The Minimum Precorneal Oxygen Tension to Avoid Corneal Edema

Brien A. Holden,* Deborah F. Sweeney,* and Gordon Sanderson†

One eye of each of eight subjects was exposed to gases containing oxygen concentrations of 1.0%, 2.5%, 4.9%, 7.5%, 10.1%, and 21.4% (oxygen partial pressures ranging from 8 to 158 mmHg) for 8 hr. The precorneal oxygen concentration required to avoid corneal edema for the group as a whole was 10.1% (an oxygen tension of 74 mmHg). There was considerable individual variation both in the corneal swelling response with each of the various oxygen concentrations and in the atmospheric oxygen concentration required to avoid edema: one subject required 7.5%, four subjects required 10.1%, and three subjects required 21.4% oxygen concentration. The results of this study suggest that the cornea requires higher levels of atmospheric oxygen than previously considered necessary for normal function. Invest Ophthalmol Vis Sci 25:476–480, 1984

Since Smelser and Ozanics discovered that atmospheric oxygen was necessary to maintain a normal level of corneal hydration, several attempts have been made to determine the minimum oxygen tension required to avoid corneal edema. This allowed us to derive a more precise estimate of the minimum oxygen tension required to avoid corneal edema.

Polse and Mandell in 1970, found that an oxygen partial pressure of 11 to 19 mmHg (oxygen concentration of 1.5 to 2.5%) was required to prevent swelling of the cornea. However, their conclusion was based on results from three subjects exposed to a narrow range of hypoxic conditions (0 to 2.5%) for 3.5 hr. A study by Carney of four eyes exposed to 2% oxygen for 2 hr supported the Polse-Mandell criterion.

Mandell and Farrell in 1980 used gases with oxygen partial pressures of 6.9, 17.1, and 20.2 mmHg (oxygen concentrations of 0.95%, 2.34%, and 2.77%, respectively) to try to determine the minimum oxygen level to avoid edema. Because most of their 28 subjects were available for measurements with only one gas mixture, their results for each gas mixture were obtained on different populations. Another problem experienced by Mandell and Farrell was that they had to extrapolate beyond their data to predict the minimum oxygen tension, as they obtained statistically significant swelling with all three gas mixtures. Nevertheless, using 4-hr exposure to the various gases, they concluded that the minimum oxygen tension needed to avoid edema lay between 23 and 37 mmHg (3.3 to 5.5%).

We were concerned about two aspects of previous studies: first, the short exposure periods used in these experiments; and second, the limited range of oxygen concentrations used. Indeed, the longest exposure used in any published study was 4 hr and the highest oxygen partial pressure was 20.2 mmHg (2.77%).

In the present study, we examined the nature of the relationship between corneal swelling and precorneal oxygen tension by monitoring corneal thickness, while one eye of each subject was exposed for 8 hr to gases with oxygen concentrations of approximately 1%, 2.5%, 5%, 7.5%, 10%, and 21%. This allowed us to derive a more precise estimate of the minimum oxygen tension required to avoid corneal edema.

Materials and Methods. Subjects: Eight subjects (five women and 3 men, ranging in age from 18 to 21 years), from whom informed consent had been obtained, were used in the study. All subjects were free from any ocular disease and were not contact lens wearers.

Materials: Gases of six different concentrations of oxygen (balance nitrogen) were used: 1.0%, 2.5%, 4.9%, 7.5%, 10.1%, and 21.4%. The gases were medical quality and certified by the supplying company (CIG Australia) to a tolerance of ±0.1%.
Goggle System: Swimming goggles were fitted with optical quality glass faces to permit corneal thickness measurements to be made with the goggles in situ. They were equipped with inlet and outlet tubes to circulate the gases in front of the cornea.

The dry gas was humidified by bubbling through water before entering the goggle. The temperature inside the goggle was monitored using a Jenco electronic thermometer. The mean temperature recorded during the various trials was 30.7 ± 0.5°C. The humidity inside the goggle averaged 71%. The gas flow rate was kept constant at 1.0 litres/min. The oxygen tensions of the ingoing and outgoing gases were checked in each experiment using a Radiometer PHM73 (Radiometer; Copenhagen, Denmark) meter and E5047 oxygen sensor to verify the levels received by the eye. Positive gas flow was checked by observing bubbling from the outlet tube into a water bath.

