Changes in Mechanical, Chemical, and Thermal Sensitivity of the Cornea after Topical Application of Nonsteroidal Anti-inflammatory Drugs

M. Carmen Acosta, Leticia Berenguer-Ruiz, Alberto García-Gálvez, David Perea-Tortosa, Juana Gallar, and Carlos Belmonte

PURPOSE. In addition to their well-known anti-inflammatory actions, some of the nonsteroidal anti-inflammatory drugs (NSAIDs) appear to have an analgesic effect. In human subjects, the changes in threshold and intensity of sensations evoked by mechanical, chemical, and thermal stimulation of the cornea induced by topical administration of two commercial NSAIDs, diclofenac sodium (Voltaren; Novartis, Basel, Switzerland) and flurbiprofen (Ocuflur; Allergan, Irvine, CA), were studied.

METHODS. Corneal sensitivity was measured in 10 young, healthy subjects with a gas esthesiometer. Chemical (10%–70% CO₂ in air), mechanical (0–264 mL/min), and thermal (corneal temperature changes between −4.5°C and +3°C around the normal value) stimuli were applied to the center of the cornea. The intensity and perceived magnitude of the psychophysical attributes of the evoked sensation were scored at the end of the pulse in a 10-cm, continuous visual analog scale (VAS). The threshold was expressed as the stimulus intensity that evoked a VAS score >0.5. Sensitivity was measured in both eyes of each subject on two separate days, one without treatment and the other 30 minutes after topical application of 0.03% flurbiprofen (seven subjects) or 0.1% diclofenac sodium (six subjects).

RESULTS. Diclofenac attenuated significantly all the sensation parameters evoked by high-intensity mechanical, chemical, and thermal stimuli. Flurbiprofen produced a slight reduction of the sensations evoked by mechanical and chemical stimulation that became significant only for the irritation caused by stimuli of maximum intensity (70% CO₂). None of the drugs modified significantly the detection threshold of the different stimuli.

CONCLUSIONS. Flurbiprofen had a very limited effect on sensations evoked by corneal stimulation, whereas diclofenac reduced the intensity of sensations evoked by stimuli of different modality, suggesting a mild local anesthetic effect of this drug on all types of corneal sensory fibers. Such anesthetic action could explain the analgesic effect that has been reported after topical application of diclofenac in inflamed human eyes. (Invest Ophthalmol Vis Sci. 2005;46:282–286) DOI:10.1167/iovs.04-0884

C 0nscious sensations arising from the eye surface depend on the excitation of different functional types of corneal sensory nerve fibers: mechanonociceptor, polymodal nociceptor, and cold-receptor fibers. In the human cornea, these different populations of sensory nerve afferents can be selectively stimulated using controlled mechanical, chemical, and thermal stimuli applied to the center of the cornea by means of a gas esthesiometer. Activation with this instrument of mechanon- and polymodal corneal fibers elicits sensations of irritation and pain whose intensity is proportional to the magnitude of the stimulus. In contrast, selective stimulation of cold receptor fibers with moderate temperature reductions evokes only sensations of innocuous cooling that become irritating when more intense cold is applied.

In addition to these sensations evoked by direct stimulation of the anterior segment of the eye, spontaneous pain is often observed in inflammatory processes of the ocular surface. Pain also appears as a consequence of corneal injury and inflammation caused by surgical manipulation, in particular after photorefractive surgery. Ocular pain caused by photorefractive keratectomy (PRK) usually begins shortly after surgery; becomes severe within 4 to 6 hours, and remains high during the first day, often persisting for days. Acute pain also develops 1 to 3 days after laser in situ keratomileusis (LASIK), although it is comparatively lower than with PRK. In addition, other long-lasting discomfort symptoms in patients subjected to refractive surgery appear in almost half of the patients who undergo PRK and LASIK. These include dryness, soreness of the eye to touch, sharp pain, and complaints of the eyelid’s sticking to the eyeball on waking.

