Topical Diclofenac Sodium Decreases the Substance P Content of Tears

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Objective: To explore the mechanism by which diclofenac sodium eyedrops exert an adverse effect on the cornea.

Methods: In 10 healthy Japanese volunteers, 0.1% diclofenac sodium solution was instilled into one eye 3 times daily for 2 weeks. Only vehicle was applied to the other eye. Tear samples were taken before drug treatment, at 2 weeks (on the final day of treatment), and at 4 weeks. Prostaglandin E2 and substance P concentrations in tears were measured using enzyme immunoassays.

Results: After treatment for 2 weeks, concentrations of both prostaglandin E2 and substance P in tears from diclofenac sodium–treated eyes had decreased significantly, and both had returned to baseline levels by 4 weeks. No significant changes were seen in prostaglandin E2 and substance P levels in vehicle-treated eyes at any time points.

Conclusions: Diclofenac sodium eyedrops concurrently reduced concentrations of prostaglandin E2 and substance P in tears. Depletion of substance P (a pain-associated neurotransmitter) by diclofenac sodium may promote development of corneal complications.

Arch Ophthalmol. 2002;120:51-54

DICLOFENAC SODIUM is a well-established nonsteroidal anti-inflammatory drug (NSAID) that blocks the cyclooxygenase pathway of arachidonic acid metabolism.1 Diclofenac sodium eyedrops have seen frequent use in the practice of ophthalmology during the past decade. The anti-inflammatory effects of diclofenac sodium have been well evaluated in patients undergoing cataract surgery and laser trabeculoplasty.2,3 Another important use for diclofenac sodium eyedrops is to ameliorate discomfort and pain after refractive surgery.4,5 Indications for these topical agents have recently been expanded to include pain relief following traumatic corneal erosion.6,7

Although the anti-inflammatory and analgesic effects of diclofenac sodium eyedrops are well recognized, adverse effects have been a concern, especially involving the cornea. A previous clinical study in Japan reported that punctate epithelial keratopathy developed in association with the use of diclofenac sodium drops in approximately 10% of patients treated in the context of cataract surgery.8 We previously reported that topical diclofenac sodium and indomethacin, another well-known cyclooxygenase inhibitor, caused significant enlargement of corneal epithelial cells as seen by specular microscopy in patients who had undergone cataract surgery.9 Recently, the American Society of Cataract and Refractive Surgery issued the statement that corneal complications after cataract and refractive surgery may be associated with the use of topical NSAIDs.10 According to this statement, at least 200 occurrences of corneal complications (ranging from punctate superficial keratopathy to full corneal melt) have been reported in the United States. However, the mechanism by which diclofenac sodium exerts an adverse effect on the corneal epithelium is not well understood.

Several authors reported a transient decrease in corneal sensitivity when diclofenac sodium was applied topically to healthy human eyes.11,12 This effect seems to be desirable when diclofenac sodium eyedrops are used for lessening pain and discomfort in the eye. On the other hand, corneal hypesthesia from other causes such as trauma, brain surgery, or herpetic infection often results in neurotrophic keratopathy.13 Although the mechanisms of neurotrophic keratopathy are not fully understood, depletion of substance P and...
other neuropeptides may be involved.14-20 The cornea is innervated by nerve fibers originating from the trigeminal ganglion that contain several neuropeptides, including substance P and calcitonin gene–related peptide.21-23 Depletion of these neuropeptides induced by capsaicin delayed wound healing in the corneal epithelium.15 Substance P, both alone and in combination with other factors such as insulin and insulinlike growth factor 1, promotes migration16-20 and proliferation16,17 of corneal epithelial cells. Nishida et al24,25 recently reported that topical application of substance P–derived peptide combined with insulinlike growth factor 1 may be effective in treating neurotrophic keratopathy.

Several studies have shown that diclofenac sodium or other NSAIDs decreased concentrations of substance P in synovial fluids from patients with arthritis and in gastric mucosa and snots from experimental animals.26-28 Therefore, we reasoned that the analgesic actions of diclofenac sodium may involve similar depletion of substance P in ocular tissues, with a risk of development of corneal complications. In the present study, we evaluated the effect of topical diclofenac sodium on concentrations of prostaglandin E2 (PGE2) and substance P in human tears.

RESULTS

Before starting treatment, the mean concentration of PGE2 in tears was 130.8±20.4 pg/mL in eyes subsequently treated with diclofenac sodium, and 125.6±19.6 pg/mL in eyes subsequently treated with vehicle (no significant difference; Figure 1). After drug treatment for 2 weeks, concentrations of PGE2 in tears from diclofenac sodium–treated eyes decreased significantly to 69.1±15.8 pg/mL (P <.001, paired t test), returning to baseline concentrations at 2 weeks after discontinuation of treatment. No significant changes were seen in concentrations of PGE2 in tears from vehicle-treated eyes throughout the experimental period.

