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Research Article

CORNEAL SENSITIVITY TO TOPICAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN TERMS OF MECHANICAL, CHEMICAL, AND THERMAL RESPONSES

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known for their anti-inflammatory effects, but they also seem to have analgesic properties. Topical administration of commercial NSAIDs, diclofenac sodium and flurbiprofen, resulted in significant changes in threshold and intensity of sensations in humans. Gas esthesiometers were used to measure the corneal sensitivity of 5 healthy, young subjects. To stimulate the center of the cornea, a variety of stimuli were applied, including chemical, mechanical, and thermal ones. During the pulse, a continuous 10-cm visual analog scale (VAS) was used to determine the intensity and perceived magnitude of the evoked sensation. We determined the threshold by measuring the stimulus intensity that evoked a VAS score greater than 0.5. All subjects were tested on two separate days on their sensitivity to flurbiprofen (seven subjects) and diclofenac sodium (six subjects) 30 minutes after topical application. In a study of high-intensity mechanical, chemical, and thermal stimuli, diclofenac significantly attenuated all sensation parameters. The effects of flurbiprofen were only significant when it came to the irritation caused by the most intense chemical stimuli (70%CO2). The different stimuli's detection thresholds were not significantly changed by any of the drugs.

Keywords: - Corneal, Sensitivity, Mechanical, Chemical, Thermal.

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INTRODUCTION

A variety of corneal sensory nerve fiber types influence conscious sensations on the surface of the eye, including mechanonociceptors, polymodal nociceptors, and cold-receptor fibers [1, 2]. By using a gas esthesiometer to apply controlled mechanical, chemical, and thermal stimuli to the center of the cornea, it is possible to selectively stimulate these different types of sensory nerve fibers [3]. When the mechanonociceptor and polymodal corneal fibers are activated, they produce sensations of irritation and pain, which increase in intensity as the magnitude of the stimulus increases. On the other hand, piquency of cold receptor fibers with balanced temperature devaluation results in feelings of harmless cooling that only develop into uncomfortable when stronger cold stimuli are applied [4, 5].

Spontaneous pain is a common occurrence in inflammatory conditions affecting the ocular surface. In addition, pain may result from corneal injury or inflammation due to surgical manipulation, particularly after photorefractive surgery. Photorefractive keratectomy (PRK) typically leads to acute ocular pain shortly after the surgery, which progressively increases in severity over the first 4 to 6 hours and persists for several days.Patients undergoing laser in situ keratomileusis (LASIK) also experience acute pain, although the intensity is relatively lower than that of PRK.

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Furthermore, about half of the in sufferer undergoing PRK and LASIK may experience long-term discomfort, including dryness, soreness, sharp pain, and eyelid adhesion to the eyeball upon waking up [6]. To summarize, ocular pain can be evoked by blunt refreshment of the anterior segment of the eye, as well as by various inflammatory conditions affecting the ocular surface, corneal injury, and surgical manipulation, particularly after photorefractive surgery. PRK and LASIK surgeries can cause acute pain, which may persist for several days. Moreover, many patients who undergo these procedures may experience long-term discomfort symptoms such as dryness, soreness, sharp pain, and eyelid adhesion [7].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in cataract surgery to reduce inflammation, and also prescribed as painkillers after photorefractive surgery. These drugs work by inhibiting cyclooxygenases (COXs), which are responsible for breaking down arachidonic acid to produce prostaglandins and other metabolites that contribute to local inflammation and pain sensation. By blocking this breakdown, NSAIDs reduce the sensitization and excitation of pain nerve endings, leading to pain relief. However, different NSAIDs have varying efficacy in reducing ocular pain, and some may also have a explicit effect on the affection of nociceptor sensory nerve incurable [8]. For example, studies on anesthetized cats have suggested that diclofenac sodium and indomethacin are more effective in reducing nerve impulses in response to chemical irritation of the cornea compared to flurbiprofen. Therefore, it is possible that some NSAIDs may have additional analgesic effects beyond their inhibition of PG production. To achieve this, the intensity-response curves of mechanical, chemical, and thermal sensations evoked by corneal stimulation were compared before and after the application of diclofenac sodium. The study aimed to determine whether non-steroidal anti-inflammatory drugs (NSAIDs) have an impact on the excitability of corneal sensory fibers in feline subjects. The results of this study could provide valuable insights into the potential therapeutic uses of NSAIDs in treating corneal pain and inflammation [9].

