The consensual ophthalmotonic reaction

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SUMMARY The consensual ophthalmotonic reaction describes the phenomenon whereby alteration of the intraocular pressure in one eye is accompanied by a corresponding pressure change in the contralateral eye. Thirteen normal and thirteen ocular hypertensive subjects received 0.5% timolol, 2% pilocarpine, 1% adrenaline, or saline unilaterally with saline to the other eye under double blind, randomised conditions. Intraocular pressure was measured by applanation tonometry at 0, 30, 60, 120, and 240 minutes. Falls in pressure were found in both treated and consensual eyes for all treatments in both subject groups. A linear relationship between the fall in pressure in the treated eye and that in the consensual eye was found for timolol and pilocarpine but not for adrenaline.

In 1924 Weekers¹ coined the phrase 'consensual ophthalmotonic reaction' to describe the phenomenon whereby alteration of the intraocular pressure (IOP) in one eye is accompanied by a corresponding pressure change in the contralateral eye. This response was reported initially in animals, where unocular fistulisation operations,² anterior chamber collapse,³ aqueous expression,⁴ and various anti-glaucoma medications^{5–7} were found to lower IOP in the consensual eye. Similarly, manoeuvres designed to increase the IOP in one eye, such as topical nitrogen mustard,⁸ stimulation of the fifth cranial nerve,⁹ and intracameral injection of prostaglandins¹⁰ were found to raise the consensual IOP in some cases.

In man a consensual response to timolol has been convincingly shown in normal and glaucomatous subjects, both in single doses and in prolonged treatment studies.^{11–13} Sporadic reports have also cited consensual pressure falls in response to unocular adrenaline¹⁴ and pilocarpine¹⁵ and following unocular tonography¹⁶ and 360° laser trabeculoplasty.¹⁷

The objectives of the present study were (1) to confirm the existence of the consensual ophthalmotonic reaction in man; and (2) to elucidate the aetiology of the consensual ophthalmotonic reaction by determining whether or not a consensual pressure response occurred regardless of the nature of the

drug used to lower the pressure in the treated eye, and if so, whether the consensual response bore a direct relationship to the effect of the drug in the treated eye.

Subjects and methods

SUBJECTS

Group A consisted of 13 healthy male volunteers aged 28 to 63 years (mean age 44 years) with normal corrected visual acuity, results of slit-lamp and ophthalmoscopic examination, IOP between 10 and 19 mmHg, full visual fields on Bjerrum screen testing, and normal optic discs. They were not taking any medication.

Group B consisted of 13 ocular hypertensive volunteers, 11 male and two female, aged 43 to 82 years (mean 63 years) with an IOP >21 mmHg in one or both eyes on three or more occasions, without glaucomatous visual field loss or optic disc cupping, and with open drainage angles.

METHODS

Every subject attended at the same time of day on four occasions, each separated by at least one week. On each visit one drop of one of the following—0.5% timolol, 1% adrenaline, 2% pilocarpine, or saline—was administered unilaterally, with saline given to the other eye. The eye treated and the treatment order were randomly selected and the drugs applied under double blind conditions.

IOP measurements were made before and at 30, 60, 120, and 240 minutes after drug administration. Measurements were made in both eyes (right eye first on each occasion) by applanation tonometry under topical 0.4% benoxinate anaesthesia. Three measurements were taken for each reading and averaged.

STATISTICAL METHODS

Repeatability was assessed by calculating the within-individual coefficient of variation for starting intraocular pressures within occasions and between occasions.

The IOP changes as a function of time were calculated for the treated and consensual eyes as the area under the curve in mmHg.min by means of the trapezoid rule. 'The integrated drug effect' (IDE) was calculated by subtracting the values obtained for the saline experiments from those of the drug experiments in order to exclude any effect that repeated tonometry or diurnal variation might have had on the IOP.

To determine the relation between drug effects on the treated and consensual eyes, regressions of IDE in the consensual eyes on IDE in the treated eyes for all subjects and treatments were calculated. The significance of differences between subjects and treatments was assessed by analysis of covariance by standard methods.

Results

0.5% Unilateral timolol administration produced a fall in IOP in both treated and consensual eyes in both subject groups. The effect of timolol as opposed to saline on the IOP in the ocular hypertensive group is shown in Fig. 1. The starting pressures and maximum pressure reductions for each group and

Fig. 1 Mean intraocular pressure in mmHg versus time in minutes after treatment in 13 ocular hypertensive subjects: in the timolol 0.5% treated eyes (—) and their consensual eyes (---); and in the saline treated eyes (....) and their consensual eyes (---).

each treatment are shown in Table 1. The IDE for both eyes of each subject group with each treatment used is shown in Table 2.

