LACRIMAL GLAND, TEAR FILM, AND DRY EYE SYNDROMES 2

Basic Science and Clinical Relevance

Edited by

David A. Sullivan
Darlene A. Dartt

The Schepens Eye Research Institute and
Harvard Medical School
Boston, Massachusetts

and

Michele A. Meneray

Louisiana State University Medical Center
New Orleans, Louisiana

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CYCLOSPORINE DISTRIBUTION INTO THE CONJUNCTIVA, CORNEA, LACRIMAL GLAND, AND SYSTEMIC BLOOD FOLLOWING TOPICAL DOSING OF CYCLOSPORINE TO RABBIT, DOG, AND HUMAN EYES

Andrew Acheampong, Martha Shackleton, Steve Lam, Patrick Rudewicz, and Diane Tang-Liu

Allergan
Irvine, California

1. INTRODUCTION

Cyclosporine is an immune modulator that inhibits T-lymphocyte-mediated immunoreactivity. Allergan is currently evaluating the clinical efficacy of 0.05%-0.4% cyclosporine emulsion for the treatment of immuno-inflammatory eye diseases, such as keratoconjunctivitis sicca, or dry eye syndrome. Topical ocular application of cyclosporine, formulated as 2% cyclosporine in olive oil, 0.2% cyclosporine in corn oil ointment (Schering-Plough), or 0.2% cyclosporine emulsion (Allergan), was found to reduce ocular surface inflammation and improve lacrimal gland secretion in dogs with KCS.[1–3]

The aim of the present research was to determine the ocular tissue distribution of cyclosporine in rabbits and dogs, and to compare tissue concentrations in rabbits, dogs, and humans after topical administration. Determination of relationships between the ocular tissue drug concentrations and efficacy is important for optimizing delivery of pharmacologically active concentrations in the target ocular surface tissues, providing support to the local mechanism of action, and optimizing dosing regimen.

2. METHODS

2.1. Animal Studies

[Mebmt -^{3}H]-cyclosporin-A was prepared by Amersham (UK) with radiochemical purity greater than 98%. Female New Zealand white rabbits (2–3 kg) received a single 50

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µl dose of 0.2% ^{3}H-cyclosporine formulation (~1 mCi/ml) into the lower conjunctival cul-de-sac of the left eye. Male beagle dogs (10–13 kg) received a 35 µl dose of 0.2% ^{3}H-cyclosporine emulsion (~1 mCi/ml) into the lower conjunctival cul-de-sac, twice daily for 7 days. Ocular tissues and systemic blood were also collected at selected time points over a 96-h period postdose. Two dogs or four rabbits were used per time point. The rabbit experiments were conducted according to USDA and Allergan ACUC guidelines. The dog study was conducted at Huntingdon Life Sciences. Tissue radioactivity concentrations were expressed as ng equivalents (eq) of cyclosporine per gram of tissue, using the specific activity of the dose formulation.

2.2. Human Range-Finding Study

One hundred sixty-two human subjects with KCS received an eyedrop of vehicle or 0.05%, 0.1%, 0.2%, or 0.4% cyclosporine emulsion twice daily for 12 weeks. Blood samples were collected from all subjects at morning troughs after 1, 4, and 12 weeks of dosing. In addition, blood samples were collected from selected subjects at 1, 2, and 4 h after the last dose at week 12. Cyclosporin A (CsA) concentrations in blood samples were measured by a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method with Cyclosporin G as the internal standard. The lower limit of quantitation of the blood assay was 0.1 ng/ml.

3. RESULTS AND DISCUSSION

Figs. 1 and 2 depict the time course of cyclosporine in tears, ocular surface tissues, and orbital lacrimal gland of rabbits and dogs after eyedrop instillation of 0.2% ^{3}H-cyclosporine emulsion. Significant cyclosporine concentrations (C_{max}, ~1000 ng/g) were found in the conjunctiva and cornea, the target tissues for CsA reduction of ocular surface inflammation. The 0.2% emulsion provided approximately 7-fold higher cyclosporine concentrations in the rabbit cornea and conjunctiva than those for 0.2% cyclosporine in pure castor oil.[4] The lacrimal gland C_{max} was several-fold that of blood (~1 ng-eq/g), especially in the dog.

The ocular absorption and disposition of cyclosporine in rabbits and dogs were characterized by rapid absorption into ocular and extraocular tissues, reservoir effect of the cornea, relatively low intraocular tissue concentrations, and a long terminal elimination half-life of 20–44 h in most ocular tissues (Figs. 1 and 2). Similar ocular distribution characteristics were noted in previous rabbit and human studies.[4–7]

Table 1 shows less than 0.2 ng/ml blood concentrations in humans following multiple topical instillation of 0.05%, 0.1%, 0.2%, and 0.4% cyclosporine ophthalmic emulsion over a 12-week period of dosing. The systemic blood CsA concentrations in humans after topical CsA doses of the emulsions were much lower than the blood trough concentrations of 20–100 ng/ml used for monitoring the safety of patients receiving systemic cyclosporine therapy.

