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The Effects of Chlorimipramine on the Pupil, Intraocular Pressure and Aqueous Humor Dynamics in Rabbits

F. Tato and A. Belmonte

Instituto de Farmacología y Terapéutica «Novo Campelo»
Facultad de Medicina
Santiago de Compostela (España)

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The chlorimipramine applied conjunctivally produced pupil size enlargement, intraocular pressure decrease and outflow facility elevation. Either systemic administered or conjunctivally applied chlorimipramine potentiated the effects on the pupil and intraocular pressure of exogenously norepinephrine Both phenoxybenzamine and superior cervical sympathetic ganglionectomy prevented the chlorimipramine inducing intraocular pressure changes.

The changes in the pupil size, intraocular pressure and aqueous humor dynamics induced by alterations in the sympathetic nervous acticity or by local administration of adrenergic substances, have been subjet of several investigations.

LANGHAM and ROSENTHAL (11), demonstrated in the rabbit that the sympathetic nervous activity lowers the intraocular pressure by a fall in the aqueous humor formation. Also, in the same animal, the local application of norepinephrine provokes intraocular pressure decrease, primarly by an elevation in the outflow facility (2, 7). Another fact supporting the intraocular pressure is influenced by the sympathetic nervous activity in the rabbit, is the finding that the superior cervical sympathetic ganglionectomy performed 18 days before, produces decrease in the intraocular pressure (12, 13), being such effect prevented by pretreatment with both reserpine and guanethidine, and greatly reduced by phentolamine (1). The fall in the intraocular pressue provoked by sympathetic ganglionectomy, may be due to a supersensitivity to circunlating sympathetic amines (4).

In man, the local administration of epinephrine and other adrenergic substances, produce changes in the intraocular pressure and outflow resistance on patients suffering open-angle glaucoma (20). In spite of the powerful ocular hypotensive effect of epinephrine, its therapeutics use as an antiglaucomatous agent declined by the side effects of adrenergic type, often severe, that it produced.

Pharmacologically, it is possible to produce supersensitivity to the endogenously

liberated and exogenously administered norepinephrine. This property in potentiating certain peripheral actions of administered norepinephrine has been demonstrated to be present in some antidepressant agents of tricyclic chemical structure, such as imipramine (15), chlorimipramine (18), desmethylimipramine (16), amitriptyline (19) and protriptyline (17).

These experiments were undertaken to investigate the effects on the intraocular pressure and pupil of chlorimipramine [3-chloro-5(3-dimethylaminopropyl)-10-11-dihydro-5H-dibenz/*b,f*/azepine hydrochloride] in the field of pharmacological adrenergic sensitization.

Materials and Methods

Adult rabbits of both sexes weighing between 2.4 and 3.5 kg were used throughout this study. Animals were distributed in several groups.

The controls of pupillary diameter and intraocular pressure were performed under anaesthesia of a mixture of diethylbarbiturate diethylamine (0.15 g/ml) and alylisopropylbarbiturate diethylamine (0.13 g/ml) (Somni Lefa®) injected intravenously (0.5 ml/kg). Superior cervical sympathetic ganglionectomy and pressure decay curves, were carried out in sodium pentobarbital (40 mg/kg i.v.) anaesthetized animals.

Control of the pupil size, intraocular pressure and aqueous humor dynamics. The horizontal pupil diameter was measured in uniform artificial illumination with a trasparent plastic milimeter ruler.

The intraocular pressure was recorded simultaneously in both eyes 15 minutes after anaesthesia using a Sanborn pressure transducer (model 267 BC) in conjunction with a Sanborn carrier preamplifier (1100 C) and a multichannel (150 M) rectilinear recorder. The anterior chamber of the eye was cannulated with a 27 gauge 5/8″ hypodermic needle pushed obliquely through the cornea from the sclero-corneal limb, trying not provoque damage of the iris or lens.