Nonsteroidal anti-inflammatory drugs (NSAIDs) that have been extensively used as anti-inflammatory agents in cataract surgery are also prescribed as analgesic drugs to reduce postoperative pain after photorefractive surgery. NSAIDs are inhibitors of the cyclooxygenases (COXs) that mediate the breakdown of arachidonic acid to produce prostaglandins and other metabolic products. Arachidonic acid metabolites contribute to the local inflammatory reaction and to the sensitization and excitation of pain nerve terminals of the injured area.

Thus, the analgesic action of NSAIDs is attributable at least in part, to their inhibitory effect on arachidonic acid breakdown and consequently the excitatory-sensitizing effects of PGs on nociceptor nerve endings. However, the different NSAIDs have a variable efficacy on ocular pain. Moreover, the attenuation by NSAIDs of nerve impulse discharges evoked by chemical irritation of the cornea in anesthetized cats was more pronounced after topical diclofenac sodium and indomethacin than after flurbiprofen. Thus, it has been suggested that in addition to the reduction of nociceptor sensitization due to decreased PG production, common to all NSAIDs, some of

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them may have a direct influence on the excitability of nociceptor sensory nerve terminals.\textsuperscript{1,2}

To assess whether the reported effects of NSAIDs on the excitability of corneal sensory fibers of the cat are reflected as changes in corneal sensitivity in humans, we compared the intensity–response curves of the sensations evoked by mechanical, chemical, and thermal stimulation of the human cornea before and after topical application of diclofenac sodium (Voltaren; Novartis, Basel, Switzerland) and flurbiprofen (Ocuflur; Allergan, Irvine, CA). Part of the results have been presented in abstract form (Belmonte C, et al. IOVS 2002;43;ARVO E-Abstract 3253).

MATERIALS AND METHODS

Subjects

Ten subjects (eight males, two females; ages, 18 –21 years) participated voluntarily in this study, which adhered to the tenets of the Declaration of Helsinki. Both eyes of each subject were explored. The subjects signed informed consents and were free to withdraw from the experiment at any time. Six individuals took part in the study with diclofenac sodium and seven in the study with flurbiprofen. None of them had any ocular diseases at the time of the experiment.

Esthesiometry

Stimulation of the corneal surface was performed with a gas esthesiometer.\textsuperscript{3} The general procedure has been described elsewhere.\textsuperscript{4} Briefly, gas jets of 3 seconds’ duration, of different flow, temperature, and composition were applied to the center of the cornea, separated by 2-minute pauses. For mechanical stimulation, nine pulses of air of variable flow between 0 and 264 mL/min (0, 33, 58, 83, 110, 138, 170, 208, and 264 mL/min) and heated to +50°C at the tip of the stimulus probe (to reach the corneal surface at a neutral temperature of 33–34°C), were applied. For chemical stimulation, eight pulses of air containing variable concentrations of CO\textsubscript{2} (0%, 10%, 20%, 30%, 40%, 50%, 60%, and 70% CO\textsubscript{2}) also heated to +50°C at the probe tip and at flow values 10 mL/min below mechanical threshold were used. Thermal stimulation was obtained with 11 pulses of air at subthreshold flow rate and temperatures between −4.5°C and +85°C at the tip of the probe, that changed the basal temperature of the corneal surface (33–34°C) between −4.5°C and +3°C (−4.5°C, −3.5°C, −2°C, −1°C, 0°C, +1°C, +1.75°C, +2.5°C, and +3°C).\textsuperscript{4} In all modalities of stimulation, pulses of different magnitude were applied at random.

The tip of the esthesiometer probe was placed at a distance of 5 mm away from the corneal surface, perpendicular to the center of the cornea. Subjects were asked to blink immediately before the onset of the stimulus, which was indicated by an audible click produced by the opening of a valve inside the probe. Immediately after each pulse, the subject evaluated in six separate, 10-cm continuous horizontal visual analog scales (VASs) the intensity and some of the psychophysical attributes of the sensation experienced (the irritative, stinging, and burning components of the sensation and the warm or cool components of the sensation).\textsuperscript{4} Sensation thresholds for the intensity of the sensation were determined with the method of minimum stimulus that defines threshold as the lowest intensity of the stimulus necessary to evoke a response of ≥0.5 VAS units.\textsuperscript{3,4,13}

Corneal sensitivity to the different stimuli was explored before and 30 minutes after instillation of a drop of 0.03% flurbiprofen or 0.1% diclofenac sodium.

