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Report

Pharmacokinetics of the Aldose Reductase Inhibitor Imirestat Following Topical Ocular Administration

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The pharmacokinetics of imirestat following topical ocular administration were evaluated in a series of studies in rabbits and dogs. Following single topical doses to both albino and pigmented rabbits, imirestat was subject to rapid uptake into the cornea followed by an initial rapid decline and then very slow elimination, with a $t_{1/2}$ of approximately 130 hr. Drug was rapidly absorbed into aqueous humor, with concentrations declining to nondetectable levels by 12 hr. Imirestat was retained in the lens following topical dosing similar to that in cornea, with an apparent elimination $t_{1/2}$ of 140 hr. Vitreous humor concentrations of drug were detectable for up to 72 hr after dosing. There was no apparent difference in the disposition of the drug between albino and pigmented rabbits. Bioavailability following topical dosing increased with dose, although not in a linear fashion. Formulation pH did not have an appreciable effect on ocular bioavailability. There was detectable systemic absorption following topical dosing, with plasma concentrations in rabbit being 50 to 75% of that observed following an equivalent intravenous dose. However, drug levels in the dosed eyes were significantly higher than in contralateral undosed eyes. Multiple dosing of imirestat for 6 weeks resulted in accumulation of drug in rabbit lens. Concentrations were higher in lens cortex than lens nucleus, with the time course for accumulation being different for the two. Our data suggest that imirestat penetrates into ocular tissue following topical dosing and is retained in lens and cornea, potential sites of action for the drug.

KEY WORDS: aldose reductase inhibitor; imirestat; AL01576; HOE843; ocular pharmacokinetics.

INTRODUCTION

Imirestat [2,7-difluro-spiro(9H-fluorene-9,4′-imidazolidine)-2′,5′dione; AL01576; HOE843; Fig. 1] is a highly potent aldose reductase inhibitor (ARI) that is currently being evaluated clinically as a potential systemic therapy for some of the pathological conditions associated with diabetes mellitus, such as neuropathy, retinopathy, and cataract (1). In addition to its ability to prevent cataract formation in experimental models of diabetes (2), imirestat has also been shown to delay or prevent lens changes in nondiabetic oxidative cataract models following topical ocular administration (3). The drug is therefore being evaluated clinically as a potential anticataract therapy via the topical ocular route of administration.

Imirestat is a weak acid with a low aqueous solubility and a pK_a of 7.35. The drug is approximately 85% bound to plasma proteins, with the protein binding being highly pH dependent at physiological pH (4). Pharmacokinetic studies in rats have shown that systemically administered imirestat is distributed extensively into body tissues and has a low systemic clearance and a long biologic half-life (5). A similar pharmacokinetic pattern has been observed in preliminary studies in rabbits. It has also been shown that the drug is retained by certain tissues of the rat (i.e., eye, testes, kidney) which contain significant amounts of aldose reductase, suggesting that high affinity binding of imirestat to the enzyme may be responsible for the persistence of drug in these tissues (5).

It has also been demonstrated that intact imirestat is the only component in rat plasma following iv or oral administration of ^{14}C-imirestat (5), suggesting that the disposition of ^{14}C-imirestat may be representative of the disposition of the intact drug. This, along with *in vitro* metabolism data which demonstrate very slow metabolism of imirestat, suggests that measurements of radioactivity following topical dosing of ^{14}C-imirestat may be representative of the disposition of the parent drug.

In order to understand better the disposition of imirestat following topical ocular administration, five separate pharmacokinetic studies were conducted: (1) single-dose ocular pharmacokinetics in rabbits; (2) effect of dose and pH on ocular bioavailability in rabbits; (3) systemic absorption following topical dosing to rabbits; (4) systemic absorption following topical dosing to dogs; and (5) multiple-dose ocular pharmacokinetics in rabbits.

MATERIALS AND METHODS

Materials

Radiolabeled ^{14}C-imirestat was synthesized by Pathfinder Laboratories (St. Louis, MO). The material was found

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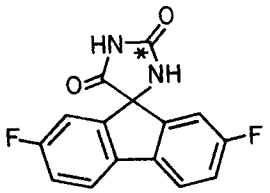

Fig. 1. Chemical structure of imirestat.

to have >98% radiochemical purity, with a specific activity of 42.3 mCi/mmol. Various suspension formulations were prepared by dispersing nonradiolabeled imirestat and ^{14}C-imirestat in a standard phosphate-buffered formulation vehicle, adjusting the pH to obtain the desired value and ball milling overnight. Each formulation studied contained 0.01% benzalkonium chloride and 0.01% EDTA.

