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Penetration of betaxolol HCL ionic suspension 0.25% and betaxolol HCL solution 0.50% into the aqueous humor

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PURPOSE. *To determine the intraocular penetration of topical drops of betaxolol HCl 0.25% suspension and betaxolol HCl 0.50% solution into the aqueous humor.*
METHODS. *Fifteen patients were randomly assigned to receive topical betaxolol HCl 0.25% suspension (n=7) or topical betaxolol HCl 0.50% solution (n=8) the day before cataract surgery. Aqueous samples were collected 2 hours after the administration of the morning dose during cataract surgery. Drug concentrations were determined by high-performance liquid chromatography with fluorescence detection.*
RESULTS. *The mean aqueous humor concentration of topical betaxolol HCl 0.25% suspension was 275.1±168.8 µg/mL (range 570–70 µg/mL) and the mean aqueous humor concentration of topical betaxolol HCl 0.50% solution was 195.4±102.4 µg/mL (range 334–50 µg/mL) (p=0.281).*
CONCLUSIONS. *The mean aqueous humor concentration of betaxolol 0.25% suspension was higher than betaxolol 0.50% solution; however, the difference was not statistically significant. With twofold reduced concentration and similar anterior chamber penetration, betaxolol 0.25% suspension could be first choice for β1 selective blocker therapy when considered for patients with glaucoma. (Eur J Ophthalmol 2007; 17: 368-71)*

KEY WORDS. *Betaxolol, Glaucoma, Aqueous humor, Penetration, High-performance liquid chromatography*

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INTRODUCTION

Betaxolol, DL-[4-{2-cycloprophylmethoxyethyl}-1-phenoxy-3-isoprophyylamino-2-propanol], is a cardioselective β-adrenergic receptor blocker which produces competitive inhibition at the β_1 subtype of the β-adrenergic receptor. Among several selective β_1-receptor blockers, betaxolol HCl is the only approved topical cardioselective β-blocker for clinical use in glaucoma therapy (1). Betaxolol is available as a racemic mixture of D- and the active L-isomers in two commercial forms: the 0.50% ophthalmic solution and the 0.25% ophthalmic suspension.
The purpose of this study is to determine the intraocular penetration of topical drops of cardioselective β-blocker betaxolol HCl 0.25% suspension and betaxolol HCl 0.50% solution into the aqueous humor.

PATIENTS AND METHODS

This prospective study comprised patients having cataract surgery at the Ophthalmology Department of Ankara Research and Education Hospital between April 2001

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and April 2002. Exclusion criteria were other ocular disease, diabetes mellitus, systemic hypertension, and current topical antiglaucoma drug treatment. The study protocol and informed consent were reviewed and approved by Ankara Hospital Ethics Committee.

The patients were randomly assigned to receive topical betaxolol 0.25% suspension and topical betaxolol 0.50% solution treatment. The topical betaxolol 0.25% suspension group comprised 3 (43%) men and 4 (57%) women with mean age of 46.3±21.9 years (range 18 to 78 years). The topical betaxolol 0.50% solution group comprised 4 (50%) men and 4 (50%) women with mean age of 51.1±15.6 years (range 18 to 71 years) (Tab. I) (p=0.627).

The study protocol was the same for both groups with starting to use the drugs 1 day before surgery twice a day and one drop in the morning on operation day. In both groups, aqueous samples were collected 2 hours after the administration of the morning dose during cataract surgery.

Drugs and dosage

Commercially available topical betaxolol 0.25% suspension (Betoptic-S®, Alcon Laboratories Inc., Fort Worth, TX) contains 0.28% betaxolol hydrochloride equivalent to 0.25% betaxolol with 0.01% benzalkonium chloride as an antimicrobial preservative. Amberlite™, a cationic exchange polymer, carbomer 934P, and mannitol 4.5% are also present in the formulation.

Commercially available topical betaxolol 0.50% solution (Betoptic®, Alcon Laboratories Inc.) contains active 5.6 mg betaxolol hydrochloride equivalent to betaxolol base 5 mg, with 0.01% benzalkonium chloride as an antimicrobial preservative.

Sample assay

Aqueous samples were obtained at the beginning of cataract surgery. Using a syringe attached to a 27-gauge needle, a paracentesis was made through a partial-thickness corneal cataract incision and 0.2 mL of aqueous humor was withdrawn.

All samples were frozen at –20 °C and subsequently analyzed for drug concentration. Drug concentrations were determined by high-performance liquid chromatography (HPLC) fluorescence detection (2).

The HPLC equipment comprised of a solvent delivery system (Shimadzu LC-10AT$_{VP}$) and a fluorescence detector (Shimadzu RF-10A$_{XL}$). The analytic column was a stainless steel column packed with 5 mm Luna C_{18} (250 mm x 4.6 mm ID, Phenomenex). The mobile phase consisted of acetonitrile and 10 mM phosphate buffer (40:60, v/v) with a flow-rate of 0.8 mL/min at ambient temperature. Fluorescence detector was set to excitation and emission wavelengths of 227 and 301 nm, respectively.