The pressure decay curve was performed by manometric procedure cannulating the anterior chambres as has been described above. It was also used the Sanborn pressure transducers. A four way block was employed to interconnect the pressure reservoir (containing physiologic saline), the pressure transducer and the anterior chamber of the eye as has been described previously (2). The pressure decay curve was obtained inmediately after the cannulation of the anterior chamber, using the same method as that employed by LANGHAM and EAKINS (9). The outflow facility was calculated from the analysis of the pressure decay curve, using the values of the pressure volume relationship of the living rabbit eye (5) in a manner identical that described by LANGHAM and EISENLOHR (10). The rate of flow of the aqueous humor was calculated from the equation: $F = C(Po-Pv)$ where F is the rate of flow of the aqueous humor in μl/min, C the outflow facility in μl/min/mm Hg, Po the steady-state intraocular pressure, and Pv is assumed to be 8.9 mm Hg for the rabbit eye (6).

Sympathectomy. — Superior cervical sympathetic ganglionectomy was performed unilaterally in antiseptic conditions to a group of rabbits. The ganglion was wholly exposed to insure a complete ganglionectomy.

Intravitreal injection.—The intravitreal injection of drugs was carried out with a micrometer syringe (Burroughs Wellcome & Co., London). The employed method was essentially the same as that described by LANGHAM and CARMEL (8). The volume of the injected solutions was kept at 10 μl to minimize trauma (14). Into the control eye a similar volume of physiologic saline was injected.

Preparation of drugs. — The following drugs were employed: chlorimipramine

hydrochloride (Anafranil[R]), phenoxybenzamine hydrochloride (Dibenzyline[R]), l-norepinephrine bitartrate (Reargon[R]) in physiologic saline for intravitreal injection, chlorimipramine hydrochloride in physiologic saline for conjunctival and intravitreal administration. For the conjunctival application of chlorimipramine was used a 100 μl micropipete.

Statistical analysis. — All results are expresed statistically by the arithmetic mean $\pm$ standard deviation of the mean. The P values were obtained from the Student's *t* test.

Results

The influence of chlorimipramine on the pupil and intraocular pressure. — The effect of 100 μl a 0.1 % solution of chlorimipramine administered conjunctivally to six rabbits unilaterally, was a pupillary dilatation and a significative decrease in the intraocular pressure (fig. 1a). The mean

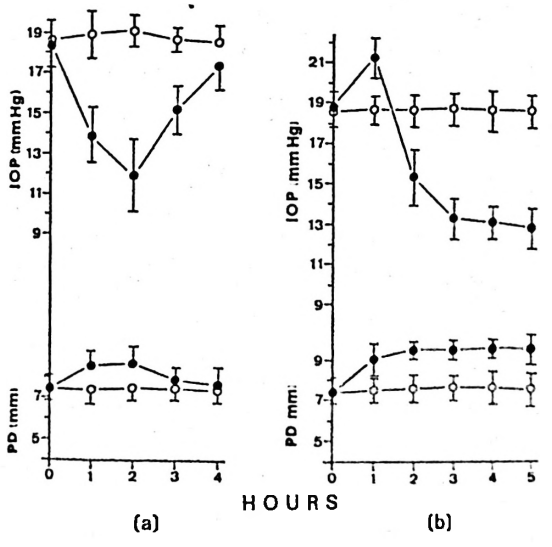

Fig. 1. *Effect of conjunctival chlorimipramine (100 μg at 0.1 %)* (a) *and of intravitreal norepinephrine (150 μg)* (b) *on the intraocular pressure (IOP) and pupil diameter (PD).* O: untreated eye; ●: treated eye. Each point and vertical bar represents arithmetic mean ± standard deviation of six experiments.

