

## Effects of topical timolol (0.5%) and betaxolol (0.5%) on corneal sensitivity

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### Abstract

There are conflicting reports on the propensity of topical  $\beta$  blockers to produce corneal anaesthesia. We measured corneal sensitivity thresholds quantitatively for 10 minutes following the administration of one drop of topical timolol maleate (0.5%), betaxolol hydrochloride (0.5%), or saline in 30 eyes of 18 normal subjects in a randomised, double-masked study. Most subjects had insignificant changes in corneal sensitivity thresholds. We identified, however, a subgroup of four subjects (five eyes) that had a marked and prolonged increase of corneal sensitivity threshold (corneal anaesthesia) after timolol (three eyes) and betaxolol (two eyes). The group mean age of these 'responders' (49.0 years) was significantly greater ( $p < 0.005$ ) than that of the non-responders (35.0). We recommend periodic measurements of corneal sensitivity in older patients receiving topical timolol or betaxolol, especially when given in higher concentrations, to identify responders, who may be at risk of developing keratitis.

$\beta$  Blockers are first line drugs for topical therapy of primary open-angle glaucoma. They lower the intraocular pressure mainly by depressing the production of aqueous. Local anaesthetic effects of  $\beta$  blockers may be from membrane stabilisation<sup>1,2</sup> or inhibition of corneal epithelial chloride transport,<sup>3</sup> which is independent of their  $\beta$  blocking effect.

Timolol maleate, the first topical  $\beta$  blocker available in the United States, is a non-selective  $\beta_1$  and  $\beta_2$ -adrenergic antagonist. Van Buskirk<sup>4</sup> reported corneal anaesthesia in four of 25 patients taking topical timolol and in a separate study<sup>5</sup> observed that, of 547 reports of adverse ocular reactions to topical timolol, 20 mentioned superficial punctate keratitis, with coexistent corneal anaesthesia in eight. More recent studies have conflicted in regard to the incidence and severity of corneal anaesthesia produced by topical timolol.<sup>6-11</sup>

Betaxolol hydrochloride, a newer, selective  $\beta_1$  adrenergic antagonist has been observed by some authors to cause mild, transient corneal anaesthesia after topical use,<sup>6,12,13</sup> while this was not observed by others.<sup>9-11,14-16</sup> We conducted a randomised, double-masked, clinical trial measuring the quantitative corneal anaesthetic side effects of the use of one drop of topical timolol 0.5% and betaxolol 0.5%.

### Materials and methods

We studied 30 eyes of 18 normal subjects. We

excluded subjects who had previous ocular surgery, photocoagulation, trauma, corneal inflammation, or infection; those who had used topical or systemic medicines known to alter corneal sensitivity, pregnant women, contact lens wearers, diabetics, and patients older than 60. (Persons above 60 years of age<sup>8</sup> may have decreased corneal sensitivity.)

Twenty-five subjects were enrolled in this study. Five were excluded because of excessive eye movement and/or inconsistent measurements during baseline threshold testing. Two other patients failed to keep scheduled appointments.

We dynamically measured corneal sensitivity thresholds using the electronic optical aesthesiometer developed by Draeger. During measurement the stimulus body length remains constant and in contact with the cornea, while the exerted force is exponentially increased by the investigator, which permits all measurements to be completed within the physiological blink interval. When subjects perceive a touch sensation, they depress a button that automatically terminates stimulus body contact with the cornea, and the threshold force (between 0 and  $999 \times 10^{-5}$  newtons) is displayed on a digital LED indicator. All threshold measurements were performed by one investigator (SSW).

Ten subjects received one drug (timolol, betaxolol, or saline), four subjects received two drugs, and four subjects received three drugs during the course of the study, in a randomised, double masked fashion. (Three subjects complained of stinging after betaxolol administration, thereby unmasking the drop to the investigator) In the multiple drug group a two-week washout period followed drug administrations. A subject never received the same drug more than once during the study.

The timolol group consisted of 10 subjects, eight females and two males, with a mean age of 41.2 (range 27-53) (Table I). Seven were black; three were white. The betaxolol group consisted of nine subjects, six females and three males, with a mean age of 35.9 (range 27-55) (Table I). Five were black, four were white. The saline control group consisted of 11 subjects, 10 females and one male, with a mean age of 39.1 (range 29-49) (Table I). Eight were black, three were white.

