ADRENERGIC BLOCKING AGENTS*† A DOUBLE-BLIND TRIAL IN THE TREATMENT OF THE EYE SIGNS OF THYROID DISORDER

BY

A. L. CROMBIE‡

Professorial Unit, Eye Department, Royal Infirmary, Edinburgh

AND

A. A. H. LAWSON

Department of Medicine, Western General Hospital, Edinburgh

LID retraction and lid lag in thyrotoxicosis have been diminished by intramuscular reserpine (Canary, 1957), oral guanethidine (Waldstein, West, Lee, and Bronsky, 1964), and oral propranolol (Buckfield and Davis, 1966), while the increasing availability of local ophthalmic preparations of adrenergic blocking agents has resulted in the local use of propranolol (Sneddon and Turner, 1966), phentolamine (Lee, Morimoto, Bronsky, and Waldstein, 1961), guanethidine (Sneddon and Turner, 1966; Gay and Wolkstein, 1966), and, more recently, bethanidine (Gay, Salmon, and Wolkstein, 1967). The purpose of this paper is to report a short-term double-blind cross-over study comparing the effects of guanethidine (Ismelin, Ciba), propranolol (Inderal, I.C.I.), bethanidine (Esbatal, Burroughs Wellcome), bretyllium (Darenthin, Burroughs Wellcome), and debrisoquine (Declinax, Roche) on the eye signs of thyrotoxicosis.

Patients and Methods

Four patients were studied in the trial, three females and one male (Table I). All had been thyrotoxic but were euthyroid throughout the study. Protein-bound iodine and I^{131} uptake were estimated for each patient before the trial and the protein-bound iodine was tested again 6 weeks later. Patient 4 was controlled on carbimazole, and Patient 3 on methylthiouracil; Patient 1 was euthyroid after a therapeutic dose of I^{131} , and Patient 2 was controlled on thyroxine because of hypothyroidism following I^{131} treatment.

TABLE I
THYROID STATUS OF THE PATIENTS STUDIED

Patient No.	Sex	Age (yrs)	I^{131} 4 hrs Uptake (per cent.)	Plasma Protein-Bound Iodine (μ g. per cent.)		Thyroid Status
				Before Treatment	After Treatment	
1	M	59	21.2	4.2	4.0	Euthyroid
2	F	61	3.0	6.4	5.9	Euthyroid
3	F	51	32.6	5.8	6.2	Euthyroid
4	F	55	34.0	7.6	7.2	Euthyroid

All four patients had had eye signs of thyroid disorder for periods of 1 to 2 years, the signs being bilateral in three of them (Table II, opposite).

* Received for publication September 29, 1967.

† Address for reprints: Department of Ophthalmology, Royal Victoria Infirmary, Newcastle upon Tyne, 1.

‡ Present address: Department of Ophthalmology, Royal Victoria Infirmary, Newcastle upon Tyne, 1.

TABLE II
EYE SIGNS PRESENT BEFORE TREATMENT

Patient No.	Conjunctival Injection		Exophthalmos		Lid Retraction		Periorbital Oedema		Duration of Eye Signs (yrs)
	Right	Left	Right	Left	Right	Left	Right	Left	
1	+	+	+	+	+	+			2
2			+	+			+	+	1
3	+	+	+		+				1½
4			+	+					2

The patients used each preparation for one week, the dosage being standardized at 1 drop in each eye twice daily. This dosage was chosen as being easy for the patients to remember and because it was thought unlikely to give rise to toxic effects. Each patient was examined at the beginning and end of each weekly period of treatment as well as 30 minutes after the first instillation of each new preparation and at 48-hr intervals throughout the week.

Subjective symptoms were noted at each visit, as were the subjective effects of instillation of each new preparation. The eye examination included visual acuity, refraction, external examination with particular reference to the conjunctiva and cornea, eye movements, exophthalmometry, and measurement of the pupil diameter, and palpebral aperture. The pupil diameter was measured directly under constant illumination and the palpebral aperture directly in the mid-palpebral line with the patient fixing a point source of light 6 metres distant.

The systemic blood pressure was measured in the erect and supine position.

The above protocol was used for the ophthalmic preparations of all the drugs, but the trial of debrisoquine was carried out separately at a later date, as the drug was not available initially. The preparations used were guanethidine 10 per cent., propranolol 1.0 per cent., and debrisoquine 2.0 per cent., all of which were supplied ready made up by the manufacturers; bretyllium 10 per cent., bethanidine 10 per cent., and a normal saline control were made up by the hospital pharmacy to the manufacturers' specifications. The hospital pharmacy selected the drugs to be given and were responsible for maintaining the double-blind character of the study.

