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ANALYSIS OF INTRAVITREAL ADMINISTRATION OF STEREOISOMERIC FORM OF BETAXOLOL IN RABBIT MODEL

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ABSTRACT

Many of the drugs currently used in ophthalmic practice are enantiomers. The majority of ophthalmic medications are formulated as eye drops. β -blockers decrease aqueous humor production by approximately one-third. To obtain the desired lowering in IOP, large quantity of conventional eye drops of betaxolol hydrochloride is used. Twelve New Zeland albino male rabbits weighing 2.3 to 3 kg were selected for this study. Animals were randomized into 3 groups of 2 each. All three groups were used to evaluate intravitreal drug disposition of betaxolol Hydrochloride, R-betaxolol and S betaxolol respectively. The drug distribution profile of betaxolol was studied. The result shows that the drug distribution after intravitreal injection is more in the enantiomeric form than the racemic form of betaxolol.

KEYWORDS: Betaxolol, intravitreal, HPLC.

INTRODUCTION

Many of the drugs currently used in ophthalmic practice are enantiomers. The majority of ophthalmic medications are formulated as eye drops. Due to anatomical constraints, the volume that can be administered is limited to approximately 30 microL. β-adrenergic antagonist records for around 70% of all the solutions for glaucoma and are valuable in the treatment of chronic open angle glaucoma. These medications lessen intra ocular pressure by contending with catecholamine for β 2-adrenoreceptor on the non-pigmented ciliary epithelium and subsequently diminishing aqueous humor creation. β-blockers have a few advantages over cholinergic and adrenergic antagonist, as these have little impact on pupil size and do not cause mydriasis or responsive hyperaemia.[1]

β-adrenergic blockers are among the first categories of drugs investigated for their chiral aspects. They contain one or several stereogenic centers in their structure and thus are able to rotate the plane of polarization of linearly polarized light either to the left (–) or to the right (+). In older literature we can also find the terms laevo (l) and dextro (d) to describe the direction of rotation of polarized light. The spatial arrangement of substituents around the stereogenic center, for example the so-called absolute configuration, can be described with the help of the Cahn-Ingold-Prelog (CIP) system.[2,3] According to their chemical structure these drugs can be classified as arylaminoethanols or aryloxyaminopropanols (Figure 1). In both groups the more active isomers pertaining to their β - adrenolytic activity are the (–)-isomers which can be attributed the (R)-configuration for the arylaminoethanol group and (S) for the aryloxyaminopropanol group.

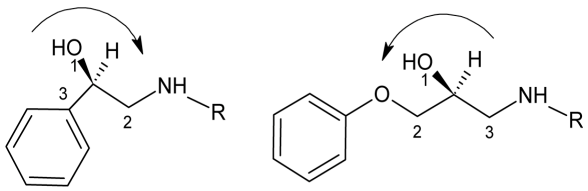

Figure 1: Structure and stereochemistry of arylaminoetanols (left) and aryloxyaminopropanols (right).

Betaxolol hydrochloride, chemically it is 2- propanol, 1- (4- (2- (cyclopropylmethoxy) ethyl) phenoxy) - 3 - ((1 - methylethyl) amino) - hydrochloride.[4] It has molecular formula C18H29NO3.HCl and molecular weight is 343.89.[5] Betaxolol hydrochloride is a white, crystalline powder. It is freely soluble in water, ethanol, chloroform, and methanol, has a pKa of 9.4.[6] The ocular hypertensive effect caused by β -blocker. is probably due to suppression of aqueous humor formation by blockage of the β adrenal receptors in the ciliary body. β -blockers decrease aqueous humor production by approximately one-third. To obtain the desired lowering in IOP, large quantity of conventional eye drops of betaxolol hydrochloride are used.[7]

MATERIALS AND METHODS

Approval was obtained from Institutional Animal Ethical Committee at Bharathi College of Pharmacy, and

the procedures adhered to the guidelines from the Association for Research in Vision and Ophtholmology or animal use in research. Twelve New Zeland albino male rabbits weighing 2.3 to 3 kg were selected for this study. Animals were kept in individual cages in a clear-dark cycle of 12 hours, and free access to water and food. Animals were randomized into 3 groups of 2 each. All three groups were used to evaluate intravitreal drug disposition of betaxolol Hydrochloride, R-betaxolol and S betaxolol respectively. Group A received S- Betaxolol, Group B received R- Betaxolol and Group C received Betaxolol Hydrochloride. Slit lamp examination and indirect ophthalmoscopy were performed on all eyes before the study. Animals with corneal or lens opacity or retinal damage before the study were excluded. Rabbits were anesthetized with a mixture of ketamine hydrochloride. (50 mg/kg) and xylazine hydrochloride (5 mg/kg). Benoxinate hydrochloride (0.4%) was applied for topical anesthesia. Eyes were dilated with topical tropicamide (1%) applications. Fluoroquinolone antibiotic was used topically before and after all surgical procedures.