The baseline threshold was determined 1 mm central to the 6 o'clock limbal position (the average of three successive measurements performed 30 seconds apart). Measurements at the corneal centre would have been less useful, as small anaesthetic side effects might have been missed at this area of maximal sensitivity. Following drug administration of one drop in the conjunctival cul-de-sac, and gentle eyelid closure

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TABLE I Relative change in corneal sensitivity thresholds

		Number of minutes after drug instillation									
		1	2	3	4	5	6	7	8	9	10
Timolol (n=10)	Mean relative change from baseline (SD)*	14.9 (35.9)	29.5 (72.9)	46.0 (123.0)	43.4 (105.1)	35.9 (87.4)	16.6 (18.5)	29.4 (75.0)	14.1 (21.0)	10.9 (20.5)	26.2 (70.9)
Betaxolol (n=9)	Mean relative change from baseline (SD)	12.3 (36.7)	16.3 (37.1)	14.2 (36.2)	14.3 (36.1)	14.7 (35.9)	10.8 (20.1)	9.8 (19.7)	5.6 (12.3)	14.4 (36.1)	15.2 (36.1)
Saline (n=11)	Mean relative change from baseline (SD)	16.2 (53.0)	18.2 (52.3)	10.8 (20.5)	2.7 (4.3)	12.1 (33.3)	14.9 (33.5)	14.4 (34.6)	9.9 (26.9)	3.3 (7.6)	1.8 (3.2)

\* We obtained an unsatisfactory threshold measurement at one of the 10 measurement periods after drug instillation in three patients. This threshold was assumed to be the average of the preceding and subsequent measurement. Paired *t* testing comparing thresholds at time *x* and time *x*+1 minutes within drug groups confirmed the validity of this assumption.

$$\text{Relative change from baseline at time } x \text{ minutes} = \frac{\text{threshold at time } x \text{ minutes} - \text{threshold at baseline}}{\text{threshold at baseline}}$$

for 5 seconds, corneal sensitivity thresholds were remeasured at the same position at 1-minute intervals for 10 minutes.

The measurements were continued for 20 minutes if thresholds had not returned to baseline at 10 minutes. The subjects were required to blink between measurements to prevent corneal desiccation.

#### STATISTICAL ANALYSIS

At each measurement period (minutes 1 to 10 after drug instillation) we compared the mean relative change in corneal sensitivity thresholds\* in the timolol and betaxolol groups to a saline control group using *t* tests. We analysed intra-group changes in relative corneal sensitivity thresholds by F ratio tests. We compared mean ages of responders and non-responders in the timolol and betaxolol groups by *t* tests. We considered  $p \leq 0.05$  to be significant.

#### Results

There was no significant change in relative corneal sensitivity thresholds in any of the drug groups ( $p=0.015$ ), and at no time interval (1 to 10 minutes) after drug instillation was there any significant difference in mean relative changes in thresholds among the three drug groups. However, three eyes tested with timolol and two eyes tested with betaxolol showed marked corneal

$$\text{*Relative change from baseline at time } x \text{ minutes} = \frac{\text{threshold at time } x \text{ minutes} - \text{threshold at baseline}}{\text{threshold at baseline}}$$

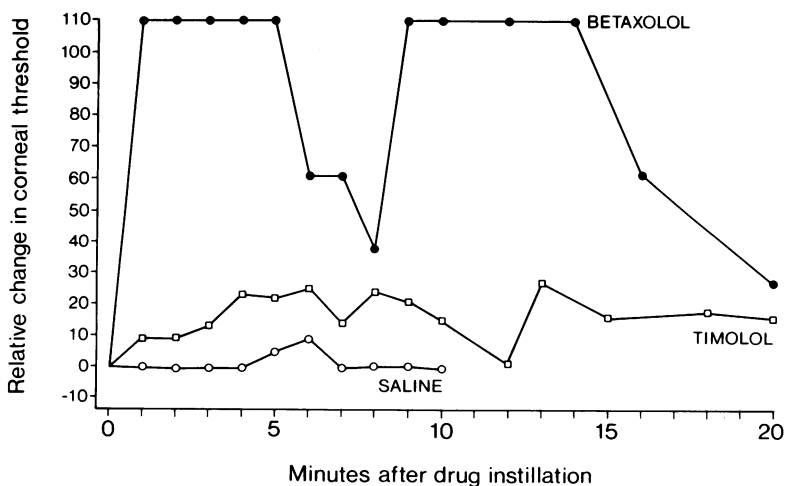


Figure 1: Note the marked and prolonged corneal anaesthesia in this subject after timolol, and after betaxolol administration.

anaesthesia, which persisted for longer than 10 minutes in all cases.

In the saline group relative changes in thresholds were mild and transient.\*

Responders (subjects who had at least a five-fold relative increase in corneal sensitivity threshold which persisted for at least 5 minutes) had the threshold of their untreated contralateral eye measured at 10 minutes. This was done to ensure that corneal anaesthetic effects produced in the treated eye were produced by the drug and were not due to patient fatigue or other non-drug-related factors. All responders had thresholds in the untreated eye that were not significantly different from baseline thresholds in the treated eye, lending support to observer reliability.