Animal Treatment and Sample Collection

Study 1. Single-Dose Ocular Pharmacokinetics of ^{14}C-Imirestat. Sixty (60) New Zealand albino rabbits weighing between 2 and 4 kg and 60 Dutch Belted pigmented rabbits weighing between 1.5 and 2.5 kg were administered a single 30-μl topical ocular dose of 0.05% ^{14}C-imirestat suspension (pH 6.5) to each eye. Four rabbits of each species were sacrificed at each of the following times after dosing: 0.33, 0.67, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hr. Aqueous humor, cornea, lens, and vitreous humor were collected separately from each eye. Aqueous humor and vitreous humor were directly analyzed for total radioactivity by liquid scintillation spectrometry. The other tissue samples were solubilized with Soluene for 2 days, followed by decolorization with 30% hydrogen peroxide prior to measurement of total radioactivity.

Study 2. Effect of Dose and pH on Ocular Bioavailability of ^{14}C-Imirestat. Forty (40) New Zealand albino rabbits weighing between 2 and 4 kg were divided into five treatment groups of eight animals each. Each group received a single 30-μl topical ocular dose to both eyes of one of the following five formulations: (1) 0.1% ^{14}C-imirestat, pH 7.5; (2) 0.1% ^{14}C-imirestat, pH 6.5; (3) 0.1% ^{14}C-imirestat, pH 5.5; (4) 0.05% ^{14}C-imirestat, pH 6.5; and (5) 0.01% ^{14}C-imirestat, pH 6.5. Four rabbits from each group were sacrificed at 20 and 60 min following dosing. Aqueous humor, cornea, lens, and vitreous humor were collected from both eyes and were analyzed as described in Study 1.

Study 3. Systemic Absorption of ^{14}C-Imirestat Following Topical Dosing to Rabbits. Sixteen (16) New Zealand albino rabbits weighing between 2 and 4 kg were divided into two treatment groups of eight animals each. One group received a single 50-μl topical ocular dose of 0.1% ^{14}C-imirestat suspension (pH 6.5) in one eye only. The other groups received an intravenous injection of 50 μg of ^{14}C-imirestat dissolved in propylene glycol:ethanol:water (5:1:4) into the marginal ear vein. The iv dose delivered an equivalent dose to the systemic circulation as was contained in the 50-μl dose of the 0.1% imirestat suspension. Four rabbits from each group were sacrificed at 4 and 12 hr after dosing. Aqueous humor, cornea, lens, and vitreous humor were collected from both eyes and were treated as described in Study 1. In addition, plasma samples were collected at 0, 1, 4, 8, and 12 hr from the groups sacrificed at 12 hr.

Study 4. Systemic Absorption of ^{14}C-Imirestat Following Topical Dosing to Dogs. Twelve (12) beagle dogs were

