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Efficacy of a Topical Ocular Drug Delivery Device (TODDD) for the Treatment of Glaucoma by Telemetric Measurement of IOP in the Normal Rabbit

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Introduction

Eye drops remain a crude way of delivering drugs to the anterior eye.

Advantages of topical ocular delivery device

- Controlled drug release over extended period
- Improved bioavailability
- Improved compliance
- Improved convenience
- Result is an improved therapeutic effect
- Enhanced safety via reduction in systemic absorption and side effects
- Absence of irritating biocidal preservatives
- Improved shelf-life due to absence of water

Purpose

To demonstrate sustained 90-day drug delivery and efficacy of a topical ocular drug delivery device (TODDD), by delivering timolol *in vivo*, continuously monitoring IOP using telemetry, and comparing aqueous and systemic drug levels to those of topical drop treatment.

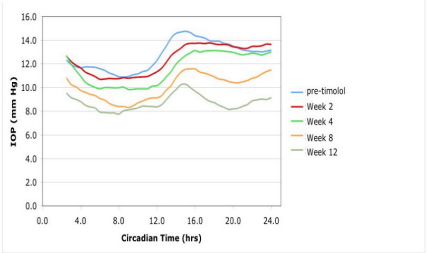
Methods

Telemetry manometer devices from DSI (St. Paul, MN) were surgically implanted into one eye each of n=4 rabbits[1]. IOP data was collected continuously from unrestrained animals over a 14 week period. Data were averaged and results reported for each 30-minute time point. After stabilization of the normal diurnal pattern of IOP, a TODDD containing a low concentration of timolol by weight was placed on the conjunctiva of one eye followed by a partial tarsorrhaphy. The drug diffuses continuously out of the solid matrix device, leaving the delivery device matrix and overall shape intact. Daily observations and monthly full clinical examinations were performed to verify the placement of the device and assess ocular tolerance. IOP reduction was determined based on pre-treatment diurnal curves in the same eye. Aqueous and blood plasma samples were taken at baseline and at necropsy.

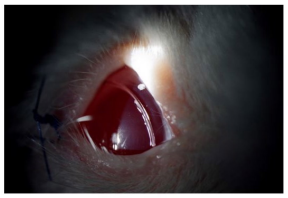
Results

The TODDD was well tolerated, with minimal to no corneal or intraocular irritation. The IOP-lowering effect, seen as a decrease in the amplitude of the circadian fluctuation in the normal rabbit[2,3], was maintained for the entire three months of the study, with statistical significance at weeks 3-12. The maximal IOP reduction in these normotensive animals was 5.5 mmHg, representing a 37% reduction in IOP from the pre-timolol average. The IOP effect was slightly greater than that typically observed with topical timolol drop treatment in this species[2,3]. Systemic levels of drug were <0.1 ng/mL (limit of detection) in the animals treated with the TODDD vs. 8.49 ng/mL in an animal treated with timolol drops for one week.

Telemetric IOP Cycle in n=4 rabbits Before and After Placement of TODDD, with smoothing



Rabbit TODDD in place



Average Daily, Peak, and Low IOP values in rabbits before and after TODDD placement

Timepoint	Average Daily IOP	Ave SEM		Average Peak IOP	Peak SEM		Ave. Low IOP	Low SEM
10 days pre-timolol	12.8	0.64		14.8	0.46		10.9	0.91
3 days post-timolol	12.9	0.57		13.7	0.52		11.3	0.87
Week 1	12.9	0.56		14.1	0.72		11.3	1.22
Week 2	12.4	0.64		13.6	0.50		10.8	1.42
Week 3	11.7	0.59		12.6	0.31	**	10.0	0.89
Week 4	11.7	0.73		12.7	0.63	*	10.0	1.51
Week 5	10.6	0.68		11.7	1.02	*	8.7	1.39
Week 6	9.7	0.54	**	10.9	1.14	*	8.4	1.37
Week 7	10.0	0.59	*	11.4	0.65	*	8.4	1.30
Week 8	10.2	0.58	*	11.5	0.80	†	8.4	0.77
Week 9	10.0	0.53	*	11.5	1.21	*	8.6	0.63
Week 10	8.9	0.36	†	10.3	1.09	**	8.3	0.67
Week 11	8.1	0.31	†	9.3	1.05	†	7.4	0.77
Week 12	8.8	0.39	†	10.3	1.00	**	7.8	0.98

