BAUSCH + LOMB

123

24-Hour Evaluation of the Ocular Pharmacokinetics of ^{14}C-Labeled Low-Concentration, Modified Bromfenac Ophthalmic Solution Following Topical Instillation into the Eyes of New Zealand White Rabbits

Baklayan G.A.
Bausch & Lomb Inc.

Abstract

Purpose: To evaluate the 24-hour ocular distribution and concentrations of ^{14}C-labeled low-concentration, modified bromfenac ophthalmic solution following topical instillation in New Zealand White rabbit eyes.

Methods: Eighteen New Zealand white rabbits were randomly assigned to 6 treatment groups (3 animals per treatment group). A single dose of 50µL of the dosing solution was topically administered into the conjunctival sac of both eyes of each animal. Animals were euthanized and the aqueous humor was collected at 1 hour ± 5 minutes, 2 hours ± 15 minutes, 4 hours ± 15 minutes, 8 hours ± 15 minutes, 12 hours ± 15 minutes, or 24 hours ± 15 minutes following dosing. The iris/ciliary body, lens, vitreous, retina, choroid, sclera, conjunctiva, and cornea (target tissues) were also collected from each eye for analysis. Dosing solutions were analyzed to confirm radiochemical purity; radioactive concentration of the dosing solutions was calculated using liquid scintillation counting (LSC).

Results: Radioactive residues of ^{14}C-labeled bromfenac, expressed as mean parts per million [(ppm) µg/g] was seen in all target tissues of the eyes, with the highest concentrations found in the cornea, conjunctiva, and sclera. The concentrations in the tissues diminished to varying degrees over the 24 hour study period, with the exception of the lens, which increased insignificantly from the 1 hour time point. The levels detected in the lens and vitreous humor were low and close to background levels.

Conclusion: Significant penetration and measurable amounts of ^{14}C-labeled bromfenac were detected in most ocular target tissues over 24 hours, with highest levels in the cornea, conjunctiva, and sclera. The ^{14}C-low concentration bromfenac residues in ocular tissues were similar to those previously reported with 0.09% ^{14}C-bromfenac, the currently available concentration of bromfenac formulation.

Introduction

Bromfenac is a non-steroidal anti inflammatory drug (NSAID) with an extensive history of clinical efficacy; it acts by blocking prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2 in the arachidonic acid pathway.

The chemical structure of bromfenac contains a bromine atom at the C4 position, which imparts distinguishing characteristics from other ophthalmic NSAIDs including improved potency and enhanced lipophilicity of the molecule, which facilitates penetration into ocular tissues. [1-3]

Introduction - continued

Bromfenac, like most of the NSAIDs, are weakly acidic drugs, which ionize at the pH of the lachrymal fluid and therefore have limited permeability through the anionic cornea, which has an isoelectric point (pI) of 3.2. Reducing the pH of the formulation increases the unionized fraction of the drug which enhances permeation. [4]

Xibrom™ (bromfenac ophthalmic solution) 0.09%, administered twice daily, was approved by the Food and Drug Administration (FDA) on March 24, 2005 for the treatment of patients with post-cataract ocular inflammation, and in January 2006 for the treatment of ocular pain following cataract surgery. [5]

Bromday™ (bromfenac ophthalmic solution) 0.09% administered once daily, was approved by the FDA on October 16, 2010 for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction. [6]

An advanced formulation of bromfenac (PROLENSA™ [bromfenac ophthalmic solution] 0.07%) has been developed which contains a lower pH (7.8) compared to earlier formulations. The lower pH facilitates corneal penetration. PROLENSA also has a lower concentration compared to other available formulations of bromfenac.[7]

Study Design

^{14}C-labeled bromfenac 0.07% was analyzed to verify the radioactive purity prior to its use in the study.

Prior to treatment, 18 animals were weighed and randomly assigned to 6 treatment groups.

A physical examination was performed on each animal including a pre-treatment ophthalmic examination (slit lamp and indirect ophthalmoscopy). Acceptance criteria for placement on study were as follows:

- Scores of ≤ 1 for conjunctival swelling
- Scores of 0 for all other observation variables

Each rabbit received topical ocular doses of a 50µL test agent dose into the conjunctival sac using a calibrated pipette and the eyelid was held closed for 5-10 seconds following the dose.