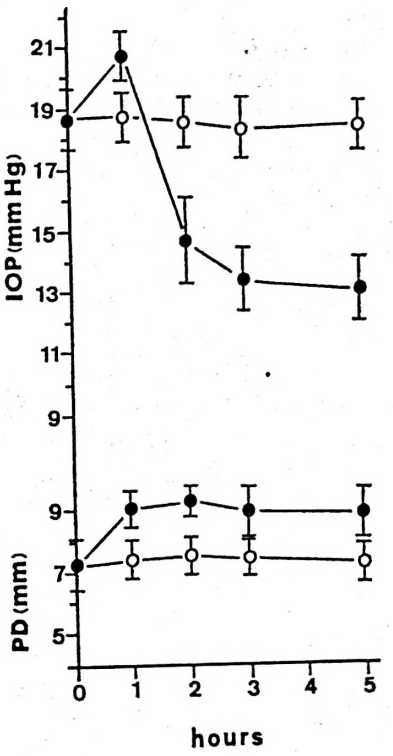

Fig. 2. *Effect of conjunctival chlorimipramine (100 μl at 0.1 %) 5 min. after the intravitreal injection of 20 μg norepinephrine on the Intraocular pressure (IOP) and pupil diameter (PD).*
Into the test eye was injected the same dose of norepinephrine than in the experimental eye. O: test eye; ●: experimental eye. Each point and vertical bar represents arithmetic mean ± standard deviation of six experiments.

of the intraocular pressure decrements after 2 hours were 7.2 $\pm$ 0.4 mm Hg ($P < 0.005$). The single administration of chlorimipramine (3 mg/kg i.v.) to six rabbits, did not produce perceptible change in the intraocular pressure (fig. 3).

The influence of intravitreal norepinephrine on the pupil and intraocular pressure. — 150 μg of norepinephrine injected unilaterally into the vitreous body to six rabbits, provoked a very evident pupil enlargement and a great fall in the intraocular pressure, begining after 2 hours. After 4 hours, the average of intraocular

pressure decrements were 5.6±0.5 mm Hg ($P < 0.001$) (fig. 1b). An increase in the intraocular pressure was detectable before the hypotensive state. When the administered dose of norepinephrine was 20 μg, no significative change in the pupil or intraocular pressure was found (fig. 2; test eye).

Potentiation of exogenously administerd norepinephrine. — The unilateral conjunctival administration of 100 μl at 0.1 % solution of chlorimipramine to six rabbits 5 minutes after the intravitreal injection of 20 μg of norepinephrine, caused an alteration on the pupil size and intraocular pressure resembling that induced by 150 μg of intravitreal norepinephrine (fig. 2). The mean of the intraocular pressure decrements after 4 hours were 5.2±0.6 mm Hg ($P < 0.02$). Into the text eye was injected the same dose of norepinephrine than in the experimental eye.

20 μg of intravitreal norepinephrine administered to six rabbits unilaterally, provoked on chlorimipramine treated rabbits (3 mg/kg i.v.) 15 minutes before, a similar response on the pupil diameter and intraocular pressure that produced by 150 μg of intravitreal norepinephrine. After 4 hours, the average of the intraocular pressure decrements were 4.8±0.7 mm Hg ($P < 0.05$) (fig. 3).

The influence of conjunctival chlorimipramine on the intraocular pressure in phenoxybenzamine treated rabbits.—With the unilateral conjunctival administration of 100 μl at 0.1 % of chlorimipramine to six rabbits 60 minutes after systemic administration of phenoxybenzamine (5 mg/kg i.v.), no significative change on the intraocular pressure was observed within 2 hours (table I).

The influence of conjunctival chlorimipramine on the intraocular pressure in

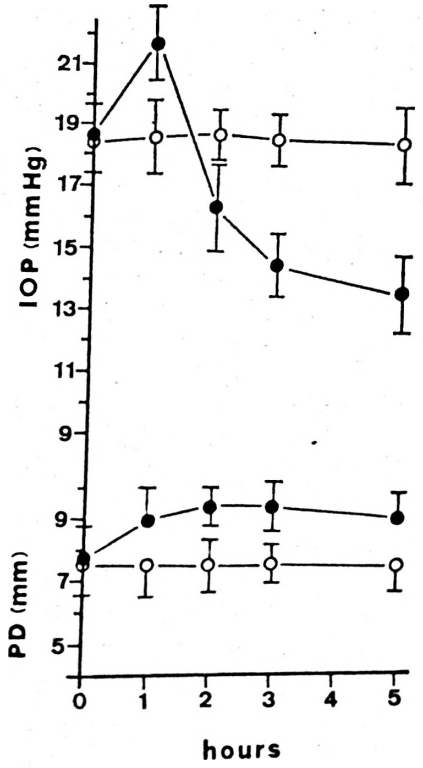

Fig. 3. *Effect of intravitreal norepinephrine (20 μg) on the intraocular pressure (IOP) and pupil diameter (PD) in chlorimipramine treated rabbits (3 mg/kg i.v.) 15 min. before* ○: untreated eye; ●: treated eye. Each point and vertical bar represents arithmetic mean ± standard deviation of six experiments.

