cent or 0.01 per cent fluorescein and then inserted into the right eye of 7 rabbits. At the same time a drop of the 0.01 per cent
solution was applied to the left eye. The lenses were removed 90 minutes later, the eyes irrigated with saline, and the corneal and anterior chamber concentrations determined. The lenses were then reinserted and the rabbits had one drop of the 0.01 per cent solution applied to the left eye every 30 minutes for 2 additional hours. Saline solution was applied to the right eye. Soflens lenses were presoaked in 0.1 per cent fluorescein for 48 hours and then inserted into the left eye of 6 rabbits. The
Table I. Corneal fluorescein concentration in rabbits with presoaked hydrophilic lenses

<table>
<thead>
<tr>
<th>Time (hr.)</th>
<th>Bionite lens presoaked in 0.1 per cent fluorescein</th>
<th>Bionite lens presoaked in 0.01 per cent fluorescein</th>
<th>Soflens lens presoaked in 0.1 per cent fluorescein</th>
<th>Topical 0.01 per cent fluorescein</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>—</td>
<td>97(7)†</td>
<td>55(6)†</td>
<td>9(7)†</td>
</tr>
<tr>
<td>3.5</td>
<td>628(7)†</td>
<td>81(7)†</td>
<td>158(6)†</td>
<td>15(10)†</td>
</tr>
</tbody>
</table>

*All values are × 10^{-5} mg. per milliliter.
†Number of animals in parentheses.

Table II. Fluorescein concentration in aqueous humor of rabbits with presoaked hydrophilic lenses

<table>
<thead>
<tr>
<th>Time (hr.)</th>
<th>Bionite lens presoaked in 0.1 per cent fluorescein</th>
<th>Bionite lens presoaked in 0.01 per cent fluorescein</th>
<th>Soflens lens presoaked in 0.1 per cent fluorescein</th>
<th>Topical 0.01 per cent fluorescein</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>—</td>
<td>45 (7)†</td>
<td>69 (6)†</td>
<td>11 (7)†</td>
</tr>
<tr>
<td>3.5</td>
<td>475 (7)†</td>
<td>53 (7)†</td>
<td>178 (6)†</td>
<td>18 (10)†</td>
</tr>
</tbody>
</table>

*All values are × 10^{-5} mg. per milliliter.
†Number of animals in parentheses.

corneal and aqueous humor fluorescein concentrations were determined at 1\(\frac{1}{2}\) and 3\(\frac{1}{2}\) hours after the lenses were inserted. The corneal and aqueous humor concentrations of fluorescein at 1\(\frac{1}{2}\) and 3\(\frac{1}{2}\) hours are shown in Tables I and II. The ocular concentrations attained with the presoaked Bionite lenses are 4 times higher than that attained with frequent drops. Increasing the concentration of the soaking solution 10-fold results in an 800 per cent increase in the ocular concentrations. Furthermore, it takes much less fluorescein to get the same ocular concentration if the fluorescein is permeated into a lens than if it is instilled topically.

Inserting Soflens lenses that had been presoaked in 0.1 per cent fluorescein also increased the ocular concentration of fluorescein compared to frequent drops. However the concentrations attained with the Bionite lenses were 3 to 4 times that attained with the Soflens lenses.

A young woman who had worn both conventional and hydrophilic lenses without difficulty was studied. On the first day she wore a Bionite lens in one eye and no lens in the other. A single drop of sterile

Table III. Effect of different types of corneal contact lenses on corneal fluorescein concentration following topical administration

<table>
<thead>
<tr>
<th>Time (hr.)</th>
<th>Bionite lens</th>
<th>Soflens lens</th>
<th>Methyl methacrylate lens</th>
<th>No lens</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>14</td>
<td>6</td>
<td>4.5</td>
<td>9</td>
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<tr>
<td>4</td>
<td>81</td>
<td>17</td>
<td>14</td>
<td>13</td>
</tr>
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<td>6</td>
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<td>25</td>
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</tr>
<tr>
<td>24</td>
<td>230</td>
<td>—</td>
<td>—</td>
<td>11</td>
</tr>
</tbody>
</table>

*Corneal fluorescein concentration (× 10^{-5} mg. per milliliter).