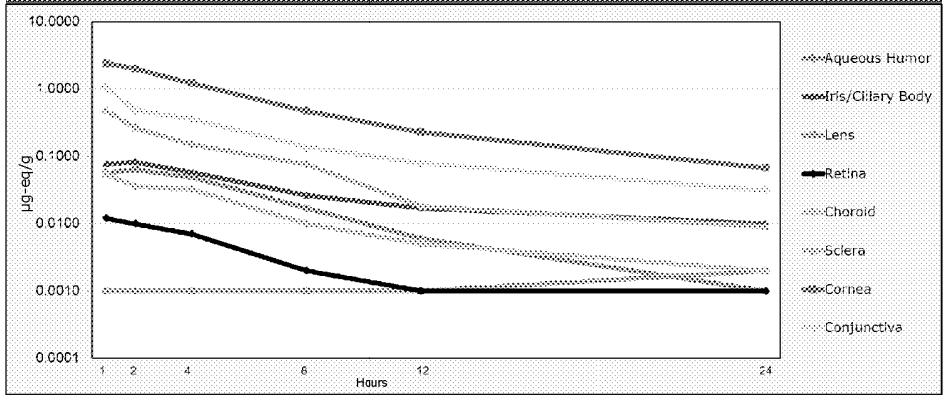
3 rabbits (both eyes) were assessed per time point over a 24 hour period

Animals were euthanized at the following 6 time points:1 hr ± 5 min, 2 hrs ± 15 min, 4 hrs ± 15 min, 8 hrs ± 15 min, 12 hrs ± 15 min, or 24 hrs ± 15 min following dosing.

The iris/ciliary body, lens, vitreous, retina, choroid, sclera, conjunctiva, and cornea were collected from each eye and weighed.

The ocular pharmacokinetics of ^{14}C-labeled bromfenac 0.07%, pH=7.8 was assessed at 6 time points over a 24 hour time interval.

Figure 2: 24 Hour Radioactive Concentrations of ^{14}C-Bromfenac in Ocular Tissues Following a Single 0.07% Dose



Results

The mean µg/g of drug-derived radioactivity follo administration of ^{14}C-bromfenac was seen in all tissu the eyes at low levels, with the highest concentra found in the cornea, conjunctiva, and sclera (Figure 1)

The concentrations in the tissues diminished to va degrees over the 24 hour study period. Levels in the were very low and remained essentially unchanged. radioactivity detected by LSC in both the lens and vitreous humor was very low and close to backgr values.

Discussion

The bromfenac 0.07% formulation has been show improve the penetration into ocular tissues the allowing for a lower concentration with comparable t concentrations to those seen with BROMDAY.

Similar to XIBROM and BROMDAY, the adva formulation of bromfenac 0.07% provides therap concentrations throughout ocular tissues for 24 h which allows for once daily dosing.

PROLENSA (bromfenac ophthalmic solution) 0.07% FDA approved on April 5th, 2013 for once daily dosin the treatment of postoperative inflammation and redu of ocular pain in patients who have undergone cat surgery.

Conclusion

Significant penetration and measurable amount ^{14}C-labeled bromfenac were detected in most oc target tissues over 24 hours, with highest levels in cornea, conjunctiva, and sclera. The 0.07% bromfenac residues in ocular tissues were simila those previously reported with 0.09% ^{14}C-bromfen

References:

1. Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. J Pharmacol Ther 2008;24(4):392-398.
2. Donnenfeld, E.D., Holland, E.J., Stewart, R.H., et.al. Ophthaln 2007; 114:1653-1662.
3. Kim, S.J., Flach, A.J., Jampol, L.M. Surv Ophthalmol. 2010; 55(2 133.
4. Ahuja M, Dhake AS, Sharma SK, Majumdar DK. AAPS J 2008;10:229
5. XIBROM™ Prescribing Information. ISTA Pharmaceuticals, Inc. 2010
6. BROMDAY™ Prescribing Information. Bausch and Lomb, Inc. 2011.
7. PROLENSA™ Prescribing Information, Bausch and Lomb, Inc. 2013

Financial support: Bausch & Lomb Inc., Irvine, CA, USA
Financial disclosures: GA Baklayan is an employee of Bausch & Lomb, Inc

Contact inform
George A. Baklayan
Pharmaceutical Development, Bausch & Lom
50 Technology Dr. Irvine, CA
Phone: (949) 788-5314 george.baklayan@baus

Animal use for this study was approved by the facility's Institutional Animal Care and Use Committee (IACUC) and conformed to the ARVO "Statement on the Use of Animals in Ophthalmic and Visual Research."

Presented at the 2013 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting; May 5-9, 2013; Seattle, WA