Effect of Topical Betaxolol on Acute Rise of Aqueous Flare Induced by Prostaglandin E\(_2\) in Pigmented Rabbits

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**Purpose:** To evaluate the effects of topical betaxolol on experimental ocular inflammation.

**Methods:** Transcorneal diffusion of 25 \(\mu\)g/mL \((7.09 \times 10^{-2}\) mmol/L) of prostaglandin \(\text{E}_2\) (PGE\(_2\)), placed in a glass cylinder, was employed to induce aqueous flare elevation in pigmented rabbits. Betaxolol was administered topically before PGE\(_2\) application. Aqueous flare was measured with a laser flare cell meter.

**Results:** Four-, two-, and one-time topical instillations of betaxolol inhibited the PGE\(_2\)-induced aqueous flare elevation by 44% ± 8%, 32 ± 7%, and 8 ± 6% (mean ± SD), respectively. The inhibition of flare elevation was dependent on the number of betaxolol instillations.

**Conclusion:** Topical betaxolol has an inhibitory effect on PGE\(_2\)-induced aqueous flare elevation in rabbit eyes.

**Key Words:** Aqueous flare, betaxolol, prostaglandin E\(_2\).

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**Introduction**

Betaxolol, a \(\beta_1\)-selective adrenoceptor antagonist, lowers intraocular pressure in humans.\(^1\) This agent has been reported to have calcium channel blocking activity.\(^2,3\) Studies from our laboratory have shown that some calcium channel blockers inhibit the experimental elevation of aqueous flare in pigmented rabbits.\(^4,5\) In the present study, we evaluated the effect of betaxolol on aqueous flare elevation induced by prostaglandin \(\text{E}_2\) (PGE\(_2\)) in pigmented rabbits.

**Materials and Methods**

**Animals**

A total of 24 pigmented male rabbits (Japanese mongrel) that weighed 2.5–3.5 kg were used. The animals were housed and treated according to the Association for Research in Vision and Ophthalmology (USA) Resolution on Use of Animals in Research. One eye of each animal was used for the experiment.

**Chemicals**

Betaxolol, 0.5% ophthalmic solution, was a gift from Alcon Japan Limited (Tokyo). PGE\(_2\), obtained from Funakoshi (Tokyo), was dissolved in 100% ethanol and stored at \(-70^\circ\)C. The PGE\(_2\) stock solution was diluted to 5% ethanol with 0.9% NaCl just before use.

**Transcorneal Diffusion of PGE\(_2\)**

For transcorneal diffusion, a glass cylinder (11 mm in diameter) was attached to the cornea, as reported by Hirata et al.,\(^6\) and 600 \(\mu\)L of 25 \(\mu\)g/mL \((7.09 \times 10^{-2}\) mmol/L) of PGE\(_2\) solution was placed in the cylinder. After 4 minutes, the solution was pipetted out. The cylinder was removed, and the corneal surface and conjunctival sac were rinsed with 20 mL of 0.9% NaCl.

The rabbits that initially received PGE\(_2\) were given
the same agent after an interval of 1 or 2 months. The eyes pretreated with betaxolol or placebo (0.9% NaCl) were used initially to determine the PGE$_2$-induced flare elevation. After the interval, the same eyes received only PGE$_2$ and served as control.

**Topical Instillation of Betaxolol**

In one eye, 50 $\mu$L of 0.5% betaxolol or placebo (0.9% NaCl) was instilled topically. Instillation took place four times (60, 45, 30, and 15 minutes), two times (60 and 30 minutes), or once (30 minutes) before PGE$_2$ application.

**Aqueous Flare Measurements**

Aqueous flare was measured with a laser flare cell meter (FC 1000, Kowa, Tokyo), according to the method described by Sawa et al.\textsuperscript{7} The laser flare cell meter measures the level of intracameral proteins. Five measurements were taken at each time point and the mean was used for the analysis. The sampling area was 0.075 mm$^3$, and measurements were taken from the midportion of the anterior chamber. The aqueous flare elevation was expressed as the area under the curve (AUC), and inhibition was calculated by the following equation:

\[
\text{Inhibition} \% = \left[1 - \frac{\text{AUC, with treatment}}{\text{AUC, without treatment}}\right] \times 100.
\]

**Statistics Analysis**

Statistical analysis was performed using Dunn’s multiple comparisons procedure. A probability ($P$) value less than .05 was considered significant.

**Results**

No remarkable changes in the systemic condition of the rabbits, including body weight and behavior, were noted following the transcorneal diffusion of 7.09 $\times$ 10$^{-2}$ mmol/L PGE$_2$, or the four-time topical instillation of 0.5% betaxolol.

After PGE$_2$ had been administered, the aqueous flare increased, to reach a maximum (470 photon counts/msec) at 60–90 minutes, and then gradually decreased and returned to the baseline level at 7–8 hours (Figure 1). When 0.5% betaxolol was topically instilled 60, 45, 30, and 15 minutes before the PGE$_2$ application, the aqueous flare increased, reached its maximum (300 photon counts/msec at 75 minutes and then gradually decreased.

The inhibition of the flare elevation was dependent on the number of instillations of 0.5% betaxolol (Figure 2). Four-, two-, and one-time instillations of betaxolol inhibited PGE$_2$-induced elevation by 44% ± 8%, 32 ± 7%, and 8 ± 6% (mean ± SD), respectively. The saline placebo had no effect on flare elevation.

**Discussion**

Changes in aqueous flare after PGE$_2$ application were quite similar in this study to that described previously.\textsuperscript{9} We reported that the PGE$_2$-induced flare elevation was inhibited by intravenous nilvadipine (a...
calcium channel blocker). We also reported that nilvadipine inhibited the iris photocoagulation-induced flare elevation more effectively than did nicardipine, and that verapamil did not inhibit flare elevation. Oyanagui and Sato reported that nilvadipine inhibited ischemic and carrageenan paw edema. Gallar et al showed that verapamil inhibited anterior segment inflammation induced by ultraviolet radiation. Thus, some calcium channel blockers possibly have anti-inflammatory activity. However, not all calcium channel blockers inhibited the acute rise of aqueous flare induced by PGE$_2$ in pigmented rabbits.

Betaxolol is reported to have calcium channel blocking activity. It is possible that the PGE$_2$-induced flare elevation may have been inhibited by the calcium channel blocking activity of betaxolol in the present study. It is unlikely that β-blocking activity and the intraocular pressure lowering capacity of betaxolol may be associated with inhibition of PGE$_2$-induced flare elevation.

References
8. Oyanagui Y, Sato S. Inhibition by nilvadipine of ischemic and carrageenan paw edema as well as of superoxide radical production from neutrophils and xanthine oxidase. Arzneimittelforschung (Drug Res) 1991;41:469–74.