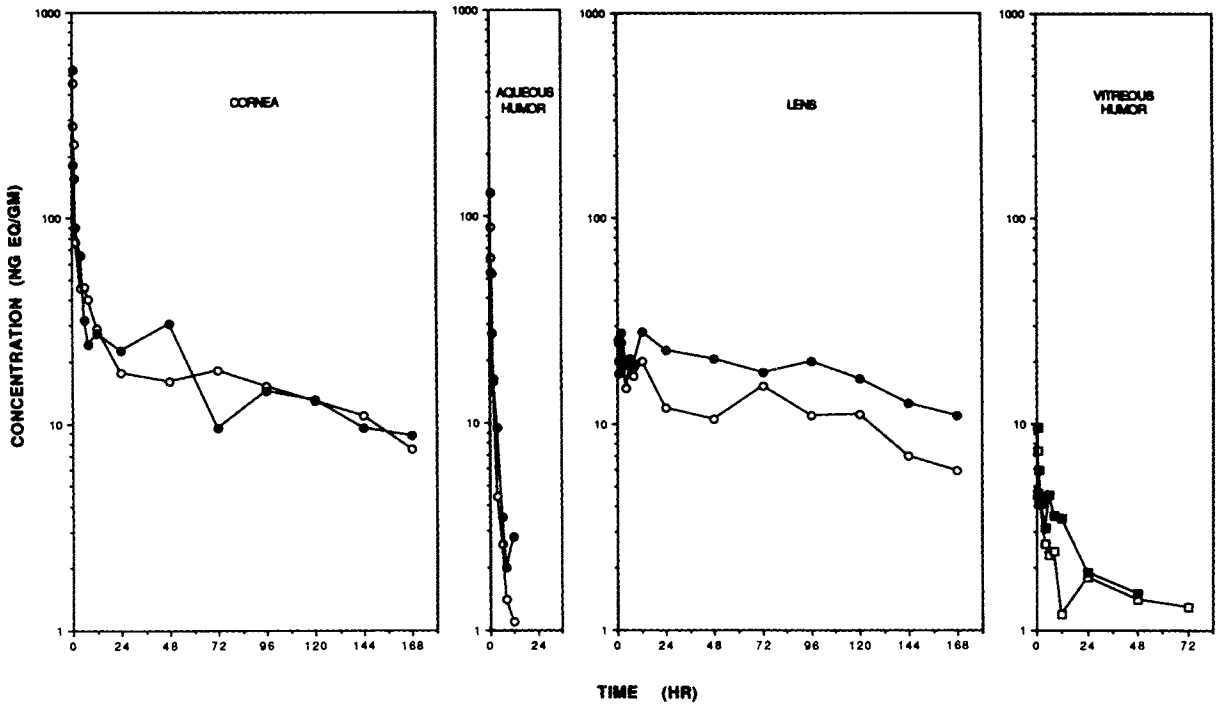

Fig. 2. Mean (N = 8) ^{14}C-imirestat concentrations in cornea, aqueous humor, lens, and vitreous humor following a single topical ocular dose of 0.05% ^{14}C-imirestat suspension in rabbits. Open circles represent data from New Zealand albino rabbits and filled circles are data from Dutch Belted pigmented rabbits.

Table I. Effect of Formulation pH on the Tissue Concentrations of ^{14}C-Imirestat Following a Single Topical Ocular Administration of a 0.1% ^{14}C-Imirestat Suspension

Tissue	Time (min)	Imirestat concentration (μg/g)[a] pH 5.5	pH 6.5	pH 7.5
Cornea	20	2.6 ± 1.0	4.2 ± 2.5	3.9 ± 1.8
	60	0.76 ± 0.30	0.92 ± 0.61	0.91 ± 0.49
Aqueous humor	20	0.36 ± 0.17	0.40 ± 0.23	0.41 ± 0.27
	60	0.12 ± 0.05	0.15 ± 0.10	0.14 ± 0.08
Lens	20	0.038 ± 0.029	0.048 ± 0.030	0.051 ± 0.026
	60	0.028 ± 0.016	0.042 ± 0.016	0.051 ± 0.026

[a] Mean ± SD (N = 8).

administered a single 50-μl topical ocular dose of ^{14}C-imirestat suspension (pH 6.5) into one eye only. Four dogs each were sacrificed 4, 12, and 24 hr after the administered dose. Aqueous humor, cornea, lens, and vitreous humor were collected from both the dosed and the undosed eye of each animal and were analyzed as described in Study 1. In addition, plasma samples were collected at 0 and 4 hr from the group sacrificed at 4 hr, at 0, 1, 4, 8, and 12 hr from the group sacrificed at 12 hr, and at 0 and 24 hr from the dogs sacrificed at 24 hr.

Study 5. Multiple-Dose Ocular Pharmacokinetics of Imirestat in Rabbits. Sixty-four (64) New Zealand albino rabbits were divided into six groups of nine animals each and two groups of five animals each. Each group of nine animals received one of the following topical ocular dosing regimens of an unlabeled imirestat suspension (pH 6.5) for 6 weeks: (1) 0.01% imirestat once daily; (2) 0.025% imirestat once daily; (3) 0.05% imirestat once daily; (4) 0.1% imirestat once daily; (5) 0.1% imirestat twice daily; and (6) 1% imirestat twice daily. Additionally, the two groups of five rabbits received the following dosing regimen for 3 weeks: (1) 0.05% imirestat once daily and (2) 0.05% imirestat twice daily. The lens was removed from each animal after either 3 or 6 weeks of dosing and was separated into lens cortex and lens nucleus for assay of imirestat concentration.

Sample Analysis

All radiometric analyses of prepared tissue samples were conducted using a liquid scintillation spectrometer (Packard Tri-Carb, Model 2000). Counting efficiency was determined using an automatic external standard method. Radioactivity measurements (dpm) were converted to imirestat concentration equivalents by correcting for the specific activity of the dosed solution. Concentrations of imirestat in the lens nucleus and cortex from Study 5 were measured by a gas chromatographic-electron capture assay (6,7). The assay involved solubilization of the lens in 0.1% sodium hydroxide and precipitation of proteins with 1% sulfosalicylic acid. The supernatant was then purfied with a C_{18} solid-phase extraction column, derivatized with pentafluorobenzyl bromide, and analyzed using a Hewlett-Packard Model

