Long-term Trial of Local Guanethidine in Treatment of Eye Signs of Thyroid Dysfunction and Idiopathic Lid Retraction

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The advent of adrenergic blocking agents has provided a new tool in the treatment of the eye signs of thyroid dysfunction and idiopathic lid retraction. The increasing availability of local ophthalmic preparations of these drugs has resulted in the trial of some of them in the treatment of these distressing eye conditions. For example, Lee, Morimoto, Bronsky, and Waldstein (1961) described the therapeutic use of local phentolamine, and Sneddon and Turner (1966) and Gay and Wolkstein (1966), in almost simultaneous communications, reported favourably on the short-term use of local guanethidine (Ismelin). Sneddon and Turner (1966) also reported on the effects of conjunctival administration of the β-adrenergic blocking agent propranolol, and Gay, Salmon, and Wolkstein (1967) have suggested that local bethanidine may also be of value.

In a short-term study, comparison between the effect of local guanethidine and propranolol eye-drops on thyrotoxic lid retraction and lid lag was made by Sneddon and Turner (1966). They concluded that local guanethidine was the more effective drug for this purpose. A similar conclusion regarding the value of guanethidine was reached by us (Crombie and Lawson, 1967) in a double-blind cross-over trial which compared the effects of bretylium, bethanidine, guanethidine, propranolol, and debrisoquine. In short-term use guanethidine was also least likely to cause significant side-effects.

A long-term trial of local guanethidine in the treatment of the eye signs of thyroid dysfunction and idiopathic lid retraction is reported here.

Patients and Methods

Twenty patients were studied, four males and 16 females (Table I). The thyroid status of all these patients was assessed by clinical examination, estimation of the serum protein-bound iodine, and a four-hour uptake of ^{131}I. Thyroid function in each case was maintained at a stable level throughout the period of study. Sixteen patients were known to have been thyrotoxic previously, and 14 of these remained euthyroid throughout this study on the treatment indicated (Table I). Four of these 14 patients were controlled on thyroxine because of hypothyroidism after ^{131}I treatment. Two patients remained mildly thyrotoxic in spite of carbimazole therapy. Of the remaining four patients one was euthyroid while on treatment with thyroxine for primary hypothyroidism and three, classified as cases of idiopathic lid retraction, showed no evidence of thyroid dysfunction at any time. All of the patients had eye signs of thyroid disorder to a greater or less degree, and these had been present for periods of up to four years (Table II).

TABLE I.—*Thyroid Status of Patients During Period of Study*

Primary Diagnosis	Thyroid Status During Study	Patients		Current Treatment		Previous Treatment ^{131}I
		M.	F.	Carbimazole	Thyroxine	
Thyrotoxicosis	Euthyroid	4	10	8	4	6
	Mild thyrotoxicosis	•	2	2		
Hypothyroidism	Euthyroid		1		1	
Idiopathic lid retraction	„		3			

TABLE II.—*Eye Signs Present Before Treatment*

Case No.	Conjunctival Injection		Exophthalmos		Lid Retraction		Periorbital Oedema		Duration of Eye Signs
	R.	L.	R.	L.	R.	L.	R.	L.	
Males:									
1	+	+	+	+	+	+			2 years
2	+	+	+	+	+	+			1 year
3	+	+	+	+	+	+			2 years
4	+	+	+	+	+	+			3 months
Females:									
5	+	+	+	+			+	+	1 year 3 months
6			+	+			+	+	2 years
7					+	±			1 year
8			+	+			+	+	1 year
9			+						3 years
10	+	+	+	+			+	+	4 years
11	+	+	+		+				1 year 6 months
12	+	+	+	+	+	+	+	+	1 year 6 months
13			+	+					1 year
14	+		+		+	+			1 year
15				+		+			2 years
16	+	+	+	+					1 year
17			+		+				2 years
18			+		+				2 years
19	+	+	+		+				1 year
20	+	+			+	+	+	+	1 year

Each patient was examined at weekly intervals to begin with and then at longer intervals, depending on the presence or absence of side-effects. The average duration of the trial was 16 weeks, with a range from 6 to 26 weeks. At each visit subjective symptoms, including the subjective effects noted on instilling the preparation, were recorded; systemic blood pressure was measured in the erect and supine positions, and examination of the eye, which included external examination, with particular reference to the conjunctiva, cornea, and eye movements, was performed. The ocular fundi were studied and visual acuity and refraction measured. Exophthalmometry (Hertel) was undertaken and an estimation was made of the pupil diameter, palpebral aperture, and, in 11 of the subjects, intraocular pressure by means of both Schiøtz and Goldmann applanation tonometers. Both the pupil diameters and the palpebral apertures were measured directly under constant illumination in the mid-palpebral line, with the patient fixing on a point source of light 6 metres distant. The eyes were photographed before starting treatment and after six weeks of continuous treatment. Guanethidine sulphate 10% eye-drops in a buffered solution of methylcellulose were used, one drop in each affected eye twice daily being the standardized dosage.