Data are expressed as the mean ± SEM of the VAS scores obtained in different subjects. Differences between groups for each magnitude of stimuli were compared with the paired \(t\)-test. Thresholds for each subject were compared before and after treatment, by paired \(t\)-test. The response curves obtained were fitted to a third-order regression curve on computer (SigmaPlot, ver. 8.0; SPSS Inc., Chicago, IL).

RESULTS

Effects of Diclofenac Sodium

Thirty minutes after application of 0.1% diclofenac sodium, the intensity of the sensation and the degree of irritation evoked by mechanical stimuli of increasing magnitude were significantly lower than in untreated eyes, particularly at higher stimulus magnitudes (Fig. 1). In untreated eyes, mechanical stimulation evoked only a discrete level of stinging and burning pain,
except at the strongest stimulus intensity. Nevertheless, the magnitude of both parameters appeared also to decrease after diclofenac treatment.

A reduction of the intensity and irritation aspects of the sensation was also observed with chemical stimulation with CO₂ (Fig. 2), although with this modality of stimulus, the VAS scores given to the different components of the sensation were overall lower, and differences between control and treated corneas, therefore, became significant only when the strongest stimuli were applied. Reported values for the thermal components of the sensations evoked by mechanical and chemical stimuli were negligible and are not represented.

Cold and hot stimuli evoked sensations that exhibited a definite thermal quality of innocuous cold or warmth when temperatures lower or higher than the neutral corneal temperature were applied. These sensations were reported as slightly irritating only at the lowest temperature applied in the case of cold stimuli and at the highest temperature for hot stimuli, with no parallel stinging or burning pain feelings (data not shown). Diclofenac decreased significantly the intensity of the sensation evoked by cold, whereas the reducing effect on heat-evoked sensation did not reach the significance level (Fig. 3).

Diclofenac increased slightly the threshold stimulus intensity values for mechanical, chemical, and thermal stimulation, but differences did not reach the significance level (Table 1).

### Table 1. Mean Intensity of the Sensation Thresholds

<table>
<thead>
<tr>
<th>Intensity of the Sensation Threshold</th>
<th>Control</th>
<th>Diclofenac (0.1%)</th>
<th>Control</th>
<th>Flurbiprofen (0.03%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical (mL/min)</td>
<td>91.0 ± 10.7</td>
<td>108.8 ± 16.0</td>
<td>115.9 ± 10.7</td>
<td>127.7 ± 16.6</td>
</tr>
<tr>
<td>Chemical (% of CO₂ in air)</td>
<td>17.5 ± 4.3</td>
<td>24.2 ± 4.0</td>
<td>19.3 ± 5.5</td>
<td>22.1 ± 5.4</td>
</tr>
<tr>
<td>Hot (°C)</td>
<td>+1.2 ± 0.4</td>
<td>+1.4 ± 0.3</td>
<td>+1.4 ± 0.4</td>
<td>+0.8 ± 0.2</td>
</tr>
<tr>
<td>Cold (°C)</td>
<td>−2.6 ± 0.4</td>
<td>−3.2 ± 0.4</td>
<td>−2.5 ± 0.4</td>
<td>−2.7 ± 0.4</td>
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</table>

Data for mechanical, chemical, and thermal stimulation of the cornea were collected before and 30 minutes after application of diclofenac 0.1% (n = 12) and flurbiprofen 0.03% (n = 14). Comparison of individual thresholds before and after treatment with the paired t-test indicated that differences were not significant.

**Effects of Flurbiprofen**

As shown in Figures 4, 5, and 6, flurbiprofen was less effective than diclofenac in reducing the different parameters of the sensation evoked by the three stimulus modalities. In the case of mechanical and chemical stimulation, the intensity, degree of irritation, and stinging and burning components of the evoked sensation were modestly reduced by the drug, and only when stimuli of maximum intensity were applied (Figs. 4, 5). Virtually no changes in the response evoked by thermal (cold and hot) stimuli were observed after treatment with the drug (Fig. 6). Detection thresholds for mechanical, chemical, and thermal stimuli were not significantly modified by flurbiprofen (Table 1).

