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PHARMACOKINETICS AND DRUG METABOLISM
DEPARTMENTAL RESEARCH REPORT

Report No.: PK–98–074

Ocular Cyclosporine Distribution During 9½ Days of Dosing of 0.05 and 0.1% ^{3}H-Cyclosporin A Emulsions to Albino Rabbit Eyes

Project name and number:	Cyclosporine, 200200401081
Study number:	PK-97-P019
Lab notebooks:	L–1998–5707 L–1998–5709
In-life test facility:	Allergan
In–life study period:	October 11-December 2, 1997
Study Technicians:	V. Baumgarten, S. Sirossian
Study Director:	D. Small

This study was conducted in compliance with the Good Laboratory Practices (GLP), 21 Code of Federal Regulations, Part 58.

Written by: _____ 10·29-98
D. Small, Ph.D., Senior Scientist — Date
Pharmacokinetics and Drug Metabolism

Reviewed by: _____ 10/29/98
A. Acheampong, Ph.D., Principal Scientist — Date
Pharmacokinetics and Drug Metabolism

Approved by: _____ 10-29-98
D. Tang-Liu, Ph.D., Director — Date
Pharmacokinetics

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STATEMENT OF COMPLIANCE

This study was conducted in accordance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). This report accurately reflects all raw data obtained for analysis. There were no significant deviations from Good Laboratory Practice Regulations that could have affected the quality or integrity of the study.

Study Director:  10-29-98

Dave Small, Ph.D., Senior Scientist Date

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SUMMARY

Cyclosporin A (CsA, AGN 192371) is being developed for the treatment of Sjögren's and non-Sjögren's dry eye. We investigated the absorption and disposition of CsA in blood and various ocular tissues of albino rabbits after repeated ophthalmic ^{3}H-CsA administration. Forty-two rabbits were dosed bilaterally with 50 µl of ^{3}H-CsA 0.05% (N=20) or 0.1% (N=20) ^{3}H-CsA emulsions twice daily for 9½ days or remained undosed (N=2) as analytical controls. Instilled doses were 0.0444 and 0.100 mg/kg/day for 0.05 and 0.1%-treated animals, respectively. Systemic blood was sampled and the tears, lacrimal gland, upper and lower bulbar conjunctiva, sclera, cornea, aqueous humor, iris-ciliary body, lens, vitreous humor, choroid-retina, and optic nerve head from each eye of two rabbits were sampled immediately before and 0.33, 1, 3, 6, 12, 24, 48, 96, and 144 hours after the last dose, after which they were analyzed by liquid scintillation analysis with or without tissue combustion. A previous study has shown that CsA is not metabolized in albino rabbit ocular tissues, and therefore radioactivity represents intact CsA.

Results in selected tissues after the last dose are shown below:

Tissue	0.05% CsA			0.1% CsA		
	Cmax (ng-eq/g)	AUC_{0-12} (ng-eq•hr/g)	$t_{1/2}$ (hr)	Cmax (ng-eq/g)	AUC_{0-12} (ng-eq•hr/g)	$t_{1/2}$ (hr)
Lacrimal gland	11.9	66.0	ND	15.4	140	ND
Lower conjunctiva	713	5,030	ND	1,920	15,600	31.8
Cornea	1,550	12,300	50.9	4,810	49,300	52.0
Sclera	84.5	848	39.2	262	2,710	40.5
Lens	18.4	186	480	55.2	529	271
Vitreous humor	2.93	22.8	ND	10.2	87.0	ND
Optic nerve head	29.3	<146	ND	67.7	<395	ND

ND: not determinable

Mean concentrations in tears at the first sampling time point of 20 minutes were 14,000 and 41,000 ng-eq/g after the last dose of 0.05 and 0.1% CsA, respectively. Tissue concentrations were generally flat through 12 hours, with no pronounced Cmax. AUC_{0-12} in external tissues followed the rank order tears >> cornea > lower conjunctiva ~ upper conjunctiva >> sclera, and in internal tissues followed the order iris-ciliary body >> choroid-retina > lens > vitreous humor > aqueous humor. Blood concentrations were <0.694 ng-eq/g and <1.88 ng-eq/g in 0.05%- and 0.1%-treated animals, respectively.

Based on previously-reported single dose data, there was moderate accumulation in most tissues. Accumulation in lens, vitreous humor, and optic nerve head was 13- to 37-fold, although concentrations in these tissues remained less than 70 ng-eq/g. Except for lens, calculable elimination half-lives ranged from 25 to 57 hours.

The results of this study indicate that CsA concentrations were substantial in ocular surface tissues, and have long elimination half-lives that are conducive to the twice-daily dosing regimen proposed for clinical ophthalmic use. Blood concentrations were below the quantitation limit, and support the systemic safety of ophthalmic CsA administration.

KEY WORDS

Cyclosporine, cyclosporin, albino rabbit, ocular distribution

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