When dry gas is humidified, the addition of water vapour reduces the oxygen concentration and consequently the oxygen tension. Oxygen tension \((pO_2)\) can be calculated (in mmHg) from the following equation:

\[
pO_2 = O_2 \times (760 - pH_2O)
\]

where \(O_2\) is the volume fraction of oxygen in the original dry gas mixture (eg, air is 0.209) and \(pH_2O\) is vapour pressure of water at room temperature 25°C (24 mmHg).\(^6\)

Pachometry: A Payor-Holden micropachometer, described elsewhere,\(^7\) was used to assess corneal thickness. It consists of a Haag-Streit pachometer (Optometric Vision Research Foundation; Sydney, Australia) that is fitted with a precision potentiometer to monitor electronically the position of the rotatable pachometer plate to an accuracy of 3 min of arc. The pachometer is mounted on a Rodenstock 2000 Biomicroscope and interfaced with an Apple II minicomputer that is used to store readings and automatically calculate corneal thickness changes for each subject. Differences from conventional pachometers include increased magnification (×32), higher light intensity (600,000 lux), and a wider angle between observation and illumination systems (65°) to increase the apparent width of the corneal section. The repeatability of 15 measurements of central corneal thickness using this instrument is ±4 μm (±0.8%).

Procedure: The subjects' facial characteristics were moulded with silastic so that they could be fitted with sealed goggles.

Central corneal thickness was measured both before and immediately after the goggles were placed on the subject, and after 1, 2, 4, 6, and 8 hr of gas flow. Fifteen measurements of central corneal thickness were recorded on each occasion.

The subjects were required to be awake at least 2 hr prior to any trial to allow the corneal thickness to stabilize after sleep.\(^8\) Three days were allowed for the cornea to recover from each trial. Baseline thickness readings were checked on each occasion to ensure that recovery had occurred.

Results. Figure 1 depicts the variation of group mean corneal edema with different levels of hypoxia over time. Table 1 records the percentage corneal swelling after 8-hr exposure to the various oxygen partial pres-
Table 1. Corneal swelling (%) after eight hours

<table>
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<th>PO2 (mmHg)</th>
<th>7.1</th>
<th>18.0</th>
<th>35.6</th>
<th>55.0</th>
<th>74.1</th>
<th>157.5</th>
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<td>% oxygen</td>
<td>1.0</td>
<td>2.5</td>
<td>4.9</td>
<td>7.5</td>
<td>10.1</td>
<td>21.4</td>
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<th>3</th>
<th>4</th>
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<th>8</th>
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<td>2.1</td>
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<tr>
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<tr>
<td>2</td>
<td>4.4</td>
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<td>3</td>
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<tr>
<td>Mean</td>
<td>1.8</td>
<td>1.4</td>
<td>0.7</td>
<td>0.8</td>
<td>1.3</td>
<td>1.1</td>
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<tr>
<td>SD</td>
<td>5.34†</td>
<td>7.98†</td>
<td>3.04†</td>
<td>0.63</td>
<td>0.73</td>
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* Using Student's two-tailed t-test, significant at † P < 0.001; ‡ P < 0.01.

The nature of the relationship between group mean edema and level of hypoxia is examined in Figure 2. The empirical relationship derived from a least squares fit of the data was as follows:

\[ S = \{5.53 \exp(-0.16 \times O_2)\} - 0.50 \]

where \( S \) is the percentage corneal swelling response and \( O_2 \) is the oxygen concentration (%) to which the eye is exposed. This equation predicts the corneal edema response to within ±0.74% (\( P < 0.05 \)).

Figure 3 shows the range in corneal swelling for the eight individuals over time for the 1.0% oxygen concentration.

**Discussion. The Level and Time Course of Hypoxic Edema:** The level of corneal swelling was dependent on both the environmental oxygen concentration and the time of exposure to that concentration.

With oxygen concentrations of 1.0% and 2.5%, edema peaked, on average, after 6 hr and then fell slightly. With concentrations of 4.9% and 7.5%, the mean edema response reached a plateau after 2 hr. With oxygen concentrations of 10.1% and 21.4% the cornea, on average, showed small transient increases in thickness, returning to baseline after 4 hr exposure (Fig. 1).

Plateauing of response indicates that a new steady state has been reached, perhaps in the rates of production and efflux of lactic acid. As can be seen from the results with 21.4% oxygen, it is quite likely that the experimental procedure itself, i.e., gas flow in goggles, induced a small transient change in corneal thickness, probably as a result of changes in precorneal tear toxicity and/or temperature. For this reason, it would be difficult with a study limited to 4 hr or less to obtain an accurate estimate of the minimum oxygen tension needed to avoid edema.
Fig. 3. Corneal swelling versus time for 1.0% oxygen for the individual subjects. The results for the individual subjects are shown as filled circles. The group mean corneal swelling responses (filled squares) and the individual swelling responses of subjects 1 and 4 with time have been delineated.