Results (Table III)

Guanethidine

All the patients experienced subjective benefit from the use of 10 per cent. guanethidine eye drops; in particular a feeling of grittiness disappeared.

TABLE III
CHANGES IN EYE SIGNS FOLLOWING TREATMENT WITH THE VARIOUS DRUGS

Eye Signs	Number of Patients																		
	Total	Saline			Guanethidine			Propranolol			Debrisoquine			Bretyllium			Bethanidine		
		A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Subjective Symptoms	4	—	4	—	4	—	—	4	—	—	—	4	—	—	4	—	—	4	—
Conjunctival Oedema	4	—	4	—	—	4	—	—	4	—	—	4	—	—	4	—	—	4	—
Conjunctival Injection	2	—	2	—	—	—	2	—	1	1	—	2	—	—	2	—	—	2	—
Periorbital Oedema	1	—	1	—	1	—	—	1	—	—	—	1	—	—	1	—	—	1	—
Palpebral Aperture	4	—	4	—	3	1	—	2	2	—	—	4	—	—	4	—	—	4	—
Exophthalmos	4	—	4	—	1	3	—	—	4	—	—	4	—	—	4	—	—	4	—
Pupils	4	—	4	—	—	4	—	—	4	—	—	4	—	—	4	—	—	4	—
Lens and Fundus	4	—	4	—	—	4	—	—	4	—	—	4	—	—	4	—	—	4	—
Refractive Error	4	—	4	—	—	4	—	—	4	—	—	4	—	—	4	—	—	4	—

A—Improved B—No change C—Deteriorated

In three patients the width of the palpebral aperture decreased by 2 to 4 mm., *i.e.* a reduction of up to 25 per cent.; in one it remained relatively unchanged. The pupils became miotic in all patients, the average diameter being 2.5 to 3 mm., but the pupils reacted to light briskly, in spite of the miosis. No change in the exophthalmometer readings were noted in three patients, but a symmetrical bilateral reduction of 3 mm. was noted in one.

A slight increase in the degree of conjunctival injection was noted in two patients while on guanethidine and no change was noted in the degree of conjunctival oedema where present.

The degree and pattern of ophthalmoplegia remained unchanged, as did the refraction values. Visual acuity improved slightly in all cases, probably due to the relative miosis present.

Peri-orbital oedema decreased markedly in one patient while on guanethidine.

No changes in systemic blood pressure occurred.

Side-effects.—An unpleasant metallic taste was experienced by Patient 4 on instillation of the drops, and Patients 1, 3, and 4 experienced mild transient irritation after the drops had been instilled. This irritation was not experienced by Patients 1 and 3 by the end of the week's treatment. No objective signs of ocular change were noted.

Propranolol

All patients experienced a slight improvement in the feeling of grittiness in the eyes. Lid retraction diminished by 1 to 2 mm. in two patients, while the pupils were slightly miotic in all, averaging 3 mm. A slight increase in the degree of conjunctival injection was seen in one patient while on the drug, but conjunctival oedema, degree of ophthalmoplegia, exophthalmometer readings, refraction, visual acuity, and systemic blood pressure remained unchanged. In one patient a slight decrease in the amount of peri-orbital oedema occurred.

Side-effects.—The main complaint of all patients was of intense local pain on instillation of the propranolol solution, lasting up to 15 minutes. This was of such severity that, although some objective improvement in the eye signs of the patients had occurred while they were on the drug, it was decided not to use it as long-term therapy. No objective signs of ocular damage were seen.

Bretyllium, Bethanidine, Debrisoquine, and Saline Control

No changes in the ocular findings were noted in any of the patients on the above drugs and control. Two complained of pain on instillation of the 10 per cent. bethanidine solution. No other side-effects were noted while the patients were on these drugs and no objective signs of ocular damage occurred.

Discussion

The local use of adrenergic blocking agents in the treatment of the eye signs of thyroid disorder stems from the concept that some at least of these are mediated through an overactive sympathetic system and the observations that a partial Horner's syndrome occurred in normal eyes (Dorian and Schirmer, 1964) and in glaucomatous eyes (Oosterhuis,

1962) when local guanethidine eye drops were instilled. Sneddon and Turner (1966) and Gay and Wolkstein (1966) in almost simultaneous papers reported a beneficial effect on the eye signs of thyrotoxicosis using local guanethidine.

