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

PLENUM PRESS • NEW YORK AND LONDON



```
Lacrimal gland, tear film, and dry eye syndromes 2 : basic science and
clinical relevance / edited by David A. Sullivan, Darlene A. Dartt,
 and Michele A. Meneray.
     p. cm. -- (Advances in experimental medicine and biology ; v.
 438.)
   "Proceedings of the Second International Conference on the
 Lacrimal Gland, Tear Film, and Dry Eye Syndromes, held November
 16-19, 1996, at the Southhampton Princess Resort, Bermuda"--T.p.
verso.
   Includes bibliographical neferences and index.
   ISBN 0-306-45812-8
   1. Lacrimal apparatus--Physiology--Congresses. 2. Tears-
 -Congresses. 3. Dry eye syndromes--Congresses.
                                                  I. Sullivan, David
 D. II. Dartt. Darlene A. III. Meneray, Michele A.
 IV. International Conference on the Lacrimal Gland, Tear Film, and
Dry Eye Syndromes (2nd : 1996 : Southampton, Bermuda Islands)
 V. Series.
   [DNLM: 1. Lacrimal Apparatus—congresses. 2. Tears—physiology-
 -congresses. 3. Dry Eye Syndromes--congresses. W1 Ad559 v. 438
QP188.T4L332 1998
612.8'47--dc21
DNLM/DLC
                                                            98-17987
 for Library of Congress
                                                                CIP
```

Proceedings of the Second International Conference on the Lacrimal Gland, Tear Film, and Dry Eye Syndromes, held November 16-19, 1996, at the Southampton Princess Resort, Bermuda

ISBN 0-306-45812-8

© 1998 Plenum Press, New York A Division of Plenum Publishing Corporation 233 Spring Street, New York, N.Y. 10013

http://www.plenum.com

10987654321

All rights reserved

No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise, without written permission from the Publisher

Printed in the United States of America



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 -3H]-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

Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2 edited by Sullivan et al., Plenum Press, New York, 1998

1001



1002 A. Acheampong et al.

µl dose of 0.2% ³H-cyclosporine formulation (~1 mCi/ml) into the lower conjunctival culde-sac of the left eye. Male beagle dogs (10–13 kg) received a 35 μl dose of 0.2% ³H-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. 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-



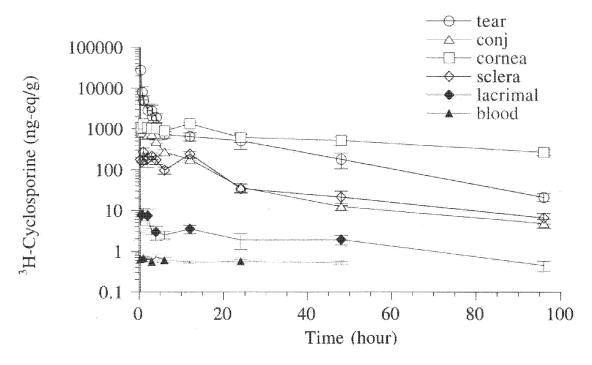


Figure 1. Total radioactivity concentrations (mean ± SEM) in rabbit eyes and systemic blood.

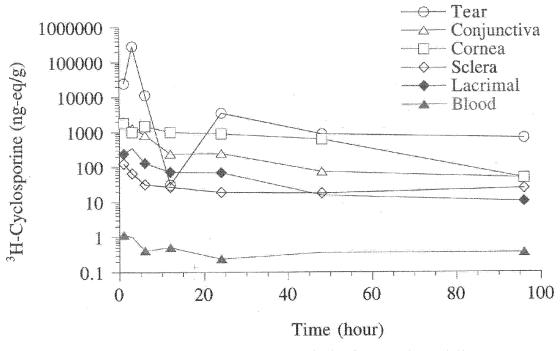


Figure 2. Total radioactivity concentrations (mean values) in dog eyes and systemic blood.



DOCKET

Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