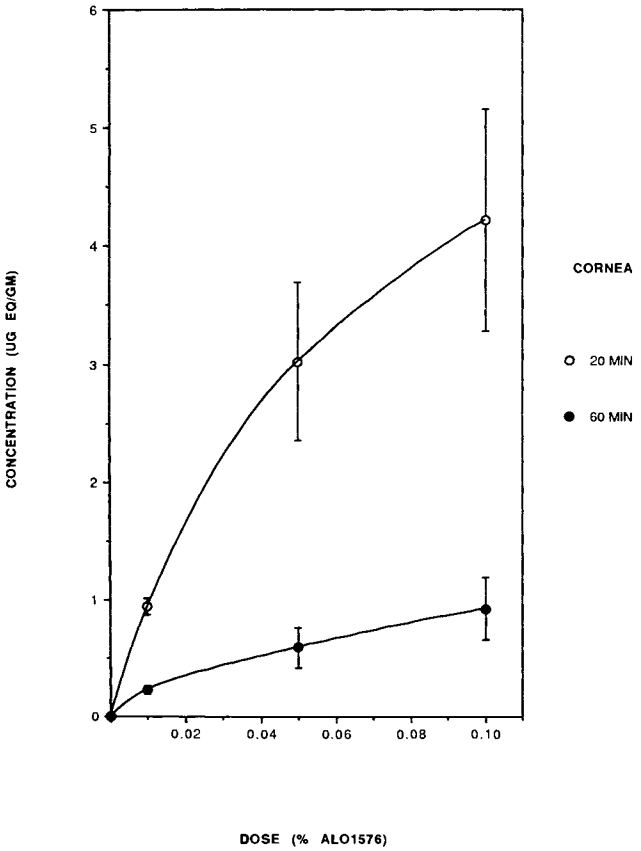

Fig. 3. Effect of dose on ^{14}C-imirestat bioavailability in cornea (mean ± SE; N = 8).

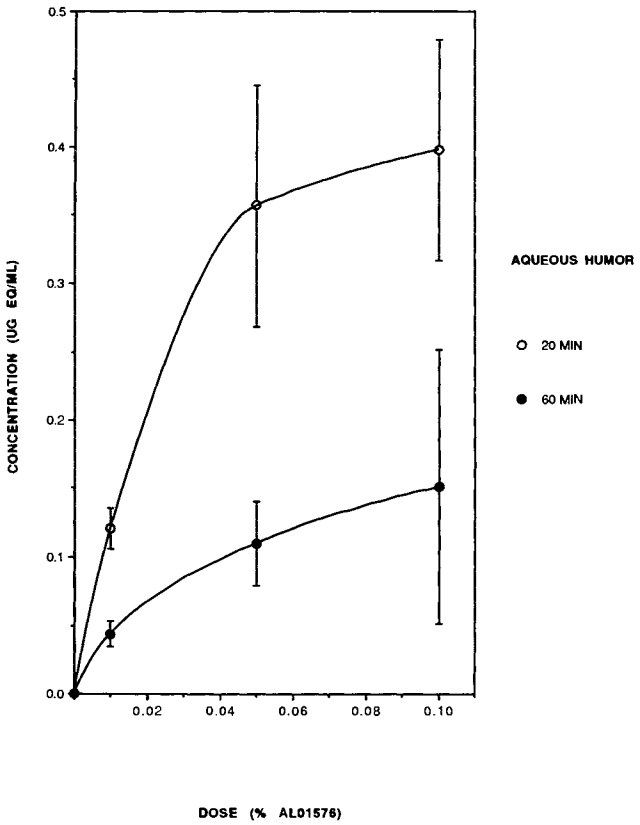

Fig. 4. Effect of dose on ^{14}C-imirestat bioavailability in aqueous humor (mean ± SE; N = 8).

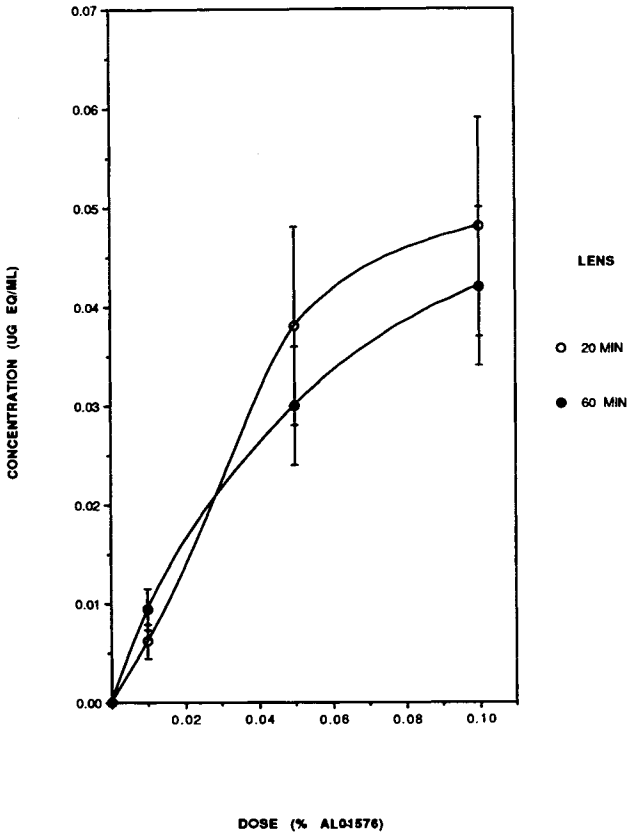

Fig. 5. Effect of dose on ^{14}C-imirestat bioavailability in lens (mean ± SE; N = 8).