This study confirms that guanethidine is effective as a local treatment, especially for lid retraction and subjective irritation in affected eyes. In this study guanethidine had only a marginal effect in decreasing the amount of exophthalmos present, only one patient showing a decrease in exophthalmometer readings which justified comment and, even then, the significance of the result being far from certain. An unexpected result was the decrease in periorbital oedema which occurred in one patient while on guanethidine therapy. This was a most marked effect, which remains unexplained. It is of interest to note that in three of the four patients the maximum effect of guanethidine was seen in 7 days, since at a later date in a long-term trial of guanethidine the readings showed no change after one month's topical guanethidine therapy. This is not in accord with Gay and Wolkstein (1966), who felt that treatment for 3 weeks was needed to produce a maximum effect.

Local pain on instillation caused us to discontinue the use of the β -adrenergic blocking agent propranolol as a long-term medicament, though it had an effect in this trial, albeit less than guanethidine, which was of therapeutic value. Since the concentration used was only 1 per cent. it must be assumed either that propranolol is much more effective than guanethidine in comparable strength in alleviating the lid retraction of thyrotoxicosis, or that the system(s) responsible for the eye signs of thyrotoxicosis are much more sensitive to β -adrenergic blocking agents than to post-ganglionic adrenergic blocking agents such as guanethidine. It must be remembered too that propranolol is a short-acting drug and that guanethidine is a long-acting one, and it is of interest that the eye signs of thyroid disorder seemed more susceptible to a drug which depleted catecholamine stores such as guanethidine, than to bretyllium, a drug which inhibits the release of these stores.

In this study bethanidine caused no changes in the symptomatology or eye signs of thyrotoxicosis. This is in contrast to the study of Gay and others (1967) who reported a beneficial but less marked effect than guanethidine in these eye signs. It is not clear from their paper whether a 10 per cent. or a 20 per cent. solution was used and the dosage was higher than in our study. It may be that the number of patients in this trial was insufficient to detect a "bethanidine" reactor among them. Debrisoquine was used in this study as a 2 per cent. solution and it may have been too dilute to be effective.

The beneficial effect of the post-ganglionic adrenergic blocking agent guanethidine in the therapy of the eye signs of thyrotoxicosis was most marked in this trial and it would seem to be the agent of choice at the present time, since propranolol is so irritative when instilled. The variable response of patients to these drugs must raise the question as to whether all the eye signs of thyrotoxicosis are caused by the same mechanism in different patients. As time goes on the use of different types of adrenergic blocking agents acceptable to the patient may help to differentiate these mechanisms and lead to their elucidation.

Summary

(1) A short-term double-blind cross-over study was carried out to compare the effects of local application of guanethidine, propranolol, bethanidine, bretyllium, and debrisoquine on the eye signs associated with thyroid disorder.

(2) Four patients were studied, three females and one male. All had previously had thyrotoxicosis but were euthyroid during the period of the trial.

(3) Local bethanidine, bretyllium, debrisoquine, and saline control did not produce any beneficial effect.

(4) Both local guanethidine and propranolol were found to be effective, but the latter drug produced intense local irritation.

(5) The therapeutic value of guanethidine and its mechanism of action in this eye disorder are discussed.

Our thanks are due to Dr. A. K. Pittman of Ciba Ltd. for supplies of guanethidine, to Dr. A. D. Mundro-Faure of the Wellcome Foundation for supplies of bretyllium and bethanidine, and to Dr. A. M. C. Duffus of Roche Products Ltd. for supplies of debrisoquine. We also thank Dr. S. A. Stephen of I.C.I. Pharmaceuticals Ltd. for supplies of propranolol.

We are grateful to Prof. J. A. Strong for his advice in the preparation of this paper.

REFERENCES

- BUCKFIELD, P. M., and DAVIS, J. A. (1966). *Lancet*, **1**, 1425.
 CANARY, J. J., SCHAAF, M., DUFFY, B. J., and KYLE, L. H. (1957). *New Engl. J. Med.*, **257**, 435.
 DORIAN, W., and SCHIRMER, K. E. (1964). *Canad. med. Ass. J.*, **90**, 932.
 GAY, A. J., SALMON, M. L., and WOLKSTEIN, M. A. (1967). *Arch. Ophthal. (Chicago)*, **77**, 341.
 ——— and WOLKSTEIN, M. A. (1966). *Ibid.*, **76**, 364.
 LEE, W. Y., MORIMOTO, P. K., BRONSKY, D., and WALDSTEIN, S. S. (1961). *J. clin. Endocr.*, **21**, 1402.
 OOSTERHUIS, J. A. (1962). *Arch. Ophthal. (Chicago)*, **67**, 802.
 SNEDDON, J. M., and TURNER, P. (1966). *Lancet*, **2**, 525.
 WALDSTEIN, S. S., WEST, G. H., LEE, W. Y., and BRONSKY, D. (1964). *J. Amer. med. Ass.*, **189**, 609.