Aqueous humor samples (30 mL) were diluted with distilled water (1:8, v/v) and metoprolol (1 mg/mL) was added as an internal standard. The mixture was alkanized (pH 9–10) with 60 mL of 0.5 M Na_2CO_3 and extracted with 1.5 mL of cyclohexane by mixing on a vortex-mixer for 15 s. After centrifugation (1000 *g*, 5 min) the organic phase was transferred to a clean tube and evaporated to dryness on a rotavapor at ambient temperature. The residue was dissolved in 240 mL of mobile phase and 20 mL of the solution was injected onto the column. All analyses were performed in duplicate.

Statistical analysis

The independent-samples *t*-test was used to determine the statistical significance of the experimental results. The results are expressed as mean±SD. A *p* value less than 0.05 was considered statistically significant.

RESULTS

In the betaxolol 0.25% suspension group, the mean aqueous concentration of the betaxolol was 275.1 ± 168.8 µg/mL (range 570–70 µg/mL). In the betaxolol 0.50% solution group the mean aqueous concentration of the betaxolol was 195.4±102.4 µg/mL (range 334–50 µg/mL) (Tab. I). The mean aqueous humor concentration of betaxolol 0.25% suspension was higher than that of betaxolol 0.50% solution; however, the difference was not statistically significant (p=0.281).

DISCUSSION

Betaxolol HCl 0.50% solution was introduced in 1985 as the first topical cardio-selective β-adrenergic antagonist for the treatment of glaucoma (1). It was shown

TABLE I - PATIENT DEMOGRAPHICS AND MEAN AQUEOUS HUMOR LEVELS OF BOTH CONCENTRATIONS OF TOPICAL BETAXOLOL

	Betaxolol 0.25% suspension, n=7	Betaxolol 0.50% solution, n=8	p
Age, yr (range)	46.3±21.9 (18–78)	51.1±15.6 (18–71)	0.627
Sex, n (%)			NA
Male	3 (43)	4 (50)	
Female	4 (57)	4 (50)	
Aqueous humor, µg/mL (range)	275.1±168.8 (570–70)	195.4±102.4 (334–50)	0.281

that betaxolol demonstrated 233-fold selectivity for β_1-receptors in guinea pigs (3). By having a greater affinity for cardiac β_1-receptors it has been reported to offer a reduced potential for pulmonary side effects, particularly in patients with pre-existing pulmonary disease (4-5). Nevertheless, betaxolol should be used cautiously in patients with asthma since some reports showed pulmonary side effects that occurred acutely or later than when using a nonselective beta-blocker (6-7). Intraocular pressure (IOP) lowering effect of betaxolol HCl 0.50% solution has been confirmed by several clinical studies in patients with open angle glaucoma and ocular hypertension (8-9).

Unlike the initially manufactured betaxolol HCl 0.50% solution (Betoptic®), betaxolol is suspended in a different delivery vehicle in betaxolol HCl 0.25% suspension (Betoptic-S®) to increase the local tolerance of the drug and allow a similarly effective twofold reduced concentration (10). The cationic exchange Ambrelite™ resin in which 0.25% betaxolol is suspended provides microscopic beads in 5 µm diameter and residence time in the cul-de-sac is increased with the addition of a polyacrylic polymer. Ambrelite™ is a sulfonic acid exchanger, which means that a negatively charged (SO_3^-) group exists on the outer surface of the polymer to which the positively charged betaxolol molecule can bind. Since betaxolol HCl and the polymer are present in Betoptic-S® in approximately equimolar ratios, conditions in the suspension allow about 85% of the betaxolol to be bound to the caution exchange polymer beads. In the eye, betaxolol is released from the polymer via exchange with sodium ions (Na^+) in the tears. The net effect of placing one drop of betaxolol ionic suspension in the eye is that, as Na^+ is exchanged for betaxolol on the polymer, betaxolol is released relatively slowly into the lacrimal film. Also, betaxolol suspension is released into the lacrimal film more slowly than betaxolol solution; ocular comfort is enhanced (11).

The effect on IOP of the two different concentrations of betaxolol has been published in several studies with different conclusions. In one study, no significant difference was found between betaxolol HCl 0.50% solution and betaxolol HCl 0.25% suspension in terms of IOP reduction whereas prevalence of ocular discomfort upon instillation was significantly lower for the 0.25% betaxolol suspension (12). However, in another study with a smaller sample size, betaxolol HCl 0.50% solution was reported to be more effective than the betaxolol HCl 0.25% suspension in diurnal control of IOP (13). The penetration into the anterior chamber of betaxolol of two different concentrations is more objective to obtain brief conclusions about effectiveness of the drugs. The penetration of betaxolol HCl 0.50% solution into the anterior chamber has been demonstrated in some studies. Our results showed similar anterior chamber penetrations of both betaxolol HCl 0.50% solution and betaxolol HCl 0.25% suspension. In conclusion, with twofold reduced concentration and similar anterior chamber penetration, betaxolol 0.25% suspension could be the first choice for β_1 selective blocker therapy when considered for patients with glaucoma.

The authors have no proprietary interest in any material or method described in this study.

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