S890 gas chromatograph with a SPB-1 capillary column and ^{63}Ni electron capture detector. The lower limit of sensitivity of the assay was 2.5 ng/g. Reproducibility of the assay (%CV) ranged from 2% at 60 ng/g to 17.5% at 2.5 ng/g.

RESULTS

The ^{14}C-imirestat concentration–time profiles in cornea, aqueous humor, lens, and vitreous humor following a single topical ocular dose of 0.05% imirestat suspension to both albino and pigmented rabbits (Study 1) are presented in Fig. 2. These data demonstrate that the drug experiences rapid initial uptake into and elimination from the cornea, followed by a very slow terminal elimination phase beginning at approximately 6 hr and proceeding throughout the 168 hr of sampling. The half-life for elimination of drug from the cornea during this slow terminal phase was approximately 130 hr for both albino and pigmented rabbits. Imirestat was rapidly absorbed into the aqueous humor, with peak concentrations occurring at 20 min and then declining to nondetectable levels within 8 to 12 hr. The very slow terminal elimination phase observed in the cornea was not apparent in the aqueous humor at detectable levels.

The initial rapid elimination phase observed in the cornea and aqueous humor was not apparent in lens. However, a slow terminal elimination phase similar to the cornea was observed, with a half-life of 140 hr for both albino and pigmented rabbits. Concentrations of imirestat were detectable in the vitreous humor for 48 to 72 hr after single ocular administration of the drug. The pharmacokinetics were similar in both the albino and the pigmented rabbit species in all tissues examined (Fig. 2).

The effect of formulation pH on the bioavailability of imirestat (Study 2) is presented in Table I. These data demonstrate that the pH had no appreciable effect on the bioavailability of imirestat from the suspension formulations that were evaluated. The influence of dose on imirestat bioavailability is shown in Figs. 3–5. Absorption of drug into all tissues increased with increasing dose, although not in a linear manner. A 10-fold increase in dose (from 0.01 to 0.1%) resulted in only a 3- to 5-fold increase in tissue concentrations of ^{14}C-imirestat.

Table II. ^{14}C-Imirestat Concentrations in Various Tissues Following Intravenous Administration of 50 μg of ^{14}C-Imirestat and Unilateral Topical Ocular Dosing of 50 μl of 0.1% ^{14}C-Imirestat Suspension to the Right Eye (OD) of New Zealand Albino Rabbits

Tissue	Time (hr)	^{14}C-Imirestat concentration (ng/g)[a]			
		Topical		Intravenous	
		OD[b]	OS[c]	OD	OS
Cornea	4	82 ± 76	2.0 ± 1.4	0.45 ± 0.18	0.31 ± 0.07
	12	49 ± 52	1.2 ± 1.1	0.40 ± 0.21	0.46 ± 0.18
Aqueous humor	4	17 ± 6.6	0.42 ± 0.18	0.48 ± 0.12	0.37 ± 0.14
	12	5.3 ± 3.5	0.22 ± 0.09	0.37 ± 0.06	0.49 ± 0.27
Lens	4	41 ± 37	0.78 ± 0.13	0.80 ± 0.26	0.78 ± 0.23
	12	13 ± 2	1.7 ± 0.38	1.9 ± 0.73	1.7 ± 0.96
Vitreous humor	4	26 ± 26	0.55 ± 0.14	0.54 ± 0.14	0.70 ± 0.34
	12	1.4 ± 0.9	0.50 ± 0.13	0.56 ± 0.26	0.82 ± 0.36
Plasma	1	2.9 ± 0.36		6.3 ± 1.8	
	4	2.8 ± 0.36		4.7 ± 1.4	
	8	2.9 ± 0.43		3.9 ± 1.5	
	12	2.7 ± 0.27		4.4 ± 2.0	

[a] Mean ± SD (N = 4).
[b] Dosed eye (right eye).
[c] Undosed eye (left eye).