Intravitreal Injection

For the intravitreal injection, a tuberculin syringe with a 30 gauge, 0.8cm needle will be insert approximately 0.2mm posterior to the surgical limbus, in the superonasal quadrant, to reach the intravitreal region.

Before intravitreal injection, it was performed paracentesis of anterior chamber (30G needle), removing 0.1ml of aqueous humor to avoid significant increase of ocular pressure. Under direct visualization, right eye of each animal were submitted to an intravitreal injection of 5mcg/0.1 ml of betaxolol using a 30G needle attached to a tuberculin syringe. Left eye received an intravitreal injection of sterile saline and used as control.

The microsampling technique consists of the aspiration directly from the living anesthetized rabbit, of small sampling of approximately 10 to 15 microlitre vitreous fluid. The samples are stored at -20 C for further HPLC assay.

RESULTS AND DISCUSSION

During the examination, before the intravitreal injection of Betaxolol (R and S form), it was observed that the structures of cornea, anterior segment and lens were normal for both eyes of the rabbits and the retina was efficiently luminous.

Clinical Observation

To detect clinical signs of toxicity, treated and control rabbit eyes were carefully evaluated by slit lamp examination and indirect opthalmoscopy. No inflammation was observed. Data were obtained from the 12 eyes of 6 rabbits. No adverse events were noted, and there were no signs of ocular inflammation. Vitreous humor samples of rabbits' eye were collected by inserting a needle into the lateral canthus of each eye. All the vitreous humor in each eye was aspirated, and care was taken to avoid damage to any loose tissue fragments around the vitreous chamber. The obtained samples were placed into polystyrene conical tubes and kept at –20 ◦C without any preservatives until analysis.[8]

Betaxolol pharmacokinetics

The HPLC method was validated, and a calibration curve was obtained. The HPLC sensitivity was 0.1 µg/mL. The vitreous concentrations of betaxolol (R and S form) are presented in figure 4.

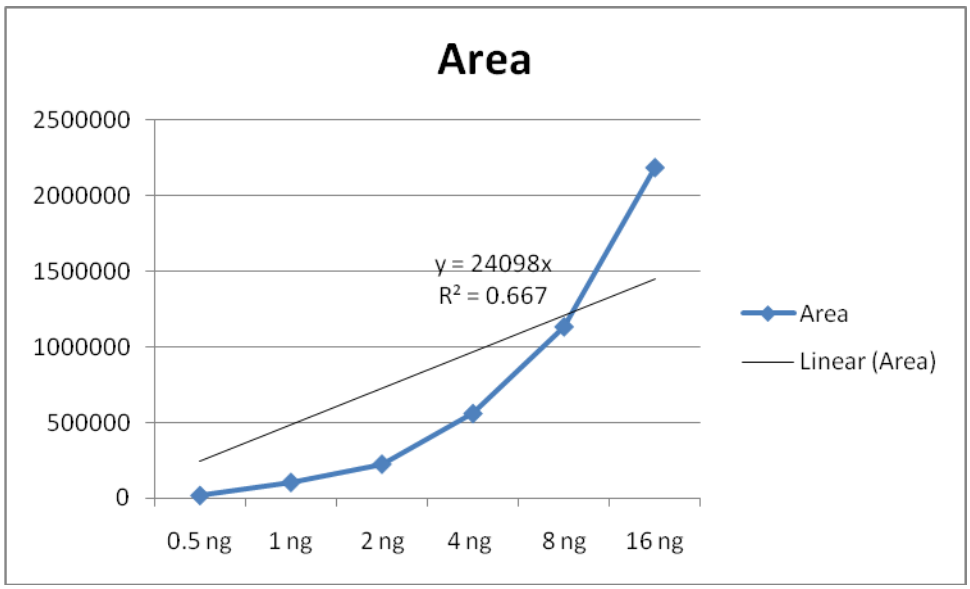

Figure 2: Calibration curve of S- betaxolol.