Results

Results are shown in Table III.

Subjective Symptoms.—With the exception of two patients (Cases 15 and 19) all of the subjects felt that guanethidine had

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been of benefit to their eyes. One of these two patients (Case 15) developed an acute local sensitivity to guanethidine six weeks after starting the drug and treatment had to be stopped. Before treatment 10 patients complained of a feeling of grittiness in their eyes, and on guanethidine therapy 9 of these 10 experienced either an improvement or disappearance of this symptom. No patient complained of dizziness, and in all cases measurements of systemic blood pressure both erect and supine did not change significantly from the pretreatment figures.

TABLE III.—*Changes in Eye Features After Local Guanethidine Treatment*

	Number of Patients			
	Total	Improved	Unchanged	Deteriorated
Subjective symptoms	20	18	2	
Systemic blood pressure	20		20	
Conjunctival oedema	14		14	
Conjunctival injection	12	3	7	2
Periorbital oedema	6	4	2	
Ophthalmoplegia	9		9	
Lens and fundus	20		20	
Refractive error	20		20	

Conjunctival Oedema.—Guanethidine therapy did not seem to influence the presence or absence of conjunctival oedema, which was present in 14 of the patients.

Conjunctival Injection.—Twelve patients had conjunctival injection at the beginning of the trial. On guanethidine therapy no significant change was noted in seven of the patients, three improved, and two became worse. The increased hyperaemia observed in these last two patients was, however, mild and did not prevent continuation of treatment.

Periorbital Oedema.—Six patients (Table II) had considerable periorbital oedema and in four of these (Cases 5, 10, 12, and 20) a marked decrease in the amount of oedema occurred a short while after guanethidine therapy was instituted. No change in the amount or distribution of periorbital oedema was noted in the other two patients.

Ophthalmoplegia.—No improvement in the field of action of any involved extraocular muscles was noted.

Lens and Fundus.—No change was noted in the lens and fundus of any patient on guanethidine therapy.

Refractive Error.—No changes occurred in the refractive errors of any of the patients while on guanethidine therapy.

Palpebral Aperture

The results are shown in Table IV. Lid retraction was markedly relieved or abolished in all nine patients who showed a reduction in palpebral aperture greater than 20%.

TABLE IV.—*Changes in Palpebral Aperture*

Eye Signs Before Treatment	No. of Patients	Percentage Reduction in Palpebral Aperture			
		≤10	11–20	21–30	>30
Lid retraction present: Unilateral	6	2		2	2
Lid retraction present: Bilateral	7	1	1	4	1
No lid retraction	7	3	4		

Six patients (Table II) with predominantly unilateral lid retraction were treated on the affected side only. In two (Cases 15 and 19) there was only 1 mm. (8%) reduction in the width of the palpebral aperture. Of the other four patients in this group, two (Cases 7 and 17) showed a narrowing of 3 mm. (20–24%) and two (Cases 11 and 18) of 4 mm. (31–33%). No change was noted in the untreated eye in any of these patients (Fig. 1).

In the group of seven patients with bilateral lid retraction (Table II) one patient (Case 12) showed a narrowing of the palpebral aperture of only 1 mm. (9%) in both eyes, and another (Case 4) obtained 2 mm. (17%) reduction in each eye. The remaining five patients (Cases 1, 2, 3, 14, and 20) derived greater relief of lid retraction, the reduction in palpebral aperture ranging from 21 to 27%. This reduction in width was symmetrical in three (Cases 3, 4, and 12), greater in the right eye in two (Cases 14 and 20), and greater in the left eye in the remaining two (Cases 1 and 2). The reduction in width of the palpebral apertures was of great cosmetic value to the patients with lid retraction (Fig. 2).

The changes in lid aperture observed in the seven patients without significant lid retraction were less marked, the reduction being on the average 12.7% (range 6–18%). None of these patients developed unsightly ptosis.

