Ocular Delivery Of Ketotifen Fumarate By Silicone Hydrogel And Conventional Hydrogel Contact Lens Materials - #6101

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Introduction

• Allergic conjunctivitis (AC) is a mast cell-mediated hypersensitivity reaction to airborne allergens which affects up to 40% of the general population.

• Ketotifen fumarate is an H1 receptor antagonist and mast cell stabilizer that is widely used in eye drop formulations to alleviate the signs and symptoms of AC.

• Unfortunately, eye drops have a number of disadvantages as a drug delivery system which decrease their effectiveness and efficiency, with the principle problem being patient compliance.

• Ideally, an effective drug delivery system must be easy for patients to use, be non-invasive and comfortable, while also providing an effective dose of medication to the target tissues for an appropriate amount of time.

Purpose

The purpose of this study was to examine the uptake and release characteristics of ketotifen from a number of commercially available daily wear, silicone hydrogel and conventional hydrogel contact lenses, and evaluate their potential as ketotifen ocular delivery devices.

Methods

Lenses

Our survey of commercially available contact lenses included 3 conventional lenses (stallafon A, polymacon, alphafilon A), 4 daily disposables (nefilcon A, omaticlon A, etafilcon A, ocufilcon B) and 5 silicone hydrogels (lotrafilcon B, balafilcon A, comfilcon A, galyfilcon A, senofilcon A). The two new silicone hydrogel daily wear lenses (narafilcon A and room II 3) were also tested. All lenses had a back vertex power of -3.00 diopters.

Ketotifen Uptake

For each uptake experiment, 4 lenses of each lens type were placed into autoclaved amber vials containing 6 ml of 0.25 mg/ml ketotifen doping solution. For the duration of the uptake phase the lenses were placed in a shaking water bath set to 34°C. Measurements were then taken over the next 24 hours. At each time point 30μl was taken from the doping solution and diluted 10 times with Unisol4 so its measured UV absorbance would fall within the linear range of the standard curve.

Ketotifen Release

After 24 hours of uptake, lenses were removed and dipped briefly in Unisol4 to remove excess doping solution and then placed into new amber vials containing 6 ml of Unisol4. The vials were again placed in a 34°C shaking water bath, and the concentration analysis monitored over the course of 24 hours.

Varying the Doping Concentration

For the ocularisation B contact lens (Biomedia 1 day), 2 additional ketotifen uptake and release experiments were performed using the same procedure described above except the doping solution was changed to 0.05 mg/ml (1/5X concentration) and 1.25 mg/ml (5X) concentration.

Data Analysis

All data is reported as mean ± standard deviation. The uptake and release results were analyzed using a repeated measures ANOVA, with time as a within measurement factor and lens type as a between measurement factor. Post-hoc Tukey tests were performed as needed. A measured concentration was considered significant with P values below 0.05.

Results

Figure 1a: Cumulative uptake of ketotifen fumarate over the 24 hour uptake period for commercially available conventional lenses: (•) etafilcon A (Acuvue2), (○) alphafilon A and (△) polymacon. Values plotted are means ± standard deviations.

Figure 1b: Cumulative uptake of ketotifen fumarate over the 24 hour uptake period for commercially available silicone hydrogel lenses: (△) balafilcon A, (△) lotrafilcon B, (○) galyfilcon A, (△) senofilcon A and (△) comfilcon A. Values plotted are means ± standard deviations.

Table 1: Total ketotifen uptake and release after 24 hours.

<table>
<thead>
<tr>
<th>Lens Type</th>
<th>Total Uptake after 24 hours (μg)</th>
<th>Total Release after 24 hours (μg)</th>
<th>Percentage of loaded ketotifen released</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stallafon A</td>
<td>83.74 (± 5.14)</td>
<td>10.9 (± 2.4)</td>
<td>13%</td>
</tr>
<tr>
<td>Polymacon</td>
<td>502.94 (± 83.74)</td>
<td>59.2 (± 8.15)</td>
<td>12%</td>
</tr>
<tr>
<td>Alphafilon A</td>
<td>1159.5 (± 115.9)</td>
<td>106.44 (± 57.43)</td>
<td>9%</td>
</tr>
</tbody>
</table>

Figure 2a: Cumulative release of ketotifen fumarate over the 24 hour release period for commercially available conventional lenses: (•) etafilcon A (1 Day Moist), (○) polymacon and (△) nfaciton A and (△) nemificon A. Values plotted are means ± standard deviations.

Figure 2b: Cumulative release of ketotifen fumarate over the 24 hour release period for commercially available silicone hydrogel lenses: (△) balafilcon A, (△) lotrafilcon B, (○) galyfilcon A, (△) senofilcon A and (△) comfilcon A. Values plotted are means ± standard deviations.

Table 2: Total uptake and release of ketotifen (μg) from ocufilcon B contact lenses when the concentration of the doping solution was varied.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Concentration of doping solution (mg/ml)</th>
<th>Uptake (μg)</th>
<th>Release (μg)</th>
<th>Percentage of loaded ketotifen released</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>0.05</td>
<td>263.17 ± 13.82</td>
<td>47.5 ± 2.4</td>
<td>18%</td>
</tr>
<tr>
<td>24</td>
<td>0.50</td>
<td>263.17 ± 13.82</td>
<td>47.5 ± 2.4</td>
<td>18%</td>
</tr>
</tbody>
</table>

Discussion

• Etalafon A lenses, ocufilcon B and balafilcon A showed the greatest uptake and release of ketotifen after 24 hours.

• Varying the concentration of the doping solution does have an effect on the total ketotifen taken up and released.

• The recommended dosage schedule when using a 0.25% ketotifen opthalmic solution is 2 drops per eye per day, or 25μg of per day. All the contact lenses tested released more than this amount, which means these lenses are capable of taking up and releasing a potentially clinically significant amount of ketotifen.

• These lenses, however, release their loaded ketotifen very quickly, as is apparent in Figures 2a-c, generally reaching release plateaus after one to three hours. This limitation would seem to prevent this drug delivery system from being used with extended wear contact lenses.

• However, the method of drug loading employed in this study may be sufficient for a daily disposable wear modality.

References


Acknowledgements

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