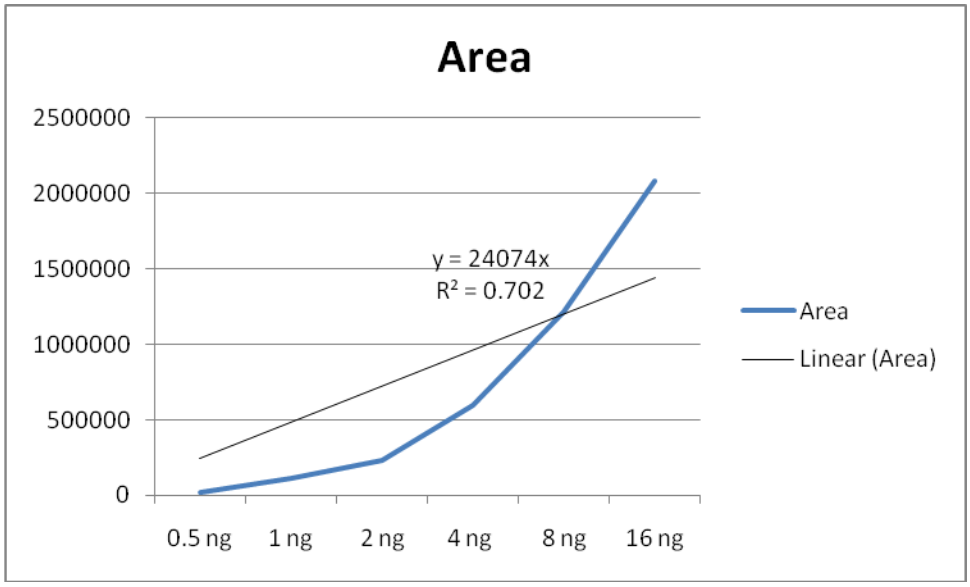

Figure 2: Calibration curve of R- Betaxolol.

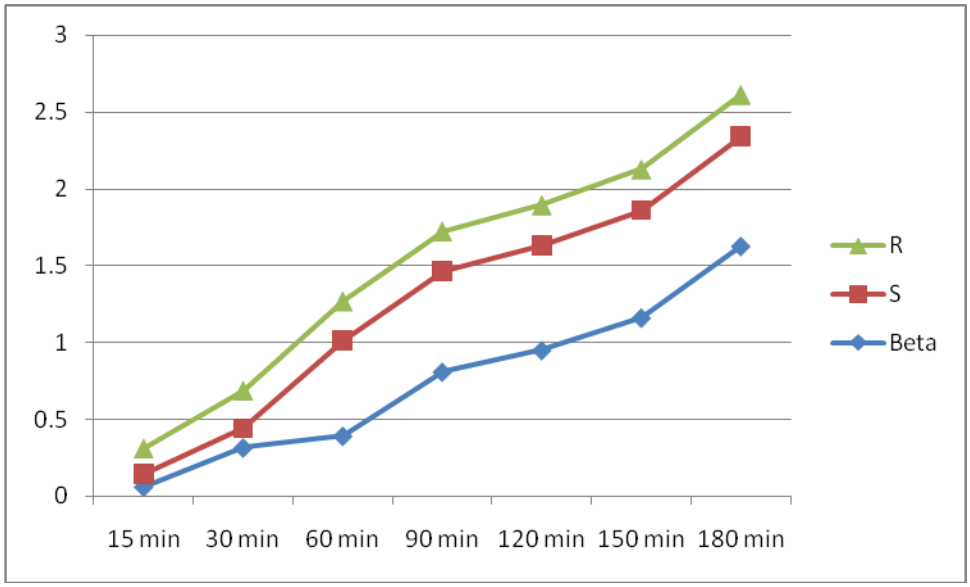

Figure 3: Betaxolol hydrochloride and Betaxolol (R and S form)in the vitreous at different point of time after intravitreal injection.

different point of time after intravitreal injection

The drug distribution profile of betaxolol hydrochloride and S-betaxolol and R-betaxolol was studied by using HPLC. The drug distribution profile of R and S betaxolol is more than the betaxolol hydrochloride. The study concluded that the enantiomeric form of the drug distribution is more than the racemic mixture of betaxolol.

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