


Twelve commercial artificial tear solutions and a newly developed one were evaluated as to their effect on tear film break-up time (BUT) in ten normal subjects. Instillation of one drop of these solutions altered the BUT in such a way that serial BUT measurements could be used as an index of retention time. Results demonstrated significantly longer retention time for three related products (Adopt, Adaptec, and Adsortear) and a newly developed product (Alcon 0413) [Tears Naturale (Alcon T*)]. This method appears to be an accurate noninjurious way of assessing retention time of tear substitute/vehicles and demonstrates values much longer than previously reported by other methods.

Artificial tear solutions are used as replacement therapy in dry eye states; virtually identical formulations form the vehicles for the delivery of locally instilled medications to the eye. These solutions contain water-soluble polymers incorporated with the intent of prolonging retention in the conjunctival sac. In practice, however, their efficacy is limited by their short duration. Studies attempting to assess their stay in the conjunctival sac (retention time, contact time) have employed visible markers, e.g., argyrol, nickel chloride, and have shown retention times of about 3 to 10 minutes; alternatively, excretion of instilled solutions through the nasolacrinial duct has been measured. Other studies have measured intraocular penetration of dyes and uptake of radioactive substances, but are only an indirect indication of relative efficacy of different solutions in facilitating incorporation of substances into the cornea.

If normal blinking is prevented, the precorneal tear film will break up, i.e., develop random dry spots. The interval between the last complete blink and the appearance of the first dry spot—breakup time (BUT)—has been found to be abnormally rapid in dry eye states. This is a reflection of decreased tear film stability. As part of a larger study of BUT in normal subjects, it was noted that after instillation of an artificial

<table>
<thead>
<tr>
<th>Prednisolone phosphate</th>
<th>Dexamethasone alcohol 0.1% solution</th>
<th>Dexamethasone phosphate suspension</th>
<th>Dexamethasone phosphate 0.1% solution</th>
</tr>
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<tbody>
<tr>
<td>18.2 ± 7.1</td>
<td>20.9 ± 3.8</td>
<td>3.8 ± 2.21</td>
<td></td>
</tr>
<tr>
<td>33.1 ± 7.2</td>
<td>30.0 ± 6.1</td>
<td>14.1 ± 4.1</td>
<td></td>
</tr>
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<td>46.6 ± 8.1</td>
<td>41.8 ± 7.1</td>
<td>22.4 ± 6.1</td>
<td></td>
</tr>
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</table>

expressed as percent difference from the mean of 12 untreated treatment protocol (p < 0.05).
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Key words: cornea, cornal inflammation, corticosteroid, steroid, prednisolone, dexamethasone, polymorphonuclear leukocytes, cornea.

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Fig. 1. This graph illustrates the magnitude of the effect of the solutions on the BUT.

tear solution, a subject's BUT was altered over a period of time. Since this might provide a convenient nonirritative marker for duration of tear substitutes in the conjunctival sac, this study was undertaken.

Methods. Twelve subjects with no evidence of ocular disease and with normal BUT, between 15 and 25 seconds, were chosen for this study. Twelve commercially available artificial tear solutions were studied; in addition, a new tear substitute developed in our laboratory with the cooperation of Alcon Laboratories was studied. These solutions were studied in a randomized order and in a double-blind fashion. All studies were carried out in a room monitored for temperature and humidity and with no discernible air currents. Baseline BUT values were measured at each visit; one 50 μl drop of artificial tear was instilled in an eye and BUT was determined at 5, 10, 15, and at approximately 15 minute intervals thereafter until three successive measurements returned to baseline values. Return to baseline values was interpreted as meaning the solution was no longer present in significant quantity. BUT measurements were performed without anesthesia or holding the eye lids as previously described.7 No more than one solution was instilled on any single day.

Statistical methods. The maximum time of duration (length of time an observable effect on the BUT was noted) was defined as the time until the last BUT value was greater than the baseline BUT (if the BUT was greater than baseline) or until the last BUT value was less than baseline BUT (if the observable effect was to decrease BUT). This duration time was analyzed to determine if there were any significant differences due to vehicle used, sex, age, or baseline BUT. The observations for each eye were analyzed separately.

Left eye. There was a significant difference (p < 0.01) due to vehicle but no significant differences due to sex or age. Since there was a significant difference due to the instilling baseline BUT, the means for vehicles were adjusted for these initial differences.

Right eye. There was a significant difference (p < 0.01) due to vehicle but neither the sex, age, nor baseline values differed significantly.

Results. Two quantitative measurements could be determined. The first of these was the magnitude of the effect of the solution on BUT. Fig. 1 shows the average change from baseline BUT noted after instillation of solution. All solutions significantly lengthened BUT with the exception of one. A lengthened BUT is interpreted as a reflection of enhanced tear film stability.

