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Pressure Lowering Effect of Timolol with Reference to Its Topical Vascular Action

G. Cristini and A. Giovannini

Universita' degli Studi di Bologna, Clinica Oculistica, Via Massarenti, 9, Bologna, Italy

Abstract. The hemodynamic effect of timolol maleate in open angle glaucoma was studied rheo-oculographically.

Increase in the ocular pulse which reaches maximal amplification 2 h after the instillation of the drug was observed.

The maximal pressure lowering effect appeared 3 h after instillation, as if the hemodynamic effect were the trigger for the pressure lowering effect.

Zusammenfassung. Mit der rheo-okulographischen Methode untersuchten die Verff. die haemo-dynamische Wirkung des Timolol-Maleats bei Glaukom mit offenem Kammerwinkel.

Sie konnten in allen Fällen eine Zunahme des Augenpulses beobachten, dessen größter Ausschlag 2 h nach Instillierung des Mittels auftrat.

Die größte druckherabsetzende Wirkung wurde erst nach 3 h festgestellt, als ob die haemo-dynamische Wirkung den Trigger für den druckherabsetzenden Effekt darstellte.

Beta-adrenergic blocking agents have been used for more than ten years in the topical treatment of open-angle glaucoma. This is a consequence of the chance discovery that these drugs, already widely employed in the treatment of hypertension, could lower intraocular pressure as well.

The first of these beta-blocking drugs to be studied was Propranolol (1967), followed by Practolol (1973–1974), Atenolol (1973–1976), Oxprenolol, and Tolamolol (1976). The most recent beta-blocking drug is Timolol maleate which received much attention at the last Glaucoma Symposium in Kyoto during the XXIII International Congress of Ophthalmology. It is a selective beta-adrenergic, beta-blocking drug without any intrinsic sympathomimetic activity and without any local anesthetic or depressive effect on the myocardium. The beta-blocking drugs used in the topical treatment of glaucoma are well tolerated and have no effect on pupillary diameter or accomodation.

Notwithstanding the large use of beta-blocking drugs, their mechanism of

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action in the eye has not yet been completely elucidated. Tonographic and fluorometric research has suggested that Timolol maleate, like the other beta-blocking drugs, acts by facilitating aqueous outflow and reducing its production [1, 2]. Scientifically, this problem is not marginal, as it is more or less directly connected with the pathogenesis of intraocular pressure in glaucoma and with its regulating factors.

It is not the purpose here to discuss the pathogenesis of intraocular pressure and the importance of the primary uveal hemodynamic changes [3, 4] which affect the phasic variations and the pathologic pressures. We thought however, that it was worthwhile to study the lowering effect of Timolol with reference to its topical vascular action. Our rheooculographic method, described in previous papers [5, 6] made it possible to study these hemodynamic changes in the ocular circulation system.

Table 1.

Case N°		Base condition			After 1 h			After 2 h			After 3 h			After 12 h		
		I.O.P.	S.A.	S.S.	I.O.P.	S.A.	S.S.	I.O.P.	S.A.	S.S.	I.O.P.	S.A.	S.S.	I.O.P.	S.A.	S.S.
1 C.E. A.65	R.E.	16	8	33	10	20	33	10	18	33	12	10	33	10	8	33
	L.E.	28	6	35	17	16	35	16	13	35	16	13	35	17	10	35
2 N.N. A. 74	R.E.	26	6	33	16	12	33	14	14	30	14	13	33	13	11	33
3 D.A. A.62	R.E.	26	2	36	11	5	36	11	12	36	11	12	36	13	8	36
	L.E.	18.5	2	35	11	10	35	12	10	35	11	10	35	13	10	35
4 M.M. A.51	L.E.	16	7	40	13	14	33	12	7	40	11	5	40	11	6	40
5 B.E. A.36	R.E.	11	10	32	6.5	17	30	6.8	27	30	6.2	20	30	5.6	10	32
6 D.F. A.52	L.E.	16	8	35	9	13	35	9	16	33	8	15	33	11	9	35
7 G.E. A.53	R.E.	20	4	36	11	7	36	9	9	36	9	8	36	12	5	36
8 C.N. A.71	R.E.	18.5	7	35	11	11	35	7.5	25	35	6.2	24	35	12	10	35
9 C.M. A.69	R.E.	24	6	36	16	10	36	12	13	36	11	10	36	16	7	36
10 O.B. A.57	L.E.	22	4	33	16	7	33	13	10	33	12	9	33	14	5	33
11 A.R. A.39	L.E.	22	3	35	14	5	33	11	6	33	11	5	35	16	3	35
12 F.L. A.60	R.E.	18.5	5	40	13	8	40	11	11	40	9	10	40	13	7	40

R.E. = Right eye, L.E. = Left eye, I.O.P. = Intraocular pressure, S.A. = Sphygmous Amplitude, S.S. = Sphygmous Speed, S.A. is expressed in millimeters with T (calibration) = 0.5 Ohm = 10 mm, S.S. expresses in percent the relationship between duration of the ascending branch and the overall wave cycle