Concentrations of substance P in tears from diclofenac sodium–treated eyes were also significantly decreased after 2 weeks of treatment (from 278.0±58.7 pg/mL to 171.7±52.2 pg/mL; P =.002, paired t test), returning to baseline concentrations at 2 weeks following discontinuation (Figure 2). Substance P in vehicle treated eyes showed no significant changes.

The ratio of PGE2 concentration in tears before treatment to the concentration at conclusion of treatment was statistically significant.
calculated in each subject, and then correlated with the ratio for substance P concentrations (Figure 3). Pretreatment and posttreatment ratios for PGE2 correlated significantly with those for substance P \( (r=0.75, P=.01) \).

**COMMENT**

In the present study, we demonstrated that diclofenac sodium, characterized as a cyclooxygenase inhibitor, reduced the PGE2 concentration in human tears. Prostaglandin synthesis in the cornea is up-regulated in response to injury, and is blocked by topical NSAIDs. The presence of PGE2 in human tears was first reported by Gluud et al, who noted that PGE2 became increased in tears in response to cataract surgery. Half of their patients with chronic conjunctivitis exhibited high concentrations of PGE2 in tears. These observations suggest that PGE2 in tears reflects prostaglandin content in ocular tissues, especially in the anterior segment of the eye. Our finding of a diclofenac-sodium–related decrease in PGE2 in tears is consistent with these observations.

The most important result of our study is that diclofenac sodium concurrently reduced substance P concentrations in tears. Not only is the cornea innervated by nerve fibers that contain substance P, but also the conjunctiva and lacrimal gland. Therefore, the source of substance P in tears remains unclear. We recently reported that substance P concentrations in tears from patients with unilateral corneal hypesthesia were decreased compared with contralateral healthy eyes. Substance P concentrations in tears from patients with diabetic keratopathy are also lower than those of healthy controls (Masaro Ogata, MD, et al, unpublished data, 2000). It is likely that substance P concentrations in tears reflect the neuropeptides levels in ocular tissues, although further studies should be done to determine the source of substance P in tears.

Diclofenac sodium reportedly reduced substance P concentrations in synovial fluid from patients with rheumatoid arthritis, and also in the murine snout. Indomethacin reduced substance P concentrations in the rat gastric mucosa. Taken together with past observations, our present findings suggest that NSAIDs decrease amounts of prostaglandins and substance P in the ocular surface as in other tissues. Proposed analgesic mechanisms of NSAIDs are multiple, including central and peripheral nitric oxide synthase inhibition, central prostaglandin suppression, and down-regulation of pain receptors. Small primary sensory nociceptive neurons contain substance P; capsaicin-induced substance P depletion also has an analgesic effect. Therefore, our finding may partly explain the analgesic effect of diclofenac sodium on the cornea.

Although beneficial analgesic effects of diclofenac sodium eyedrops are marked, potential adverse effects, especially damage to the corneal epithelium, have become a major concern. Results of experimental studies are conflicting. Most in vivo studies have reported that diclofenac sodium and other NSAIDs did not have a significant effect on the rate of wound healing in corneal epithelium, while one study found that impairment of corneal epithelial wound healing resulted from applica-
tion of these agents. In vitro studies have failed to dem-
strate a delay of epithelial wound healing in the cor-
nea.41,42 Some clinical studies3,8 have reported that punctate
epithelial keratopathy developed in association with post-
operative use of diclofenac sodium eyedrops. In con-
trast, Shimazaki et al13 failed to detect any significant
changes, speculating that the discrepancy could have
involved differing incision lengths. Longer incisions cause
a decrease in corneal sensitivity, resulting in alterations
of corneal epithelium. The fact that corneal complica-
tions from use of diclofenac sodium eyedrops are likely
to occur in patients with diabetes mellitus8 or in those
who have undergone keratoplasty44 may also implicate
prior insults. Our present study demonstrates that topi-
cal diclofenac sodium decreases the substance P con-
tent of tears. Depletion of substance P may be involved in
the development of neurotrophic keratopathy.13-22
Therefore, we speculate that additional depletion of sub-
stance P occurs when diclofenac sodium eyedrops are used
in patients with corneal hypesthesia, which may pro-
mote development of corneal complications.

Accepted for publication September 5, 2001.

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