**DISCUSSION**

The present results show that diclofenac sodium, applied topically to the eyes of healthy human subjects, reduced rapidly the magnitude of the sensations evoked by mechanical, chemical, and thermal stimulation of the cornea. In contrast, flurbiprofen had a much more modest effect.

Experiments performed in human subjects of different age and sex and with various ocular diseases have shown that the gas esthesiometer permits satisfactory discrimination of the differences in corneal sensitivity associated with these condi-
Corneal Sensitivity after NSAIDs

Diclofenac sodium, a drug that rapidly decreased the response of corneal polymodal fibers of the cat to chemical stimulation with CO₂, also lowered corneal sensitivity to mechanical, chemical, and cold stimulation, whereas flurbiprofen, which was much less effective in reducing corneal nerve impulse responses to acidic stimuli in the cat, had a similarly modest attenuating effect on human corneal sensitivity.

It is well established that the intensity of peripheral noxious stimuli is encoded by nociceptors as an increase in the impulse firing rate of individual fibers, as well as by a progressive recruitment of nerve fibers of increasingly higher threshold. The conscious sensation threshold is reached when a certain sensory inflow reaches the brain and the subjective intensity of the acutely evoked sensation is proportional to the magnitude of the fiber population's response. The flattening of all the stimulus–response functions elicited by diclofenac suggest that after application of the drug, the number of corneal sensory fibers activated by a given stimulus intensity and/or the firing frequency of each fiber were reduced. The effect was observed as early as 30 minutes after topical administration of the drug. Based on the reduction of all modalities of sensation, it can be speculated that diclofenac affected not only polymodal nociceptor fibers but also mechanonociceptor and cold-sensitive fibers. This unspecific action of diclofenac on all functional types of corneal nerve fibers supports the hypothesis that this drug has a direct and moderate anesthetic effect on peripheral corneal sensory afferents that is absent in flurbiprofen. This difference may explain the higher acute analgesic efficacy attributed to topical diclofenac in comparison with flurbiprofen.

In conclusion, the data reported herein provide objective proof of the analgesic action of topical diclofenac in the human cornea and suggest that the attenuation of evoked pain is the consequence of a local, direct blockade of corneal sensory nerve afferents. This appears to be independent of the analgesia that this drug may cause secondarily to its effects on inflammation and the consecutive attenuation of the excitation-sensitization of nociceptors by locally released arachidonic acid metabolites.

References


Figure 5. VAS scores for the different components of the sensation evoked by selective chemical stimulation of the cornea in control eyes and after 0.03% flurbiprofen treatment. *P < 0.05, paired t-test.

Figure 6. VAS scores for the different components of the sensation evoked by selective thermal stimulation of the cornea in control eyes and after 0.03% flurbiprofen treatment. *P < 0.05, paired t-test.

Threshold increases caused by the two NSAIDs tested were not significant. Threshold measures of pain sensitivity are limited in that they cannot be used to assess changes in pain sensitivity that may occur over a wide range of nociceptive stimulus intensities. For this reason, direct scaling methods have been developed for measurement of pain intensity and affect parameters. With this procedure, a reduction of pain intensity and affect after diclofenac application was evidenced. The lack of change in intensity threshold after diclofenac is attributable in part to the higher variability of the VAS scores when the magnitude of the sensation is low; however, it may also be caused by an accumulation of the inhibition with higher frequency nerve discharges as occur during stronger stimulation, the so-called use-dependent block characteristic of local anesthetic drugs.

In conclusion, the data reported herein provide objective proof of the analgesic action of topical diclofenac in the human cornea and suggest that the attenuation of evoked pain is the consequence of a local, direct blockade of corneal sensory nerve afferents. This appears to be independent of the analgesia that this drug may cause secondarily to its effects on inflammation and the consecutive attenuation of the excitation-sensitization of nociceptors by locally released arachidonic acid metabolites.


