J. Pharm. Pharmacol., 1964, **16**, 630–631 Received February 28, 1964

Action of *N-o*-Chlorobenzyl-*N'N''*-dimethylguanidine (BW 392C60), a bretylium-like drug in lowering the intraocular pressure of rabbit eyes

G. L. GESSA AND G. SANGIORGI

N-o-Chlorobenzyl-*N'N''*-dimethylguanidine (BW392C60), a potent bretylium-like drug, lowers the intraocular pressure in rabbits either when injected intravenously or when instilled into the conjunctival sac. The lowering of the intraocular pressure is accompanied by miosis and relaxation of the nictitating membrane.

THE role of the sympathetic nervous system in the regulation of the intraocular pressure has been widely studied. However, conflicting results have been obtained by the use of sympathomimetic and sympatholytic agents, of cervical sympathetic nerve stimulation or surgical sympathectomy. (For a literature review see Grant, 1955.)

Recently the effect of guanethidine in lowering the intraocular pressure in man and animals has been demonstrated (Oosterhis, 1962). The mechanism of action may be due to initial active release of catecholamines from tissue stores or to catecholamine depletion (Bonomi & Comite, 1963).

The Compound *N-o*-chlorobenzyl-*N'N''*-dimethylguanidine (BW392C60) is an adrenergic neurone blocking agent, 20 times more potent than bretylium in inhibiting the release of noradrenaline caused either by sympathetic stimulation, or by drugs such as guanethidine (Boura & Green, 1963; Costa, Kuntzman, Gessa & Brodie, 1962). It seemed to us that a study of the effect of this compound on intraocular pressure would contribute to the understanding of the role of the sympathetic nervous system in the regulation of this property.

TABLE 1. EFFECT OF BW 392C60 (15 mg/kg i.v.) ON THE INTRAOCULAR PRESSURE OF ANAESTHETISED AND UNANAESTHETISED RABBITS

Treatment	No. of animals	Intraocular pressure mm Hg (mean ± s.d.) at various times (min) after treatment							
		0	15	45	70	110	140	190	255
Saline	13	29·8±1·9	—	29·4±1·7	—	—	—	29·8±1·8	29·7±2·0
BW 392C60	5	30·6±1·5	—	24·4±2·9	—	—	—	20·9±4·4	20·6±3·3
Chloralose + saline	11	29·4±2·3	29·4±2·2	—	29·8±1·8	29·8±1·8	—	29·2±1·7	29·7±1·5
Chloralose + BW 392C60	21	29·8±1·8	23·9±3·5	23·5±4·2	18·5±4·2	18·5±3·0	20·4±4·8	20·5±3·1	20·6±3·3

Methods and results

Adult, male, pigmented rabbits weighing between 1·6 and 2·5 kg were used. In some experiments, the animals were anaesthetised with chloralose (80 mg/kg i.v. in 3 ml H_2O). In other experiments, the animals were held still. Handling did not cause the intraocular pressure to change. It was measured from the right eye with a Schötz tonometer after anaesthetising the cornea with 2 drops of a solution of 0·5% amethocaine. Each measurement was made with 2 tonometer weights (5·5 and 10g) and corrected for scleral rigidity. BW 392C60 was administered either

From the Departments of Pharmacology and Opthalmology, University of Cagliari, Italy

by slow intravenous injection of 15 mg/kg or by topical application into the conjunctival sac using 3 drops of a 10% solution. In control experiments the animals were given saline. The intraocular pressure in the right eye of treated animals was compared with that in the right eye of the control group.

Table 1 shows the results obtained after intravenous injection of the drug in anaesthetised and unanaesthetised rabbits. Within 15 min there was a marked fall in the intraocular pressure accompanied by miosis and relaxation of the nictitating membrane which persisted. Table 2

TABLE 2. EFFECT OF TOPICAL APPLICATION OF BW 392C60 10% ON UNANAESTHETISED RABBITS, WITH OR WITHOUT PRECEDING TONOMETRY (p.t.)

Treatment	No. of animals	Intraocular pressure mm Hg (mean ± s.d.) at various times (hr) after treatment			
		0	3	7	24
Saline with p.t.	13	29·5 ± 1·5	29·8 ± 1·9	29·6 ± 1·8	29·2 ± 1·9
Saline without p.t. ..	5	—	—	—	29·6 ± 2·8
BW 392C60 with p.t. ..	20	23·2 ± 2·2	26·6 ± 4·6	23·2 ± 4·4	20·6 ± 2·6
BW 392C60 without p.t...	5	—	—	—	22·8 ± 1·9

summarises the results obtained after the drug was applied topically, either with or without preceding tonometry. Eyes treated with BW 392C60 showed a lowering of the intraocular pressure lasting more than 24 hr, and relaxation of the nictitating membrane. Usually these effects were accompanied by miosis but in some animals a mydriasis occurred which was over in 8 hr. No significant changes were observed in the untreated eyes. Stimulation of the cervical sympathetic nerve failed to evoke a mydriatic response in eyes treated with BW 392C60.

Discussion

These results suggest that BW 392C60 lowers the intraocular pressure by an action on sympathetically innervated ocular structures. It might be concluded that the blockade of release of noradrenaline leads to a lowering of the intraocular pressure. The effect is exerted by BW 392C60 applied topically, but its effects were limited to the treated eyes. The initial mydriasis sometimes observed after topical application of BW 392C60 might be related to the monoamine oxidase-inhibiting action of BW 392C60 recently demonstrated by Gessa, Cuenca & Costa (1962).

Studies are in progress to ascertain whether the lowering of the intraocular pressure is caused by a decreased rate of formation of aqueous humour or by an increase in its rate of absorption.

Acknowledgements. We are indebted to Drs. J. Burns and R. Kuntzman from the Wellcome Research Laboratories, Tuckahoe, N.Y., U.S.A. for a supply of BW 392C60.

References

Bonomi, L. & Di Comite, P. (1963). *Ann. Oftalmol. e Clin. Oculistica*, **89**, 135–145.
Boura, A. L. A. & Green, A. F. (1963). *Brit. J. Pharmacol.*, **20**, 36–55.
Costa, E., Kuntzman, R., Gessa, G. L. & Brodie, B. B. (1962). *Life Sciences*, **3**, 75–80.
Gessa, G. L., Cuenca, E. & Costa, E. (1962). *The Pharmacologist*, **4**, 179.
Grant, W. M. (1955). *Pharmacol. Rev.*, **7**, 143–182.
Oosterhuis, J. A. (1962). *Arch. Ophtalmol.*, **67**, 592–599; 802–810.