MATERIALS AND METHODS

In this study, ten subjects (eight men and two women, aged 18–21) voluntarily participated, adhering to the Declarat's tenets. Each subject had both eyes examined. Diclofenac sodium was studied on six people and flurbiprofen was studied on seven people [10]. A consent form was signed by each subject, and the subjects were free to withdraw from the experiment at any time. At the time of the experiment, neither of the subjects had any ocular diseases.

Esthesiometry

This procedure has been described elsewhere. Gas esthesiometers were used to stimulate the corneal surface. A series of 3 second gas jets of differing flow rates, temperatures, and compositions were applied to the cornea's center, separated by 2-minute pauses. In order to stimulate the cornea at a neutral temperature of 33-34°C, nine pulses of air, with a variable flow between 0 and 264 mL/min, were applied at the tip of the stimulus probe heated to +50°C. Air pulses with variable amounts of CO2 were used for chemical stimulation at flow values 10 mL/min below mechanical threshold and at temperatures of +50°C. An air flow of subthreshold speed and temperature of between -4.5°C and +85°C at the tip of the probe was used to induce thermal stimulation, which led to a change in the basal surface temperature of the cornea (33–34°C). At random, different magnitudes of pulses were applied in all stimulation modalities. A 5 mm distance was placed between the tip of the esthesiometer probe and the corneal surface, perpendicular to its center. The stimulus was triggered by opening a valve inside the probe that produced an audible click as soon as the subject blinks before it starts [11]. Six separates, 10- cm continuous horizontal visual analog scales (VAS) were used after each pulse to assess the intensity of the sensation experienced and some of its psychophysical characteristics (irritative, stinging, and burning sensations, as well as warmth and cool sensation. Using the method of minimum stimulus, the threshold for sensation intensity was defined as the lowest intensity of stimulus required to elicit a response of 0.5 VAS. A drop of flurbiprofen or diclofenac sodium was instilled into the cornea 30 minutes before and after examination of its sensitivity to different stimuli. A paired t-test was used to compare differences between groups for each magnitude of stimulus obtained in different subjects. A paired t-test was used to compare thresholds before and after treatment. Third-order regression curves were fitted to the responses.

RESULTS

Diclofenac sodium effects

Upon application of 0.1%diclofenac sodium, thirty minutes after treatment, the intensity of the sensation and the degree of irritation evoked by mechanical stimuli of increasing magnitude were significantly lower than in the untreated eyes, especially at higher stimulus magnitudes. During mechanical stimulation, stinging and burning sensations were evoked in the untreated eyes to an extent only discrete to the untreated eyes. Except when the intensity of the stimulus is at its highest. Nonetheless, after treating with diclofenac, both parameters also seemed to show a downward trend in magnitude after treatment with

diclofenac [12]. Chemical stimulation with CO2 also reduced the intensity and irritation aspects of the sensation, although the VAS scores associated with this modality of stimulus were generally lower for different components of the sensation, and the difference between the treated and control corneas only became significant when the strongest stimuli were applied, and this was the case despite the fact that with this modality of stimulus the VAS scores were overall lower. There has been no report on the thermal components of the sensations evoked by mechanical and chemical stimuli, and accordingly, no representation of their thermal components has been provided in this publication.

