Topical NSAIDs Effect on Corneal Sensitivity

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Purpose: Topical nonsteroidal antiinflammatory drugs (NSAIDs) are administered topically for a variety of ophthalmologic conditions. Brand diclofenac and brand ketorolac were previously shown to have topical anesthetic effects in addition to analgesic effects. Using the same method, we measured similar anesthetic effects of the 4 currently available topical NSAIDs—generic diclofenac, generic ketorolac, brand bromfenac, and brand nepafenac.

Methods: Baseline corneal sensitivity was measured on 10 healthy adult volunteers with a Cochet–Bonnet esthesiometer. One drop of the agent being studied was applied to the right eye every 5 minutes for a total of 4 drops. Corneal sensitivity was measured immediately after the last topical application and every 15 minutes for 60 minutes. After a 1-week washout period, a different agent was studied until all 4 NSAIDs were evaluated.

Results: Corneal sensitivity profiles over time were similar for all NSAIDs. Corneal sensitivity decreased significantly from baseline immediately after topical application remaining flat from 0 to 30 minutes and then rising from 45 to 60 minutes back toward baseline in all treatment groups ($P < 0.001$). The maximal absolute drop in corneal sensitivity as measured by pressure thresholds was greatest for diclofenac [28.6 mm (95% confidence intervals [CI], 19.8–37.4)], followed by ketorolac [21.1 mm (95% CI, 15.1–27.1)], bromfenac [16.9 mm (10.7–23.1)], and nepafenac [16.4 mm (95% CI, 12.7–20.1)]. Only diclofenac and nepafenac were statistically different in maximal decrease in sensitivity.

Conclusions: All 4 currently available NSAIDs demonstrated anesthetic effects similar to brand diclofenac and brand ketorolac.

Key Words: cornea, sensitivity, NSAIDs, anesthetic

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One of the key responses of the body to ocular surgery or injury is inflammation, which involves release of many inflammatory mediators including prostaglandins and cytokines. Inflammation can complicate healing and result in poor outcomes. Inflammation also enhances postoperative or postinjury pain.

Topical nonsteroidal antiinflammatory drugs (NSAIDs) have been approved for treatment of postcataract inflammation and reduction of postoperative pain.1,2 Ketorolac has also been shown to reduce or prevent cystoid macular edema after routine cataract surgery.3 Brand diclofenac and brand ketorolac were previously shown to have anesthetic effects causing immediate reduction in corneal sensitivity.2,4 The anesthetic effect may contribute to delay in wound healing or disruption of the normal epithelial surface, especially when used frequently or on compromised ocular surfaces. The anesthetic effect, however, may also contribute to the use of these agents to reduce pain during and after ocular surgery. Both brand diclofenac (0.1%) and brand ketorolac (0.5%) have essentially disappeared from the market. Instead, generic formulations are available. In addition, there are reformulated versions of the ketorolac molecule in the form of ketorolac 0.4% and nonpreserved ketorolac 0.45%. Two additional NSAIDs have also entered the market in the United States—brand nepafenac and brand bromfenac—both of which have already released new formulations. It has been implicitly assumed that these newer topical agents will mimic the same anesthetic effects as the original agents. The purpose of this study was to test whether that assumption was correct.

MATERIALS AND METHODS

Study Design

The study used the same methodology as that of the study by Seitz et al2 for comparative purposes.

Patients and Procedure

Ten healthy adults with normal ocular examinations, no history of ophthalmic disease, and no use of contact lenses volunteered to participate in the study. Informed consent and baseline demographic data were obtained. Baseline corneal sensitivity was measured using the Cochet–Bonnet esthesiometer (Luneau, France). This instrument contains nylon filaments of 0.1 mm in diameter and 60 mm in length, which can apply pressure to the subject’s cornea ranging from 11 to 200 mg/0.0113 mm depending on the length of exposed filament. Longer lengths of exposed filaments correspond to lower applied pressure.

Study subjects were examined with a slit lamp and asked to fixate their vision on a distant point. The esthesiometer filament was slowly advanced perpendicularly toward the subject’s right eye until it just touched the cornea as seen through slit-lamp examination. Determination of baseline corneal sensitivity started with the longest filament, thus the lowest pressure. If the patient could not feel the filament,
the process was repeated with progressively shorter filaments until the subject indicated feeling pressure immediately upon contact with the cornea. Reflex blinking of the eyelids was not considered as evidence that the subject felt the filament. Measurements were taken centrally and in the 4 quadrants of the cornea and averaged for each subject.

Each subject was then randomized to receive 1 of 4 topical NSAIDs: (1) generic 0.1% diclofenac sodium ophthalmic solution, (2) generic 0.5% ketorolac tromethamine ophthalmic solution, (3) brand 0.3% nepafenac ophthalmic suspension (Ilevro; Alcon, Ft. Worth, TX), and (4) brand 0.07% bromfenac ophthalmic solution (Prolensa; Bausch + Lomb, Bridgewater, NJ). A single drop of the topical agent was applied to the right eye every 5 minutes for a total of 4 drops. Immediately after the last drop, corneal sensitivity was measured and repeated at 15-minute intervals for 60 minutes.