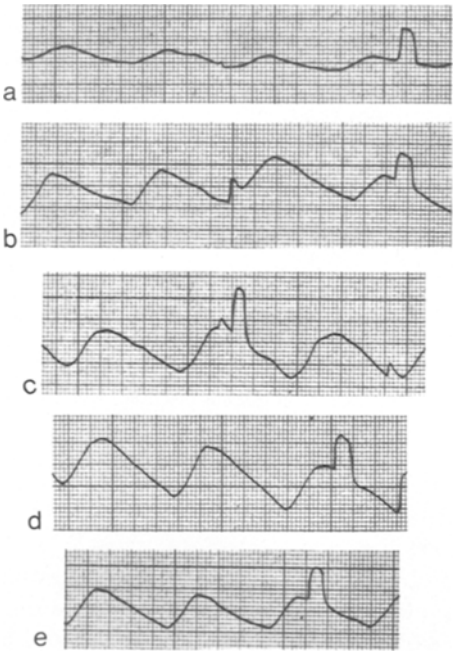

Fig. 1. Case 1: L.E. **a**=Base condition; **b**=After Timolol (1 h); **c**=After Timolol (2 h); **d**=After Timolol (3 h); **e**=After Timolol (12 h)

Case Studies

Twelve subjects between 36 and 74 years of age with open-angle glaucoma (14 eyes) were examined. Eleven patients were emmetropic or had hypermetropia not greater than 2.50 D; one was affected by high myopia.

Three days before the instillation of Timolol maleate (0.25%) all other treatment was interrupted. For 11 patients the earlier treatment consisted of a miotic alone (Pilocarpine 1% or 2%) and for one of a miotic (Pilocarpine 2%) and Clonidine.

Before interrupting the above treatment, each patient was examined rheographically to determine the ocular pulse; the intraocular and arterial pressures were also measured (occasional variations in heart rate can be seen from the rheographic tracings) in base conditions at 8:00 A.M. and 1, 2, 3, and 12 h after the instillation of the beta-blocking drug. Patients showing diurnal-type ophthalmotonic curves were chosen in order to avoid biorhythm interference.

Results

The results are reported in Table 1.

Conclusions

Timolol maleate has a strong ocular vasoactive effect: it always increases the pulse amplitude (Fig. 1) so that the ocular pulse is amplified five times or more (case 3).

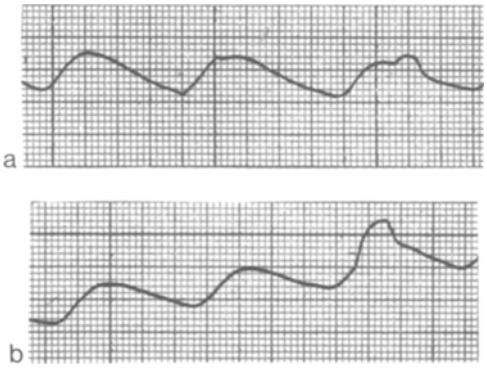

Fig. 2. a Base condition; **b** After Pilocarpine 2% (3 h). Miotic treatment does not produce sphygmous amplitude increase

The variation in the sphygmous speed was less pronounced. When present, the typical 'delayed' glaucomatous pulse [7] was 'accelerated'.

The pressure-lowering effect of Timolol maleate reached its climax about 3 h after instillation. The lowest degree of intraocular pressure occurred towards the third hour. The maximum pulse amplification, however, was observed 2 h after instillation, as if the vasoactive action were the trigger for its pressure-lowering effect. The vasoactive effect is not observed after the instillation of a miotic (Pilocarpine) (Fig. 2) coased. Significantly no theooculographic rebound was observed when the vasoactive effect of Timolol maleate.

References

1. Kaufman, M.E.: Timolol and facility of outflow. Invest. Ophthalmol. **16**, 623–624 (1977)
2. Yablonski, M.E., Zimmerman, T.J., Waltman, S.R., Becker, B.: A fluorophotometric study of the effects of topical timolol on aqueous humor dynamics. Exp. Eye Res. **27**, 135–142 (1978)
3. Cristini, G.: The rationale of ocular hypertension in glaucoma. Acta XVI Concilium Ophthalmologicum (Britannia). II, 865–871 (1950)
4. Cristini, G.: Common pathological basis of the nervous ocular symptoms in chronic glaucoma. Br. J. Ophthalmol. **35**, II (1951)
5. Cristini, G., Meduri, R., Garbini, G.C., Giovannini, A.: A new method for determining the blood quantity in the eye in a unit of time. Albrecht von Graefes Arch. Klin. Ophthalmol. **197**, 1–11 (1975)
6. Cristini, G., Meduri, R., Giovannini, A.: Semeiologia reografica bulbare. Ann. Ottalmol. Clin. Ocul. **C1**, 319–334 (1975)
7. Cristini, G., Meduri, R., Giovannini, A.: Indici reografici e flussimetrici bulbari nel glaucoma cronico semplice. Ann. Ottalmol. Clin. Ocul. **C1**, 335–350 (1975)

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