The second measurement was that of duration of effect noted. Fig. 2 shows this in graphic form. Interestingly, BUT values were altered after
instillation of solution and remained altered for a given time, reverting to baseline values without an intermediate period permitting accurate assessment of duration. In general, two groupings of duration are discernible: those formulations employing cellulose ethers or polyvinyl alcohol tended to last about 35 to 60 minutes. The formulations employing BP polymer and the newly developed tear substitute (Alcon 0413) were noted to last about 90 minutes.

**Discussion.** Attempts to measure duration of tear substitute/vehicles have been hampered by the difficulty in finding a suitable way of marking and measuring the solution without inducing reflex tearing. While currently available tear substitutes are limited by their short retention time, clinical experience suggests they last much longer than the few minutes reported in previous studies.

The rationale for using polymers in solutions has been one primarily of increasing viscosity. Recent studies show that viscosity seems to have little effect on retention time; it has been stated that the rate of tear secretion is the primary determinant. If this is true, then solutions should show longer retention time in dry eyes than in normal eyes.

An alternative approach in the development of tear substitutes would lie the use of water-soluble macromolecular compounds with an adsorptive affinity for the ocular surface. In this way an effective stitching action could be effected, promoting retention. Such an approach was used in developing the new tear substitutes tested here (Alcon 0413), using methods described elsewhere. Evidence has been presented showing that the solutions containing BP polymer (Adapt, Adapette, and Adsorbotear) display some absorptive properties. These solutions, therefore, might be expected to show longer retention times.

The instillation of a drop of solution into the tear system results, however, in a complex series of interactions involving tear mucin, lipid, and inorganic salts with the constituents of the instilled solution. It is interesting that all but one solution resulted in prolonging BUT, indicating an enhancement of tear film stability. The one solution (Tearsol) that decreased BUT employs hydroxypropylmethyl cellulose as do a number of other solutions. Complete formulations, however, are complex mixtures of polymers, preservatives, and salts. Laboratory experience has demonstrated that seemingly small changes in inorganic salts can profoundly influence polymer behavior. Therefore, adverse effects on tear film stability might be the result of formulation differences in salt content.

It has also been suggested that drop size is an important determinant of retention time; in this connection, all drops were of the same size to eliminate a possible source of error.

An interesting finding in this study concerns the baseline BUT values. Because of the study design we were able to determine serial BUT's in a given subject over a several week period. Results indicate that this value is remarkably constant in an individual. Table 1 shows the mean BUT determined for each of the 12 participating subjects with standard deviations.
Table 1. Serial baseline BUTs on ten subjects taken on twelve different days. The mean BUTs are listed with one standard deviation (S.D.).

<table>
<thead>
<tr>
<th>Subject ID number</th>
<th>OD Mean BUT</th>
<th>S.D.</th>
<th>OS Mean BUT</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>23.66</td>
<td>±4</td>
<td>22.16</td>
<td>±3</td>
</tr>
<tr>
<td>02</td>
<td>17.83</td>
<td>±3</td>
<td>20.16</td>
<td>±5</td>
</tr>
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<td>03</td>
<td>27.50</td>
<td>±5</td>
<td>28.00</td>
<td>±6</td>
</tr>
<tr>
<td>04</td>
<td>24.91</td>
<td>±6</td>
<td>25.66</td>
<td>±8</td>
</tr>
<tr>
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<td>23.00</td>
<td>±5</td>
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<td>29.16</td>
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<td>29.58</td>
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</tr>
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<td>09</td>
<td>25.00</td>
<td>±3</td>
<td>23.33</td>
<td>±3</td>
</tr>
<tr>
<td>10</td>
<td>25.85</td>
<td>±7</td>
<td>28.50</td>
<td>±8</td>
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</table>

The results of the study indicate that the instillation of a drop of an artificial tear solution into the conjunctival sac affects the BUT in such a way that a definite, reproducible alteration in BUT occurs over a certain period of time. While the mechanism by which this change is effected is unknown, the measurement of serial BUTs after instillation of a tear substitute seems to provide an efficient convenient nonirritative method of assessing retention time. This assumes that the observable effects of the solution or the BUT are an indication of the remaining presence in the conjunctival sac. Values reported are much longer than those reported with previous methods and are consistent with clinical experience. This method seems to be sufficiently discriminatory to define significant differences in duration and to indicate efficacy (positive effect on tear film stability) between different tear substitutes. The results demonstrate greater retention times for four products: these results are consistent with laboratory data suggesting greater absorptive properties for their constituents. It would seem that this method offers an excellent means of assessing new tear substitute/vehicle solutions.

From the Georgetown University Medical Center, Washington, D. C. This study was supported in part by United States Public Health Service Grants 5RO1 EY00988-02, and a grant from Alcon Laboratories, Inc. Submitted for publication Oct. 1, 1974. Reprint requests: Dr. M. A. Lemp, Director, Cornea Service Georgetown University Medical Center, 3800 Reservoir Rd., N.W., Washington, D. C. 20007.

Key words: tear film break up time, retention time, tear substitutes, ophthalmic polymers.

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