From the mean data for the eight subjects, the minimum oxygen tension to prevent corneal swelling was assessed as being 74 mmHg (10.1%). This critical oxygen tension is considerably higher than that calculated by Mandell and Farrell. There was very good agreement in the levels of edema reported by Mandell and Farrell and those recorded in this study, when using comparable oxygen tensions and exposure times. For example, with 4 hr exposure to 1% oxygen, we found a mean edema response of 4.7%, they reported 5.1%; with 4 hr of approximately 2.5% oxygen, we found 2.4% edema, they recorded 2.1%. However, it is clear from our data that higher levels of oxygen than those used by Mandell and Farrell, eg, 4.9% and 7.5%, also produce small but significant amounts of edema. It appears that the reduction in edema with higher levels of atmospheric oxygen is gradual, following an exponential course (Fig. 2).

The exponential nature of the relationship between edema and the level of hypoxia (Fig. 2) derived from using a wider range of oxygen levels, explains the difference between our findings and those of earlier studies.

Individual Variation in the Response to Hypoxia: In our data, there was considerable individual variation both in the edema resulting from exposure to the same oxygen concentration and in the oxygen level needed to avoid edema. For example, Figure 3 demonstrates the range of edema responses for the subjects over 8 hr exposure to 1% oxygen. It can be seen, for instance, that subject 4 showed consistently higher corneal swelling and subject 1 consistently lower corneal swelling than the group mean response (Student's two-tailed t-test, \( P < 0.05 \)). This finding goes some way towards explaining the clinical observation that individuals fitted with identical contact lenses, which provide the same level of oxygen, are found to have large variations in the corneal swelling response with those lenses.

As evidenced in Table 1, there was also variation in the minimum oxygen level to avoid edema. One of the eight subjects showed no significant edema (0.1%) after 8 hr of 7.5% oxygen, while three subjects showed significant corneal swelling with 10.1% oxygen.

Avoiding Contact Lens-induced Corneal Edema: This study shows that a relatively high level of atmospheric oxygen availability was needed to avoid measurable amounts of edema for all subjects. Reducing the oxygen level below 10% does not, on average, allow the cornea to maintain normal thickness. It may be that over a longer period of time than that used in this study, the cornea may be able to adapt to reductions in oxygen availability. It may also be that the cornea can tolerate small amounts of edema without detriment to its structure or function. Ideally, such adjustments should not be necessary, and hypoxia should be avoided. These considerations are of particular importance in the design of contact lenses, especially those intended for extended wear.

Assuming that hypoxia is the only etiologic factor in contact lens-induced edema, the oxygen level beneath a contact lens needs to be maintained at 74 mmHg (10.1%) to avoid any edema in the majority of the contact lens-wearing population. That this level is two to three times greater than previous estimates.
of the minimum oxygen level needed to avoid edema may explain why even the present generation of highly oxygen-permeable lenses still induce significant corneal edema. Key words: cornea, minimum oxygen tension, edema, individual variation, contact lenses

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References

Human InterferonαA or αD and Trifluridine Treatment for Herpetic Keratitis in Rabbits

Melvin D. Trousdale and Anthony B. Nesburn

Recombinant human interferon (IFN) αA and αD combined with 1% trifluridine ophthalmic solution gave beneficial results when applied topically at a dose of 1 × 10^6 U per eye four times a day commencing 4 hr after eyes were inoculated with herpes simplex virus (HSV-1). Acute herpetic keratitis was suppressed by trifluridine alone and the combined therapies, but the high-titered interferon preparations, alone, had little effect. Duration of HSV-1 shedding into tear film during topical treatment for acute herpetic keratitis was reduced slightly by combined therapy with either IFNαA or IFNαD with trifluridine. Invest Ophthalmol Vis Sci 25:480–483, 1984

Three antigenically distinct classes of interferons (IFN) have been described in humans. The new nomenclature, on the basis of antigen specificities, is alpha (α), beta (β) and gamma (γ); these designations correspond to previous designations of leukocyte (Le), fibroblast (F) and type II (immune) IFN, respectively. At least 8 to 10 IFNα gene products from human leukocytes have been identified and are designated with letters A, B, C, D (ie, IFNαA). Recent advances in genetic engineering technology have resulted in the availability of large quantities of recombinant IFN of very high potency. Smolin et al reported that topical treatment of herpetic keratitis with cloned IFN A was effective in suppressing epithelial damage. This report describes the topical use of purified, high-titered, recombinant-derived human IFNα preparations of both IFNαA and IFNαD for treatment of acute herpetic keratitis in rabbits. Each was employed alone and in combination with Viroptic, 1% Trifluridine (TFT), ophthalmic solution.

Materials and Methods. Ocular Infection: New Zealand white male rabbits, weighing 3 to 4 kg, conforming to the ARVO Resolution on the Use of Animals in Research were used for all experiments. Both eyes of all rabbits were examined with a slit-lamp biomicroscope to confirm the absence of any external pathology prior to inoculation with HSV-1 (McKrae strain, 10^6 PFU/eye).

Antiviral Treatment: Lyophilized recombinant IFNαA and recombinant IFNαD were reconstituted