Systemic absorption following topical ocular dosing and crossover into the contralateral undosed eye is presented in Table II for rabbit (Study 3) and Table III for dog (Study 4). Concentrations of drug in the tissues of dosed eyes were generally greater for rabbit than dog. Drug concentrations in the dosed eyes were considerably greater than those in the undosed eye in both species, although measurable concentrations of drug were detectable in all tissues sampled. Drug concentrations in the undosed eye of rabbits following topical dosing were similar to those measured following an equivalent intravenous dose. Plasma concentrations of ^{14}C-imirestat following topical ocular administration to rabbits were about 50 to 75% of those following iv dosing (Table II), suggesting significant systemic absorption of drug following topical administration. Following both topical and systemic dosing, plasma drug levels declined little over the 12 hr of sampling, suggesting very slow elimination from plasma, similar to that observed with cornea and lens.

Concentrations of imirestat measured by the gas chromatographic assay from the nucleus and cortex of lenses of rabbits dosed topically with various multiple dosing regimens of imirestat (Study 5) are presented in Table IV. Drug concentrations were consistently higher in the lens cortex than in the nucleus. The relationship between the apparent steady-state lens imirestat concentration and the administered dose is shown in Fig. 6. The pattern observed is similar to that in the single-dose studies, with lens drug concentrations increasing with dose but not in a linear fashion. A 10-fold increase in dose, from 0.01 to 0.1% dosed once a day, resulted in only a 3-fold increase in steady-state total lens concentrations, while an increase from 0.1 to 1% dosed twice a day afforded only a 2-fold increase in total lens concentrations. Similar relationships are also noted for lens nucleus and cortex drug concentrations.

Table III. ^{14}C-Imirestat Concentration in Various Tissues Following Unilateral Topical Ocular Dosing of 50 μl of 0.1% ^{14}C-Imirestat Suspension to the Right Eye (OD) of Beagle Dogs

Tissue	Time (hr)	^{14}C-Imirestat concentration (ng/g)[a] OD[c]	OS[d]
Cornea	4	58 ± 25	0.30 ± 0.28
	12	20 ± 6	0.30 ± 0.12
	24	11 ± 18	0.14 ± 0.03
Aqueous humor	4	13 ± 8	0.011 ± 0.099
	12	3.2 ± 2.5	0.036 ± 0.029
	24	0.17 ± 0.04	0.033 ± 0.021
Lens	4	9.8 ± 3.0	0.38 ± 0.52
	12	7.0 ± 3.6	0.72 ± 0.20
	24	2.0 ± 1.6	0.12 ± 0.04
Vitreous humor	4	0.85 ± 0.87	0.14 ± 0.22
	12	0.77 ± 0.93	0.048 ± 0.036
	24	0.12 ± 0.16	0.021 ± 0.025
Plasma[b]	1	0.086 ± 0.063	
	2	0.12 ± 0.59	
	8	0.11 ± 0.07	
	12	0.098 ± 0.075	
	24	0.058 ± 0.051	

[a] Mean ± SD (N = 4).
[b] Data for 1, 4, 8, and 12 hr taken from dogs sacrificed at 12 hr; data for 24 hr taken from dogs sacrificed at 24 hr.
[c] Dosed eye (right eye).
[d] Undosed eye (left eye).

Table IV. Concentrations of Imirestat in Rabbits Dosed Topically with Various Dosing Regimens of Imirestat

Treatment	n	Mean (±SD) imirestat concentration (μg/g) Nucleus	Cortex	Total lens
1% BID,[a] 6 weeks	9	0.56 ± 0.18	0.78 ± 0.05	0.71 ± 0.07
0.1% BID, 6 weeks	9	0.18 ± 0.05	0.43 ± 0.06	0.34 ± 0.05
0.1% QD,[b] 6 weeks	9	0.11 ± 0.03	0.29 ± 0.08	0.23 ± 0.05
0.05 QD, 6 weeks	9	0.081 ± 0.032	0.18 ± 0.06	0.14 ± 0.03
0.025% QD, 6 weeks	9	0.044 ± 0.011	0.16 ± 0.03	0.11 ± 0.02
0.01% QD, 6 weeks	9	0.024 ± 0.011	0.094 ± 0.021	0.072 ± 0.012
0.05% QD, 3 weeks	4	0.041 ± 0.001	0.17 ± 0.04	0.11 ± 0.02
0.05% BID, 3 weeks	5	0.077 ± 0.015	0.38 ± 0.05	0.27 ± 0.05

[a] Twice-daily dosing.
[b] Once-daily dosing.

The accumulation of drug in the cortex, nucleus, and total lens during the 3 and 6 weeks of once-daily dosing of 0.05% imirestat (Study 5) is presented in Fig. 7. Whereas drug concentrations in the cortex do not show appreciable increases from 3 to 6 weeks, concentrations in the nucleus do continue to accumulate during this period. This suggests that the uptake of drug into different sections of the lens may be driven by different kinetic mechanisms.