One responder received all three drops during the course of the study (Fig 1). After timolol administration her relative change in thresholds included 8.9 at 1 minute and a peak of 26.8 at 13 minutes. A marked corneal anaesthetic effect (relative change in threshold of 16.4) persisted at 20 minutes. After receiving betaxolol this subject had the following relative change in thresholds: 110.0 at 1 and 10 minutes and 25.6 at 20 minutes. After saline administration this subject had relative threshold changes of 4.7 at 5 minutes and 9.0 at 6 minutes, but the remainder of the measured thresholds were approximately equal to baseline.

A second responder received both timolol and saline during the course of the study. Relative threshold changes after timolol were 231.5 at 2 minutes, 394.5 at 3 minutes, and 9.0 at 20 minutes. After saline testing, relative changes in thresholds were 5.1 at 4 minutes, 15.8 at 6 minutes, and 1.3 at 10 minutes. The third responder received timolol only and had relative threshold changes of 16.6 at 4 minutes, a peak of 21.7 at 5 minutes, and a return to baseline at 19 minutes. The fourth responder received only betaxolol and had relative threshold changes which peaked at 13.5 at 3 minutes, with a return to baseline by 19 minutes.

The responders (timolol and betaxolol groups combined) ranged in age from 39 to 53 with a mean age of 49.0 (SD 6.2). The non-responders differed significantly, they ranged in age from 27 to 52 and had a mean age of 35.0 (SD 8.8) ( $<0.005$ ).

\* Differing baseline values obtained from the same subject on different days, and variability in threshold values following saline administrations, were presumed to be due to the inexact placing of the stimulus body on the cornea, and variation in subject response times.

### Discussion

The cornea has a rich sensory nerve supply, which is derived from the ophthalmic division of the trigeminal nerve. Trigeminal neurons are presumed to transport trophic substances which regulate the corneal epithelial respiratory, glycolytic, and mitotic activity. Postulated mediators of this trophic effect include epinephrine,<sup>17-20</sup> cyclic AMP,<sup>3</sup> acetylcholine,<sup>17</sup> serotonin,<sup>21</sup> and substance P.<sup>22</sup> The clinical effects of these metabolic derangements associated with corneal anaesthesia include epithelial defects, stromal ulceration, and perforation.

The mechanism of  $\beta$  blocker induced corneal anaesthesia has not been delineated. The demonstration of adrenergic corneal nerves in variety of species,<sup>17,18</sup> as well as the increased corneal epithelial chloride transport<sup>3</sup> and decreased mitotic rate<sup>19,20</sup> following  $\beta$  adrenergic stimulation, suggest an adrenergic regulation of the corneal epithelium. In addition topical timolol has been reported to antagonise dopamine stimulated release of norepinephrine from sympathetic nerve endings in isolated rabbit corneal epithelium.<sup>23</sup> However, the local anaesthetic properties of  $\beta$  blockers are probably independent of  $\beta$  blockade.<sup>24</sup>

Stabilisation of ocular axonal cell membranes has also been proposed as the mechanism for the local anaesthetic actions of  $\beta$  blockers.<sup>12</sup> However, Yasuhara and associates<sup>25</sup> demonstrated a dissociation between membrane stabilisation and corneal anaesthetic side effects in rats after topical  $\beta$  blocker administration.

An alternative mechanism is the antagonism by  $\beta$  blockers of serotonergic activation of corneal epithelial chloride transport.<sup>21,26</sup> A variety of  $\beta$  blockers have been shown to have a strong affinity for the 5 HT binding site.<sup>27</sup> The importance of serotonergic nerves in corneal sensation is suggested by the detection of serotonin

in bovine corneal nerves<sup>28</sup> and human aqueous humour,<sup>29</sup> and also by the increase in both corneal epithelial acetylcholine content and corneal sensitivity in rabbits following serotonin administration.<sup>30</sup>

Vale and associates<sup>31</sup> as early as 1972 described corneal anaesthesia with topical propranolol use. Van Buskirk<sup>4,5</sup> reported both severe corneal anaesthesia and superficial punctate keratitis resulting from topical timolol use. All of Van Buskirk's patients with markedly diminished corneal sensation were more than 70 years of age.

More recent reports<sup>6-16,32</sup> have conflicted with regard to the incidence and severity of corneal anaesthetic side effects produced by topical timolol and betaxolol. A variety of methods were used in these studies to measure corneal sensitivity (Table II). Draeger<sup>8</sup> used the aesthesiometer employed in the present study and found transient corneal anaesthetic effects following a one-time administration of topical timolol, but only in subjects older than 40. He also noted subjects in whom marked and prolonged corneal anaesthetic effect occurred following administration of several different  $\beta$  blockers. He postulated a genetically determined enzyme variation to explain these patients' susceptibility to  $\beta$  blocker induced corneal anaesthesia.