After 1-week washout periods, the subjects were sequentially randomized to the other 3 topical agents. A different agent was administered each week until all subjects had received all 4 agents in a random order. Corneal sensitivity measurements were repeated as above. Study subjects and the investigator measuring corneal sensitivity were masked to study drug assignment.

Data Analysis

Continuous data were summarized as mean and SD or 95% confidence intervals (CI). Binary data were summarized as percentage frequency of occurrence. Comparison of corneal sensitivities (measured in millimeters of monofilament) over time was performed with repeated-measures analysis of variance. Comparison of corneal sensitivities among treatment groups at various time points was performed with analysis of variance. $P \leq 0.05$ was considered statistically significant.

RESULTS

We studied 10 subjects whose mean (SD) age was 37.0 (13.1) years (range, 25–39 years); 90% were females. None of the study subjects experienced any adverse reactions.

Corneal sensitivity profiles over time were similar for all 4 topical NSAIDs (Table 1). Corneal sensitivities dropped significantly from baseline immediately after topical application remaining flat from 0 to 30 minutes and then rising from 45 to 60 minutes back toward baseline in all treatment groups.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Diclofenac</th>
<th>Ketorolac</th>
<th>Bromfenac</th>
<th>Nepafenac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>59 (2.1)</td>
<td>57 (6.3)</td>
<td>54 (7.7)</td>
<td>57 (4.7)</td>
</tr>
<tr>
<td>0 min</td>
<td>41 (10.7)</td>
<td>41 (10.6)</td>
<td>44 (9.4)</td>
<td>42 (7.0)</td>
</tr>
<tr>
<td>15 min</td>
<td>37 (12.9)</td>
<td>41 (7.1)</td>
<td>39 (9.1)</td>
<td>41 (7.3)</td>
</tr>
<tr>
<td>30 min</td>
<td>39 (13.2)</td>
<td>40 (7.2)</td>
<td>41 (9.1)</td>
<td>43 (7.6)</td>
</tr>
<tr>
<td>45 min</td>
<td>38 (12.8)</td>
<td>43 (9.5)</td>
<td>42 (7.8)</td>
<td>8 (9.1)</td>
</tr>
<tr>
<td>60 min</td>
<td>43 (12.3)</td>
<td>49 (9.4)</td>
<td>41 (11.7)</td>
<td>54 (8.4)</td>
</tr>
<tr>
<td>Maximum change</td>
<td>29 (12.3)</td>
<td>21 (8.4)</td>
<td>17 (8.6)</td>
<td>16 (5.1)</td>
</tr>
</tbody>
</table>

DISCUSSION

Two previous studies demonstrated the anesthetic effects of brand diclofenac and brand ketorolac 0.5%, neither of which remain readily available today.2–4 Our results demonstrate that the 4 topical NSAIDs studied significantly decrease corneal sensitivities similar to the effect seen with the earlier agents. Although there were minor, yet significant, differences among the agents, this effect on corneal sensitivity seems to be a class action. The exact mechanism of action of the topical NSAIDs is unclear. Phillips et al4 suggested that the NSAIDs anesthetic mechanism of action is by inhibiting cyclooxygenase. In contrast, Szerenyi et al8 suggest that diclofenac sodium has a direct anesthetic effect on the A-delta and C fibers that innervate the cornea.

Although there were statistically significant differences among the 4 topical NSAIDs studied, it is unclear whether these differences have any clinical relevance or significance. It is unclear whether or not reduction in corneal sensitivity by topical NSAIDs is beneficial or deleterious to patients. When applied after corneal surgery, an anesthetic effect in addition to an antiinflammatory effect might be beneficial in helping to reduce pain. In contrast, some studies suggest that topical anesthesia might delay wound healing.7 Whether NSAIDs...
with anesthetic effects can affect wound-healing remains to be determined. However, a systematic review that included 5 blinded randomized placebo-controlled trials involving topical NSAIDs for corneal abrasions found no evidence that healing was delayed. Furthermore extensive work by Srinivasan also demonstrates that although NSAIDs can inhibit arrival of polymorphonuclear cells into the tear fluid after injury, they do not inhibit reepithelialization either by corneal or conjunctival epithelial cells. In addition, a decrease in corneal sensitivity may increase the likelihood of the patient inadvertently touching their eye, potentially leading to further trauma or infection.

Study Limitations

Our study has several limitations. First, the study was conducted using healthy volunteers without corneal surgery or pathology similar to the volunteers used in the original studies on brand diclofenac and brand ketorolac. Thus, it remains unclear whether the effects on corneal sensitivity would differ after surgery or injury. Second, we only evaluated short-term use of topical NSAIDs. It is possible that impaired corneal sensitivity might be more severe or prolonged after longer use. However, it is reassuring that the pattern of corneal sensitivity loss and recovery was similar to the original NSAIDs studied. Although this study did not measure long-term effects of topical NSAIDs on wound healing, it is somewhat reassuring to find that even with the longer-acting agents, the effects on corneal sensitivity seems to be short and temporary. In conclusion, all 4 topical nonsteroidal antiinflammatory agents exhibited anesthetic effects similar to those originally reported for brand diclofenac and brand ketorolac.

REFERENCES