Table I. *Effect of 0.1 % conjunctival applied chlorimipramine unilaterally on the intraocular pressure (IOP) in rabbits treated with phenoxybenzamine (5 mg/kg i.v.) 60 min. before (a) and 18 days after unilateral superior cervical sympathetic ganglionectomy (b).*
In group «b», the denervated eye was the experimental. T: test eye; E: experimental eye. Values are means ± standard deviation of six experiments.

Group	Time (min)	IOP (mm Hg)	
		T	E
a)	0	18.4±0.7	18.4±0.8
	30	18.6±0.8	18.5±0.9
	90	18.4±0.7	18.5±0.7
	120	18.4±0.8	18.4±0.7
b)	0	18.6±0.9	18.5±0.9
	30	18.7±0.9	18.6±0.8
	90	18.5±0.8	18.6±0.8
	120	18.6±0.9	18.5±0.8

Table II. *Effect of conjunctival applied (100 µl at 0.1 %) (a) and intravitreal injected (50 µl) (b) chlorimipramine on the intraocular pressure (IOP) and outflow facility 3 hours after its administration.*

T: test eye; E: experimental eye. Values are means ± standard deviation. N: number of rabbits.

	IOP (mm Hg)		OUTFLOW FACILITY (µl/min/mm Hg)		
N	T	E	T	E	P <
6 a)	20.2±0.5	16.0±0.6	0.23±0.1	0.31±0.04	0.01
6 b)	19.6±0.6	17.1±0.6	0.24±0.1	0.29±0.05	0.05

sympathectomized rabbits. — 100 µl a 0.1 % solution of chlorimipramine applied conjunctivally (unilaterally) to six rabbits 18 days after to be performed unilateral superior cervical sympathetic ganglionectomy caused no intraocular pressure decrease during 2 hours (table I).

The influence of conjunctival and intravitreal chlorimipramine on the outflow facility and aqueous humor formation. — Either the conjunctival application (100 µl at 0.1 %) or the intravitreal injection (50 µg) of chlorimipramine, produced 3 hours after its administration an increase in the outflow facility of the aqueous humor. The mean of increase in the outflow facility was 0.08±0.007 µl/min/mm Hg for the conjunctival chlorimipramine, and 0.05±0.008 µl/min/mm Hg for that intravitreal administered (table II). The rate of aqueous humor formation in six experiments, was for the test eye 2.46±0.2 µl/min, and for the experimental eye was 2.2±0.3 µl/min.

Discussion

The fact that the chlorimipramine potentiates the effects of the exogenously administered norepinephrine on the pupil and intraocular pressure, is in accordance with previous findings demonstrating the ability of chlorimipramine and other analogous psychotherapeutics agents to enhace certain peripheric actions of norepinephrine (17-19).

With regard to the action mechanism of chlorimipramine inducing intraocular pressure changes, it seems to be related to a sympathomimetic action, thus the alpha-adrenergic receptor antagonist phenoxybenzamine prevents the intraocular pressure decrement produced by chlorimipramine. Nevertheless, this sympathomimetic action should not be due to a direct stimulation of the adrenergic receptors, since the superior cervical sympathetic ganglionectomy performed 18 days before inhibits the intraocular pressure change, and as has been demonstrated by EAKINS and EAKINS (3), between 3 and 21 days after superior cervical sympathetic ganglionectomy, detectable amounts of adrenergic neurotransmiter do not exist in the eye. The chlorimipramine inducing increase in the outflow facility, may also be due to an indirect sympathomimetic action.

It is difficult to predict the action of chlorimipramine in the human eye, since the sympathetic nervous activity plays an important role in the control of the intraocular pressure in the rabbit, the value of such activity in man is less evident.

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