GROUP A

In the normotensive group the starting IOP was 13.9 ± 0.1 mmHg (mean $\pm$ SEM). The coefficient of variation for starting IOP within occasions was 4.3% and between occasions was 8.9%.

Timolol produced a maximum fall in IOP in the treated eye of 5.2 ± 0.3 mmHg and in the consensual eye of 2.6 ± 0.3 mmHg. This resulted in a significant IDE in both the treated eye ($p < 0.0005$) and the contralateral eye ($p < 0.025$).

Adrenaline produced a maximum fall in IOP in the

Table 1 Mean starting IOP $\pm$ SEM and maximum fall in IOP $\pm$ SEM in mmHg for treated and consensual eyes for each treatment and each subject group

	Normotensives		Ocular hypertensives	
	Starting IOP	Maximum fall in IOP	Starting IOP	Maximum fall in IOP
Treated eyes				
Timolol	14.1 ± 0.4	5.2 ± 0.3	23.8 ± 0.8	10.9 ± 0.7
Adrenaline	14.5 ± 0.5	3.7 ± 0.3	23.8 ± 0.5	6.8 ± 0.5
Pilocarpine	13.7 ± 0.3	3.4 ± 0.2	22.6 ± 0.6	5.6 ± 0.5
Saline	13.5 ± 0.3	1.2 ± 0.3	21.7 ± 0.5	2.2 ± 0.4
Consensual eyes				
Timolol	13.8 ± 0.4	2.6 ± 0.3	22.9 ± 0.6	5.9 ± 0.5
Adrenaline	14.0 ± 0.4	2.2 ± 0.2	22.8 ± 0.5	3.7 ± 0.3
Pilocarpine	14.0 ± 0.3	2.3 ± 0.2	22.0 ± 0.5	3.0 ± 0.4
Saline	13.7 ± 0.3	1.4 ± 0.3	22.3 ± 0.4	2.1 ± 0.4

Table 2 Mean integrated drug effect in mmHg.min $\pm$ SEM for treated and consensual eyes for each treatment and each subject group.

	Normotensives	Ocular hypertensives	All subjects
Treated eyes			
Timolol	$14.06 \pm 2.09^{***}$	$33.48 \pm 4.16^{***}$	$23.77 \pm 2.99^{***}$
Adrenaline	$6.00 \pm 1.77^{**}$	$13.35 \pm 3.72^{**}$	$9.67 \pm 2.15^{***}$
Pilocarpine	$5.64 \pm 1.42^{**}$	$10.76 \pm 2.50^{***}$	$8.20 \pm 1.50^{***}$
All treatments	$8.57 \pm 1.18^{***}$	$19.20 \pm 2.58^{***}$	$13.88 \pm 1.53^{***}$
Consensual eyes			
Timolol	$4.16 \pm 1.66^*$	$12.92 \pm 3.55^{***}$	$8.54 \pm 2.11^{***}$
Adrenaline	-0.05 ± 4.19 NS	$4.27 \pm 2.18^*$	$3.65 \pm 1.49^{**}$
Pilocarpine	1.63 ± 2.18 NS	$5.98 \pm 2.19^{**}$	$3.80 \pm 1.58^{**}$
All treatments	$2.94 \pm 1.14^{**}$	$7.72 \pm 1.64^{***}$	$5.33 \pm 1.03^{***}$

*= $p < 0.05$, **= $p < 0.0125$, ***= $p < 0.001$.

treated eye of 3.7 ± 0.3 mmHg and in the consensual eye of 2.2 ± 0.2 mmHg. This resulted in a significant IDE in the treated eye ($p < 0.0025$) but not in the consensual eye.

Pilocarpine produced a maximum fall in IOP in the treated eye of 3.4 ± 0.2 mmHg and in the consensual eye of 2.3 ± 0.2 mmHg. This resulted in a significant IDE in the treated eye ($p < 0.0025$) and a consensual response that did not reach statistical significance.

When all treatments were considered together, the IDEs in both the treated and consensual eyes were statistically significant ($p < 0.0005$ and $p < 0.01$, respectively).

GROUP B

In the ocular hypertensive group the starting IOP was 22.7 ± 0.2 mmHg. The coefficient of variation for the starting IOPs within occasions was 3.4% and between occasions was 9.6%.

Timolol produced a maximum fall in IOP in the treated eye of 10.9 ± 0.7 mmHg and in the consensual eye of 5.9 ± 0.5 mmHg. This resulted in a significant IDE in both the treated eye ($p < 0.0005$) and the consensual eye ($p < 0.0025$).