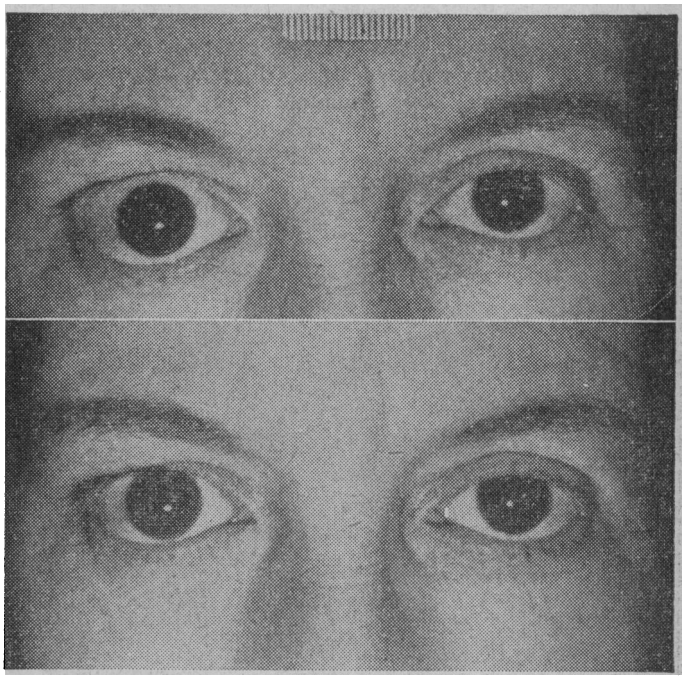

FIG. 1.—Case 18. Patient with unilateral idiopathic lid retraction. Above, before treatment. Below, after six weeks' local guanethidine (10%) to the right eye alone.

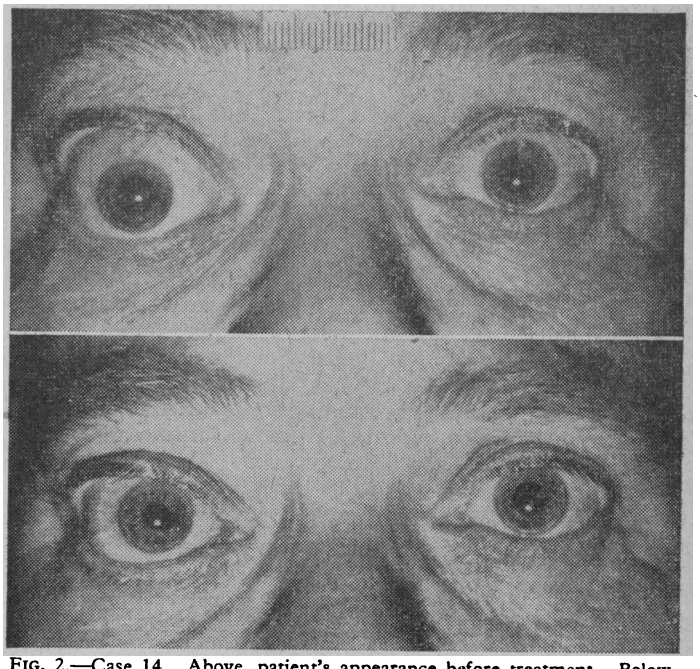

FIG. 2.—Case 14. Above, patient's appearance before treatment. Below, after six weeks' local guanethidine (10%).

Pupils

Meiosis occurred in all the treated eyes except in two patients. The pupil diameter never became less than 2 mm. and the pupil remained reactive to light and accommodation. No restriction in the field of vision was noted by any of the patients, and in 10 of the 20 patients the visual acuity improved by one line on the Snellen chart, irrespective of the refractive error present.

Exophthalmos

Bilateral exophthalmos was present in 11 of the patients. In another seven it was mainly unilateral and in the remaining two was not thought to be a significant eye sign. Exophthalmometer readings decreased by 3 mm. (14–18%) bilaterally in two patients (Cases 1 and 10) and by 4 mm. (16%) in the treated eye of a patient (Case 14) with unilateral exophthalmos (Fig. 2). In another patient (Case 2) the decrease was remarkable, being in the region of 10 mm. (25%) in each eye (Fig. 3).