DISCUSSION

Topically administered aldose reductase inhibitors have demonstrated potential in preventing cataract formation in both diabetic and nondiabetic animal models (2,3). There is also some thought that a topical aldose reductase inhibitor may be beneficial in corneal healing and integrity in diabetic patients (8–10). Clinical evaluation of a potential anticataract agent is a difficult challenge due to the slow progression of the disease and difficulty in measuring lens changes. Therefore, considerable emphasis must be placed on data obtained from animal studies in choosing an appropriate dosing regimen for clinical evaluation. In this respect, the pharmacokinetic behavior of drugs following topical dosing and the relationship between this and their biochemical and pharmacological effects is a very important area for study. Drug disposition in the lens and cornea is particularly important, as these are potential sites of action for an aldose reductase inhibitor.

The pharmacokinetics of imirestat following topical ocular administration are characterized by rapid uptake of drug into the cornea followed by initial rapid decline and then slow elimination. Drug is rapidly absorbed into aqueous humor, with peak concentrations occurring within 20 min (the

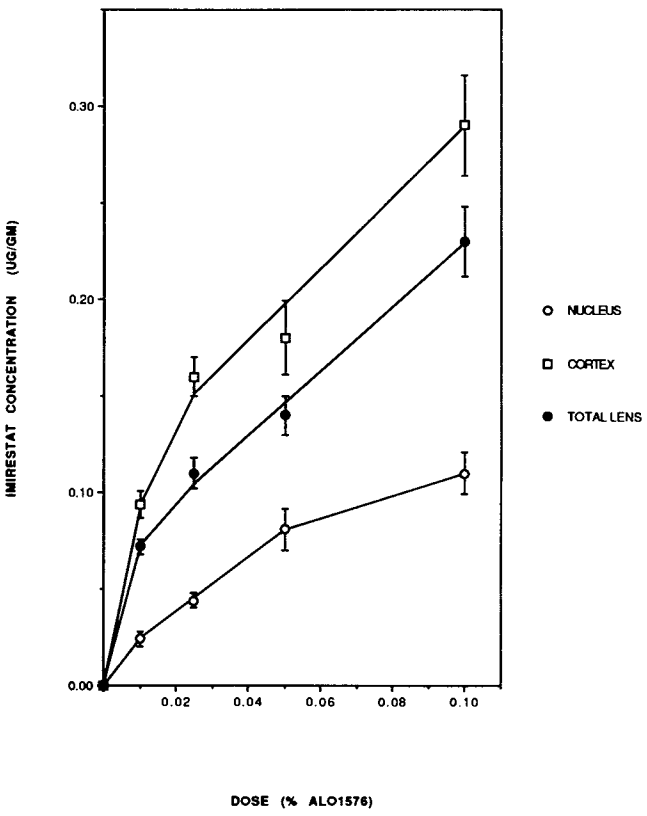

Fig. 6. Effect of dose on steady-state lens concentrations of imirestat following once daily topical dosing for 6 weeks (mean ± SE; N = 9).

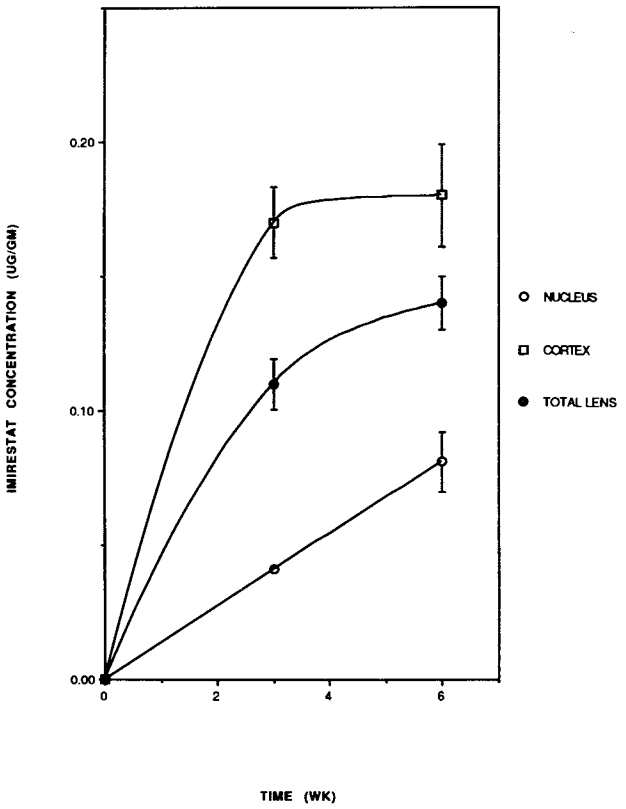

Fig. 7. Time course for accumulation of imirestat in lens during once daily topical dosing of 0.05% imirestat suspension (mean ± SE; N = 4, for 3-week data, N = 9 for 6-week data).

first sampling time) and declining to nondetectable levels by 8 to 12 hr. Concentrations in lens decline very slowly, in a fashion similar to that seen in the cornea. Drug does reach the vitreous humor and levels were measurable up to 72 hr after a single topical ocular dose. The pharmacokinetics of this compound were similar in both albino and pigmented rabbits.