4. CONCLUSIONS

Topically applied cyclosporine emulsion can produce significant concentrations in the cornea and conjunctiva to exert a local immunomodulatory effect. The ocular distribu-

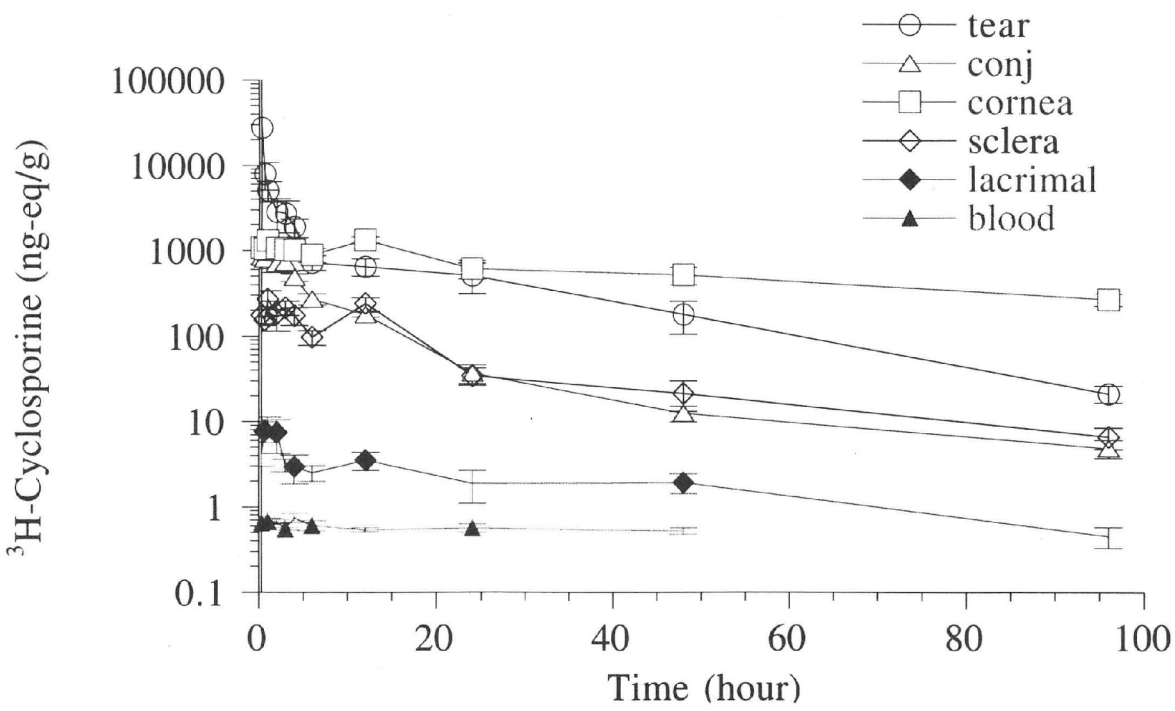

Figure 1. Total radioactivity concentrations (mean ± SEM) in rabbit eyes and systemic blood.

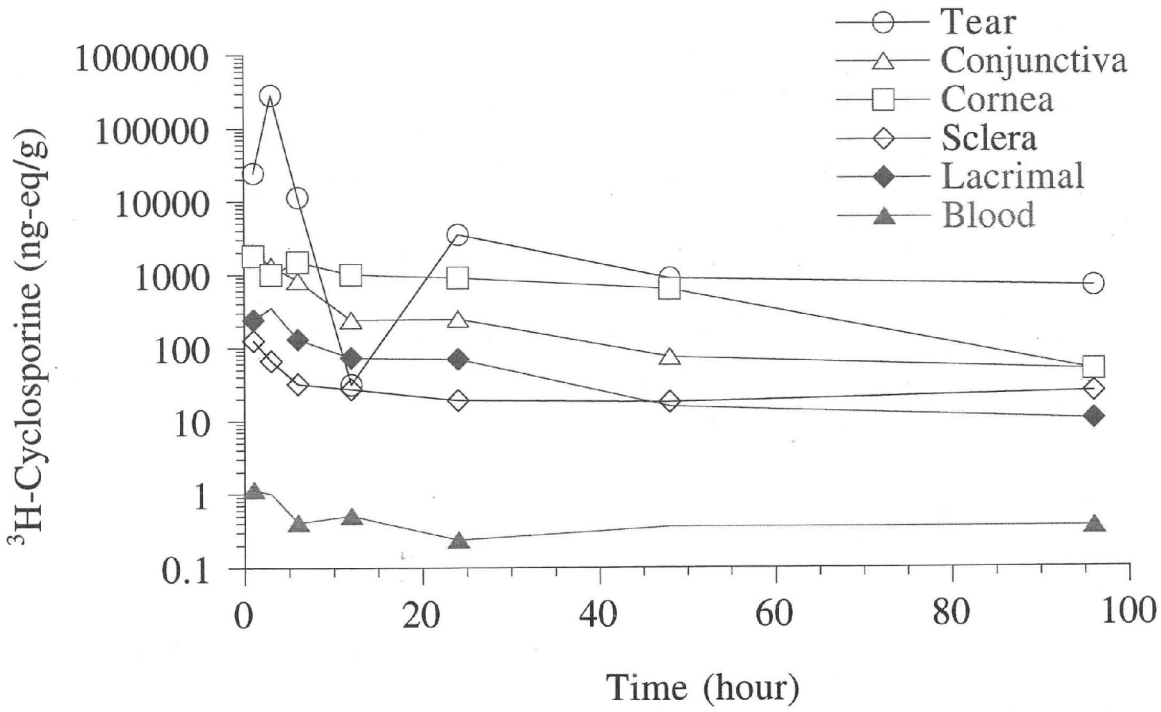

Figure 2. Total radioactivity concentrations (mean values) in dog eyes and systemic blood.

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