Adrenaline produced a maximum fall in IOP in the treated eye of 6.8 ± 0.5 mmHg and in the consensual eye of 3.7 ± 0.3 mmHg. This resulted in a significant IDE in the treated eye ($p < 0.0025$) and in the consensual eye ($p < 0.05$).

Pilocarpine produced a fall in IOP in the treated eye of 5.6 ± 0.5 mmHg and in the consensual eye of 3.0 ± 0.4 mmHg. This resulted in a significant IDE in both treated and consensual eyes ($p < 0.005$ and $p < 0.01$, respectively).

When all treatments were considered together, the IDEs in both treated and consensual eyes were highly statistically significant at $p < 0.0005$.

Table 3 Relationship between the integrated drug effect in the treated eye and that in the consensual eye for all subjects for each treatment and the analysis of covariance for this relationship

	Slope	r	p
Timolol	0.48	0.678	<0.001
Adrenaline	0.09	0.135	NS
Pilocarpine	0.59	0.565	<0.01
All treatments	0.37	0.545	<0.001
Analysis of covariance		F	p
Between treatments		3.241	<0.05
Between subjects		0.768	NS
Comparison of slopes between subject groups		0.253	NS
Comparison of elevations between subject groups		0.096	NS

COMBINED SUBJECT GROUPS

When both subject groups were considered together, timolol was seen to produce highly significant IDEs in both treated and consensual eyes at $p < 0.0005$. Adrenaline also produced significant IDEs in both treated and consensual eyes ($p < 0.0005$ and $p < 0.0125$, respectively) as did pilocarpine ($p < 0.0005$ and $p < 0.0125$, respectively).

The graph of IDE in the consensual eyes versus IDE in the treated eyes for all subjects and treatments is shown in Fig. 2, while Table 3 shows the regression correlation and analysis of covariance.

A statistically significant correlation between IDEs in the treated and consensual eyes was found for timolol ($p < 0.001$) and pilocarpine ($p < 0.01$) and for all treatments when considered together ($p < 0.001$) but not for adrenaline. Analysis of variance confirms a source of variance between treatment groups but not between subject groups.

Fig. 2 Integrated drug effect in mmHg.min in the treated eye versus that in the consensual eye for all subjects and treatments. The line of best fit calculated by the method of least squares is shown.

Discussion

In this study a consensual fall in IOP was seen to occur following unocular administration of timolol, adrenaline, and pilocarpine in the hypertensive study group. This supports the hypothesis that the consensual ophthalmotonic reaction (COR) occurs in man regardless of the drug used to lower IOP in the treated eye. In the normotensive group, however, a significant COR was seen only with timolol.

The correlation shows that for all subjects and treatments the fall in IOP in the consensual eye is directly linearly related to that in the treated eye. It should be noted that each drug produced a smaller IDE in the treated eyes of the normotensive group than in the ocular hypertensive subject group. Since the COR is proportional to the IDE in the treated eye, this might account for the COR of the normals treated with pilocarpine and adrenaline failing to reach statistical significance. Adrenaline is unusual, however, in that it does not show a statistically significant regression correlation between treated and consensual eyes when considered alone.

Several hypotheses have been formed to try to explain the consensual ophthalmotonic reaction. One suggests that topical medication is absorbed systemically and either has its action on the fellow eye via the blood stream or acts centrally on IOP control mechanisms. The incidence of systemic side effects after topical timolol supports this theory, but studies with pindolol by Smith *et al.*¹⁸ tend to refute it. They measured IOP falls after topical and intravenous administration of pindolol. Pindolol treatment to one eye resulted in a pressure fall in the contralateral untreated eye. This was unlikely to have resulted from systemic absorption of the drug, since the contralateral fall occurred in the presence of far lower plasma concentrations than were present after intravenous administration, which gave a comparable reduction in pressure. The theory is also unable to explain the consensual ophthalmotonic reaction seen on mechanical alteration of IOP such as following laser trabeculoplasty and tonography.

An alternative hypothesis suggests that a nervous mechanism exists whereby changes in IOP in one eye provoke a reflex alteration in pressure in the fellow eye. This was first postulated by Leplat,¹⁹ who found that a controlled blow to a rabbit eye produced a more marked consensual response if the animal was unanaesthetised and that the response could be abolished by retrobulbar cocaine to the treated eye.

If such a nervous reflex exists it is unusual in that the reflex pressure response is in the same direction as the original pressure disturbance—a form of positive feedback which would exclude it from

serving any homeostatic purpose. The practical importance of the consensual ophthalmotonic reaction is that in studies of IOP responses to a particular treatment the fellow eye should not be used as a control.

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