The retention of drug in the cornea and lens and its subsequent slow elimination from these tissues are likely related to high-affinity tissue binding. Similar retention of drug in selected tissues of rats (i.e., eye, testes, kidney) following systemic dosing has been previously observed (5) and an elimination pattern similar to that seen in lens and cornea was observed in the plasma of human subjects receiving oral doses of imirestat (11). The high affinity of imirestat for the aldose reductase enzyme (12), along with the retention of drug in tissues of rats known to have high concentrations of the enzyme (5), has led to speculation that the binding of imirestat to the aldose reductase enzyme may play a role in the very slow elimination of drug from the eye and the body as a whole.

Bioavailability of imirestat from the topical route of administration increased with increasing dose in both single- and multiple-dose studies, although not in a linear fashion (Figs. 3–6). Formulation pH did not have an appreciable effect on bioavailability (Table I).

There was detectable systemic absorption following topical ocular administration of imirestat, with detectable plasma concentrations being observed in both dog and rabbit following topical dosing. Plasma levels in rabbits following the topical dose were 50 to 75% that observed following an equivalent intravenous dose. Imirestat concentrations in ocular tissues were similar in the undosed eye after unilateral topical dosing to that seen with an equivalent intravenous dose. However, drug concentrations in the dosed eye were considerably higher than the undosed eye in all tissues. Corneal drug concentrations in dogs following topical ocular administration were 80 times greater in the dosed eye than in the contralateral undosed eye. In aqueous humor, vitreous humor, and lens the ratios were 5, 10, and 20, respectively. However, despite these differences, the data suggest that systemic absorption may play a role in the ocular pharmacokinetics of imirestat.

Multiple dosing of topical imirestat results in accumulation of drug in the lens, perhaps related to binding of drug to the aldose reductase enzyme. Concentrations were higher in the lens cortex than in the lens nucleus, with the accumulation pattern being different in the two tissues (Fig. 7). Steady-state drug concentrations in the cortex appear to be achieved within 3 weeks of once daily dosing, whereas accumulation in the nucleus continues for at least 6 weeks, and perhaps longer. The explanation for this difference and its potential implications are unknown at this time, but these data do emphasize the complex ocular pharmacokinetics of imirestat.

The results of this study demonstrate that imirestat penetrates into the tissues of the eye following topical ocular administration and that the drug appears to be retained in

both lens and cornea, potential sites of action for this aldose reductase inhibitor.

REFERENCES

1. M. Averbuch, M. Weintraub, J. Liao, R. K. Brazzell, and R. E. Dobbs. *J. Clin. Pharm.* 28:757–761 (1988).
2. M. L. Chandler, J. Boltralik, B. York, and L. DeSantis. *Invest. Ophthalmol. Vis. Sci.* 22:1576 (1982).
3. O. Hockwin, A. Wegener, D. R. Sisk, B. Dohrmann, and M. Kruse. *Lens Res.* 2:321–335 (1984/1985).
4. P. J. McNamara, R. A. Blouin, and R. K. Brazzell. *Pharm. Res.* 5:319–321 (1988).
5. Y. H. Park, C. B. Wooldridge, J. Mattern, M. L. Stoltz, and R. K. Brazzell. *J. Pharm. Sci.* 77:110–115 (1988).
6. B. McCue, Y. H. Park, and R. K. Brazzell. *Pharm. Res.* 5:S29 (1988).
7. O. Hockwin, P. Müller, J. Krokzyk, B. A. McCue, and P. R. Mayer. *Ophth. Res.* 21:285–291 (1989).
8. L. A. Meyer, J. L. Ubels, and H. F. Edelhauser. *Invest. Ophthalmol. Vis. Sci.* 29:940–948 (1988).
9. M. Matsuda, T. Awata, Y. Ohashi, M. Inaba, M. Fukuda, and R. Manabe. *Curr. Eye. Res.* 6:391–397 (1987).
10. L. M. Cobo and D. L. Hatchell. *Invest. Ophthalmol. Vis. Sci.* 26:176 (1985).
11. R. K. Brazzell, P. R. Mayer, J. T. Slatterry, M. Weintraub, and B. A. McCue. *Pharm. Res.* 5:S182 (1988).
12. B. W. Griffin, L. G. McNatt, M. L. Chandler, and B. M. York. *Metabolism* 36:486–490 (1987).