Data are average for one eye of of n=4 rabbits +/- SEM for circadian day IOP values during each time period and average IOP values during circadian hours 13-15, On Day 0, the TODDD containing 3 mg Timolol was placed in the measured eye. Statistically significant from pre-timolol values by the student two sample t-test: * p≤0.05, ** p≤0.02, † p≤0.01. Average Peak IOP is for Hrs 13-15, Ave. Low IOP is Average Low IOP for Hrs 6-8.

Change in IOP at peak hours from Pre-Timolol values

Timepoint	IOP Difference	SEM		IOP % Decrease	SEM
3 days post-timolol	1.1	0.49		7.0	3.23
Week 1	0.7	0.72		4.5	4.79
Week 2	1.1	0.37		7.6	2.47
Week 3	2.2	0.27	†	14.7	1.6
Week 4	2.1	0.44	**	14.0	3.05
Week 5	3.1	0.76	*	21.1	5.44
Week 6	3.9	1.07	*	26.2	7.41
Week 7	3.3	0.73	**	22.5	4.58
Week 8	3.2	0.39	†	22.1	3.08
Week 9	3.3	0.89	*	22.8	6.21
Week 10	4.5	0.74	†	30.8	5.37
Week 11	5.5	0.87	†	37.4	6.16
Week 12	4.5	0.92	**	30.3	6.35

Data are average difference in IOP from pre-Timolol 10 day average during circadian hours 13-15 for one eye of n=4 rabbits +/- SEM. On Day 0, the TODDD containing 3 mg Timolol was placed in the measured eye. Statistically significant from pre-timolol values by the student's paired t-test: *p≤0.05, ** p≤0.02, † p≤0.01.

Linear Curve: 0.1ng/mL to 100 ng/mL; Lower Limit of Quantification (LLOQ): 0.1 ng/mL	Treated Eye	Control Eye
Animal 01 A.humor Day 90	<LLOQ	<LLOQ
Animal 02 A.humor Day 90	14.5	<LLOQ
Animal 03 A.humor Day 90 sampled after two-week washout	<LLOQ	<LLOQ
Animal 04 A.humor Day 90 sampled after two-week washout	<LLOQ	<LLOQ
Animal 05 A.humor Day 7 treated with drops in one eye	>> 100	4.96

Linear Curve: 0.1ng/mL to 100 ng/ml; LLOQ: 0.1ng/mL		
Animal 0001 TODDD	pre-necropsy / PLASMA	<LLOQ
Animal 0002 TODDD	pre-necropsy / PLASMA	<LLOQ
Animal 0003 TODDD	Day 90 PLASMA	<LLOQ
Animal 0003 2-wk washout	Day 104 PLASMA	<LLOQ
Animal 0004 TODDD	Day 90 PLASMA	<LLOQ
Animal 0004 2-wk washout	Day 104 PLASMA	<LLOQ
Animal 0005 DROPS	Pre-dose Day 1 PLASMA	<LLOQ
	pre-necropsy / PLASMA	8.49

Conclusions

IOP results indicate that statistically significant sustained release and efficacy was achieved after two weeks of treatment and continued for the entire three-month treatment period. The IOP-lowering effect was comparable to perfect compliance with drops. These results, along with the timolol blood level data, indicate that this device is able to deliver therapeutic levels of drug to the target tissue while minimizing systemic exposure.

References

1. McLaren et al, IOVS, 1996; 37: 966

2. Dinslage, McLaren and Brubaker, IOVS, 1998; 39: 2485

3. Akaishi et al, JOPT, 2005; 21: 436

Commercial Relationships

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