We did not detect in 18 subjects (30 eyes) significant relative change in corneal sensitivity thresholds from baseline in either the timolol or the betaxolol groups in comparison with placebo (saline) group. We compared relative changes in thresholds at each measurement interval (1-10 minutes after drug administration) between the three drug groups, and found no point at which a significant intergroup difference existed.

We identified a subgroup of four subjects (five eyes) that showed marked and prolonged corneal anaesthetic effects after topical timolol (three eyes) and topical betaxolol (two eyes). One

TABLE II Timolol and betaxolol studies

Study	Drugs tested	No of patients	Mean age (yr)	Method of measuring corneal sensitivity	Duration of study	No of patients with corneal anaesthesia
Van Buskirk <sup>4</sup>	Timolol (?%)	547 adverse reactions	?	?	?	8 (20 had superficial punctate keratitis)
Van Buskirk <sup>4</sup>	Timolol (0.5%)	25	? (range 45-84)	Cotton wisp	13 weeks	4 with marked anaesthetic effect, all in patients older than 70
Spinelli <i>et al</i> <sup>6</sup>	Timolol (0.25% & 0.5%)	30	57	Cotton wisp and Cochet Bonnet aesthesiometers	18 months	3 with remarkably decreased sensitivities
Draeger <sup>8</sup>	Timolol (0.25%, 0.5% 1%)	20	7 (range 20-60)	Draeger aesthesiometer	15 minutes	Rapid and transient anaesthetic effects, only in patients older than 40
Allen <i>et al</i> <sup>9</sup>	Timolol (0.25% and 0.5%) and Betaxolol (0.25% & 0.5%)	38	65	Cochet Bonnet aesthesiometer	26 weeks	5, all noted in patients who had received timolol
Hoh <sup>11</sup>	Timolol (0.5%) and Betaxolol (0.5%)	40	31	Draeger and Cochet Bonnet aesthesiometers	30 minutes	Marked and prolonged anaesthesia noted in 1 patient after betaxolol
Present study	Timolol (0.5%) & Betaxolol (0.5%)	18 (30 eyes)	40	Draeger aesthesiometer	20 minutes	Marked and prolonged anaesthesia noted in 4 patients; in 2 after timolol, in 1 after betaxolol, and in 1 after both timolol and betaxolol
Radius <sup>12</sup>	Betaxolol (0.125%)	20	?	Cotton wisp	6 weeks	Several patients with mild anaesthetic effects before, during, and after treatment interval; but no difference between betaxolol and placebo
Berrosopi and Leibowitz <sup>14</sup>	Betaxolol (0.25%)	12	67	Cotton wisp	52 weeks	0 (but transient superficial keratitis in several)

responder had a corneal anesthetic effect which persisted for 20 minutes on two occasions, once after receiving timolol and again after receiving betaxolol. The magnitude of the absolute increase in thresholds was similar in this subject after receiving both timolol and betaxolol, but the relative increase in thresholds was greater after betaxolol owing to higher baseline thresholds measured prior to timolol administration.

The two other responders who received timolol (but not betaxolol) had a return of their corneal thresholds to baseline at 10 minutes and 19 minutes respectively. The responder who received betaxolol (but not timolol), had a return of thresholds to baseline at 19 minutes.

The mean age of responders to timolol or betaxolol was significantly greater than that of non-responders ( $p < 0.005$ ). The youngest responder was 39 years of age.

The identification in this study of a subgroup of generally older patients showing marked and prolonged corneal anaesthetic side effects after topical timolol 0.5% confirmed previous investigations by Van Buskirk,<sup>4</sup> Spinelli and associates,<sup>7</sup> and Draeger.<sup>8</sup> In addition, we demonstrated that this effect may also occur after topical betaxolol 0.5% administration.

The failure of many previous reports to document these corneal anaesthetic side effects of topical timolol and betaxolol may be attributed in some instances to use of lower concentrations of topical  $\beta$  blockers, use of less sensitive methods to measure corneal sensitivity, and to study populations which consisted of mostly young subjects with few or no responders.

We recommend performing periodic corneal aesthesiometry in patients receiving topical timolol and betaxolol to identify responders. More frequent monitoring is suggested in patients with pre-existing corneal hypoaesthesia, in older patients, and in those receiving higher concentrations of these topical  $\beta$  blockers. If a significant keratitis is shown to occur frequently in responders treated with topical  $\beta$  blockers, therapy with an alternative class of intraocular pressure lowering medication may be preferable in these susceptible patients.

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