When temperatures below or above the neutral corneal temperature are applied, cold or hot stimulations produce sensations that exhibit a distinct thermal quality of innocuous cold or warmth that can be described as a sensation of innocuous cold or warmth. Interestingly, a few people reported that when cold stimuli were applied to their skin, the lower temperature caused them to feel slightly irritated, while when hot stimuli were applied to their skin, some felt slight stinging or burning (data not shown) [13]. It was noted that only at the highest temperatures were cold stimuli reported to produce these latter sensations. There was a significant reduction in the intensity of cold evoked sensations by diclofenac, whereas there was no significant reduction in heat evoked sensations by diclofenac. When diclofenac was administered, there was a slight increase in the threshold stimulation intensity values for mechanical, chemical, and thermal stimulation, but no significant differences were observed (Table 1).

Flurbiprofen's effects

The results of the study showed that flurbiprofen was less effective than diclofenac in in reducing the parameters of the different sensory responses elicited by the three types of stimuli. There was a modest reduction in the intensity, degree of irritation, stinging, and burning components of the sensation evoked by mechanical and chemical stimulation, when the drug was applied only when the intensity of the stimulus was the maximum. A treatment with the drug was not found to have any significant impact on the response to thermal (cold and hot) stimuli elicited by thermal (cold and hot) stimulus. There was no significant difference between the thresholds for mechanical, chemical, and thermal stimuli when flurbiprofen was administered (Table 1) [14]

Table 1. Sensation thresholds measured by mean intensity.

Sensation threshold intensity	Control	Diclofenac	Control	Flurbiprofen
Mechanical (mL/min)	90.9 ± 9.8	107.7 ± 15.9	114.8 ± 10.6	126.5 ± 15.5
Chemical (% of CO_2 in air)	16.8 ± 3.8	23.7 ± 4.5	18.5 ± 5.1	21.8 ± 4.9
Hot (°C)	+1.3 ± 0.3	+1.3 ± 0.4	+1.5 ± 0.3	+0.7 ± 0.3
Cold (°C)	—2.4 ± 0.6	—3.3 ± 0.6	—2.6 ± 0.5	—2.6 ± 0.5

DISCUSSION

When mechanical, chemical, and thermal stimulation was applied to the corneas of healthy humans, diclofenac sodium reduced rapidly the magnitude of the sensations evoked. The effects of flurbiprofen, however, were much less pronounced. Various corneal sensitivity meters have been found to be reliable in discriminating between corneal sensitivity differences associated with various ocular diseases and ages. By measuring the quality of sensations evoked at the ocular surface, it is possible to determine how different modes of stimulation affect afferent sensory fibers innervating the cornea. We have demonstrated in this study that this instrument can be discriminatory and that direct-magnitude-scaling methods are useful for measuring changes in pain intensity and affect, because humans can represent sensation intensity on another physical continuum, such as the VAS, as a perceived intensity. The diclofenac sodium drug decreased corneal polymodal fiber response to cattochemical stimulation with CO2, as well as corneal sensitivity to mechanical, chemical, and cold stimulation. The human corneal sensitivity was modulated in a similar manner by flurbiprofen, which reduced corneal nerve impulse responses to acidic stimuli less effectively in cats. There was no significant increase in threshold pain sensitivity with either of the NSAIDs tested. This approach, however, does not provide sufficient information and does not capture changes in the sensitivity to pain across a broad range of stimulus intensities [15]. Measurement of pain intensity and affect parameters have been developed using direct scaling methods to address this limitation. Diclofenac application decreased the intensity and affect of pain. When the intensity threshold is low, there is a higher degree of variability in the VAS scores, which may explain the lack of change in intensity threshold after diclofenac. There is also the possibility that reliance on local anesthetic drugs could lead to accumulation of inhibition with higher frequency nerve discharges, particularly with stronger stimulation.

Conclusion

According to this report, topical diclofenac relieves corneal pain when applied topically. There is a

direct local inhibition of corneal sensory nerve fibers that is responsible for the reduction of pain sensation. As a result of diclofenac's effect on inflammation and the subsequent decrease in the stimulation-sensitization of nociceptors resulting from locally released arachidonic acid metabolites, this response seems distinct from the secondary analgesic effects that may occur as a result of diclofenac's impact on inflammation.

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