Table IV. Effect of different types of corneal contact lenses on aqueous humor fluorescein concentration following topical administration

<table>
<thead>
<tr>
<th>Time (hr.)</th>
<th>Bionite lens</th>
<th>Soflens lens</th>
<th>Methyl methacrylate lens</th>
<th>No lens</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>17</td>
<td>6</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>115</td>
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<td>19</td>
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<td>6</td>
<td>235</td>
<td>27</td>
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<td>28</td>
</tr>
<tr>
<td>24</td>
<td>184</td>
<td>—</td>
<td>—</td>
<td>14</td>
</tr>
</tbody>
</table>

*Aqueous fluorescein concentration (× 10^{-5} mg. per milliliter).*
2 per cent fluorescein was applied to each eye at 0, 2, 4, 6, and 11 hours. The corneal and anterior chamber concentrations were measured at 2, 4, 6, and 24 hours; each time the lens was removed 10 minutes prior to measurement. One week later the subject wore a Soflens in one eye and a methyl methacrylate conventional hard lens in the other. Drops were applied at 0, 2, and 4 hours and measurements made at 0, 2, 4, and 6 hours at which time the Soflens was removed. The corneal and anterior chamber concentrations of fluorescein are shown in Tables III and IV. Slit lamp examination revealed an intact corneal epithelium at all times during the studies with the various lenses in place. It was apparent that the Bionite lens had taken up much more fluorescein than the Soflens lens although this was not quantitated.

The corneal and anterior chamber concentrations were higher with the Bionite lens than with the other type of lenses. There was essentially no difference between using no lens, standard methacrylate lens, or the Soflens. At the end of 6 hours the corneal and anterior chamber concentrations of fluorescein in the eye with the Bionite lens were 6 to 8 times that attained with any other mode of treatment. Furthermore, the Bionite lens was able to maintain the fluorescein concentration in the ocular tissues for 24 hours despite the known rapid exit of fluorescein from the eye. It should be noted that the lens had not been pre-soaked in fluorescein prior to insertion.

It is interesting to note how little of the applied drug actually gets into the ocular tissues following topical application in a patient. After 3 drops of 2 per cent fluorescein 2 hours apart, the maximal attained corneal concentration of fluorescein was less than 0.0001 that of the applied solution. Further studies are under way to explore possible ways to increase this ratio.

By presoaking the Bionite lenses prior to instillation, a very high fluorescein concentration could be attained in the anterior segment of a rabbit’s eye. A 4-fold increase in drug concentration was attained with the presoaked lenses in place compared to topical drops every half hour using the same concentration of fluorescein.

Increasing the concentration of fluorescein in the soaking solution correspondingly increased the anterior segment concentration. Since a rabbit blinks very slowly, medication placed in the cul-de-sac tends to remain there for a long time. Therefore, it is to be expected that the advantage to be gained by using these lenses in patients would be greater than those in the test animals.

Bionite lenses result in higher anterior segment concentrations than Soflens lenses as they take up and release fluorescein more rapidly. In the human experiments there was no difference in corneal or aqueous humor fluorescein concentrations when a Soflens was in place as opposed to wearing no lens. Furthermore, a well-fitting hard contact lens did not increase the penetration of fluorescein into the cornea. This is in agreement with the findings of Maurice. By contrast, the use of a Bionite lens increased the concentration of fluorescein in the anterior segment 7-fold. This was with a lens that had not been previously pretreated with fluorescein. This Bionite lens was then left in place overnight and was able to maintain the fluorescein concentration in the cornea and aqueous at the level that had been attained the previous day. This was without any additional
medication and suggests that these lenses could obviate the need for frequent topical medication.

REFERENCES