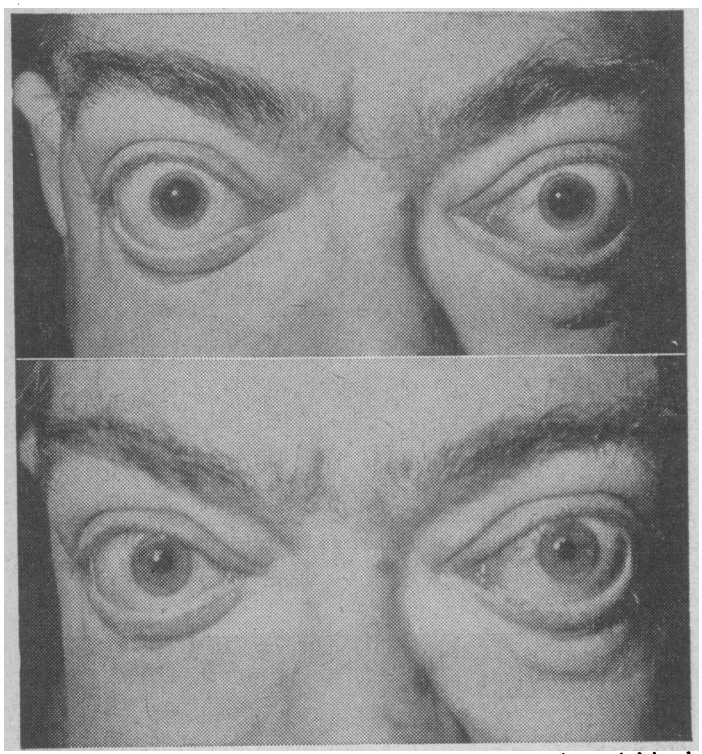

FIG. 3.—Case 2. Above, before treatment. Below, after six weeks' local guanethidine (10%).

Intraocular Pressure

The results are shown in Table V. With the exception of one patient (Case 4), all of the 11 patients in whom measurements of intraocular pressure were made were found to have reductions in pressure after guanethidine treatment. In four patients (Cases 2, 10, 12, and 20), all of whom had moderate proptosis, the intraocular pressures before guanethidine therapy were over 21 mm. Hg, measured on the Goldmann applanation tonometer, on more than one occasion. Schiøtz tonometry consistently underestimated the intraocular pressure in these cases. In the other seven patients intraocular pressures were 21 mm. Hg or below. While on guanethidine therapy the intraocular pressure fell on an average by 4 mm. Hg in the first week and did not fall thereafter. In one patient (Case 4) a rise of 2 mm. Hg occurred in both eyes on guanethidine therapy, and this slightly raised level of intraocular pressure remained unchanged while he was on treatment.

TABLE V.—*Changes in Intraocular Pressure in 11 Patients While on Local Guanethidine Treatment*

Intraocular Pressure (I.O.P.) Before Guanethidine	No. of Patients	Percentage Increase in I.O.P. ≤10	Percentage Decrease in I.O.P.			
			≤10	11–20	21–30	>30
≤21 mm. Hg	7	1	1	2	2	1
>21 mm. Hg	4			3	1	

Side-effects

The toxic effects of local guanethidine are shown in Table VI. Three patients complained of mild nasal congestion while on treatment and one complained of an unpleasant metallic taste a short while after administration of the drug. One patient developed an acute local sensitivity reaction to 10% guanethidine after six weeks' therapy and the drug had to be discontinued. Ten of the patients complained of brief local irritation on instillation of the drug. These complaints of pain on instillation of the drops were mild and of little consequence in themselves, but all of these 10 patients subsequently developed a superficial punctate keratitis in their treated eyes usually affecting the lower half of the cornea. The keratitis developed after one week's treatment in four cases, after three to four weeks in another two, and after seven to eight weeks in the remaining four. The keratitis was bilateral in five cases and unilateral in five, the unilateral group including three patients who were receiving therapy to one eye only. Three cases were very mild and the keratitis did not increase in severity even though treatment was not discontinued. Treatment was discontinued in the other seven cases, and within one week the keratitis had disappeared without further treatment. When guanethidine 10% was again administered to these patients the keratitis usually reappeared within five to seven days, disappearing again when the guanethidine 10% was stopped, though the lid retraction recurred within 48 hours of discontinuation.

TABLE VI.—*Side-effects of Local Guanethidine Treatment in 20 Cases*

Nasal congestion	3	Local irritation on instillation	10
Unpleasant taste	1	Superficial punctate keratitis	10
Local sensitivity	1	No side-effects	10

Because of this effect of the guanethidine 10% solution, guanethidine 5% drops were substituted during the last two to four weeks of the trial. The keratitis improved markedly on this therapy ; and it had disappeared in seven of the nine cases within seven days and in the other two cases within 14 days. The other effects of the 5% guanethidine drops were not as marked as when the 10% solution was used, in that on average the palpebral apertures were 1 mm. wider and the pupil diameter 0.5 mm. greater. On the other hand, the improvements in intraocular pressures were maintained, as was the subjective relief of symptoms.

Discussion

The results of this trial indicated that improvement in the eye signs associated with thyroid dysfunction after the short-term use of guanethidine reported previously (Sneddon and Turner, 1966 ; Gay and Wolkstein, 1966 ; and Crombie and Lawson, 1967) can be maintained when the drug is used for longer periods and that this therapy is also of value in cases of idiopathic lid retraction. On discontinuation of the drug a return of signs and symptoms occurred within 48 hours, irrespective of the previous duration of guanethidine therapy. In contrast to Gay and Wolkstein (1966) this study indicated (1) that in most cases treatment for one week with guan-

ethidine 10% will achieve maximum results—only 2 of the 20 patients in this trial showed any further improvement in signs and symptoms after the initial seven days' therapy; and (2) that the response to guanethidine appeared to have little relation to the thyroid status at any one time or in any one individual.

It is also of interest that, in this limited study, 4 patients out of 10 with bilateral exophthalmos for a year or more had an intraocular pressure of over 21 mm. Hg on more than one occasion. In all these cases Schiøtz tonometry gave false low readings compared with applanation tonometry. Guanethidine 10% caused a reduction in the increased intraocular pressure in these four cases, the effect being more pronounced the higher the initial intraocular pressure. Guanethidine 5% maintained this reduction in intraocular pressure in each case. No mention of side-effects was made by Gay *et al.* (1967) in relation to the long-term use of guanethidine. One patient in our trial developed an acute skin-sensitivity reaction to guanethidine after six weeks' therapy. In a separate series of 10 patients treated with guanethidine for chronic simple glaucoma, two developed this type of reaction after six and eight weeks' therapy respectively. That the reaction was due to guanethidine was not in doubt, since it occurred again when guanethidine 2.5% drops were used.

In this trial 50% of patients developed a superficial punctate keratitis after one to eight weeks' therapy, unrelated to corneal exposure and relieved by discontinuing treatment, which was done in 7 of the 10 patients involved. There seems little doubt that this complication was due to guanethidine 10%, since it reappeared on resumption of therapy with this concentration of guanethidine. No cases have been reported of punctate keratopathy due to methylcellulose, the vehicle in this case, and corneal exposure could not be implicated, since lid retraction returned on discontinuation of the therapy yet improvement in the corneal condition occurred.

In the trial mentioned above, in which guanethidine 10% was used to control chronic simple glaucoma, two identical cases of superficial punctate keratitis occurred after approximately four months' therapy. A point of speculation raised by these results is whether the cornea in patients with thyroid dysfunction is more susceptible than the normal cornea to a punctate keratitis when guanethidine 10% therapy is in use. One of the three patients, however, with idiopathic lid retraction and normal thyroid function also developed a punctate keratitis. Oosterhuis (1962) and Gay and Wolkstein (1966) reported an increase in conjunctival injection on guanethidine (10%) therapy. In our study there was no relation between conjunctival injection and the development of punctate keratitis. It seems unlikely, therefore, that the increase in conjunctival injection reported in these previous communications was associated with corneal damage. The absence of superficial punctate keratitis when using guanethidine 5% was most striking, and this would seem to be a safer and yet equally effective concentration.

Where topical guanethidine is to be used in the treatment of lid retraction syndromes the following precautions are advisable: (1) guanethidine 5% should be used initially in all cases, and only where it is unsatisfactory should a 10% solution be considered; (2) a close watch by an ophthalmologist on the treated eyes is essential; and (3) raised intraocular pressure should be looked for in all cases of exophthalmos, since in some patients with this condition the rise in pressure may be pronounced, with danger of ultimate impairment of vision.

Summary

A long-term trial of local guanethidine in the treatment of the eye signs associated with thyroid dysfunction and idiopathic lid retraction was undertaken in 20 patients (4 males and 16 females).

Subjective benefit was obtained in 18 patients. Nine out of 10 patients who had had troublesome "grittiness" experienced great improvement in or complete disappearance of this symptom on guanethidine treatment.

Other benefits obtained included reduction in lid retraction, periorbital oedema, exophthalmos, and raised intraorbital pressure, where these abnormalities were present.

No change was found in conjunctival oedema, conjunctival injection, ophthalmoplegia, pupils, lens, fundus, and refractive error.

The main toxic effect of this treatment was the development of a superficial punctate keratitis, which occurred in 10 patients.

The therapeutic value of local guanethidine in these eye conditions was confirmed. A number of precautions are suggested for long-term maintenance therapy in the light of the toxic effects found.

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