

Dysthyroid eye disease

A trial of Guanethidine eye drops

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Previous reports have indicated the usefulness of 10 per cent. Guanethidine eye-drops in reducing lid retraction and relieving symptoms in patients with dysthyroid eye disease (Sneddon and Turner, 1966; Gay and Wolkstein, 1966; Crombie and Lawson, 1967). Administration of these eye drops produces local irritation in about 50 per cent. of patients and, although this is rarely severe, superficial punctate keratitis may occur if the drops are continued for longer than one week (Crombie and Lawson, 1967).

We have used the less concentrated 5 per cent. Guanethidine eye drops and report results on 21 patients with dysthyroid eye disease.

Case material

21 patients (12 female, 9 male) were included in the trial. All had symptoms of conjunctival irritation and all had eye signs of Graves's disease, which were bilateral in eleven cases. The eye signs had been present on average for 25 months (range 5 to 60), and in nineteen patients for longer than 12 months. The eye symptoms and signs had been stationary for at least 6 months in all but one patient.

All the patients but one were clinically euthyroid. All had shown radioiodine evidence of dysthyroidism, the T₃ suppression test (Bowden and Rose, 1969) being abnormal in the sixteen patients in whom it had been performed. Seven patients had been hyperthyroid before or at the onset of eye symptoms, two having had a partial thyroidectomy. During the trial nine patients received neomercazole, two neomercazole and thyroxine, and ten no treatment; the therapy remained unchanged during the trial.

Methods

Of the 42 eyes available for study in the 21 patients, 32 showed signs of Graves's disease and ten were normal. The main signs present at the start of the trial are summarized according to treatment group in Table I. In the ten patients with unilateral eye disease, the abnormal eye was treated; in the

Table I *Pre-treatment eye signs in 21 patients (42 eyes) with dysthyroid eye disease, by treatment group*

Treatment	Total no. of eyes	Number of eyes with				
		Conjunctival lesions	Lid retraction	Lid-lag	Exophthalmos	Raised ocular tension
5 per cent. Guanethidine	23	16	22	22	11	1
Inactive drops	13	8	12	13	9	1
None	19	3	6	7	5	0

eleven patients with bilateral eye disease, the more affected eye was treated in nine patients, and both eyes in the other two. Thus 23 of the 32 abnormal eyes received Guanethidine drops and, of these, thirteen received drops for an initial period of 2 weeks. Nine abnormal eyes and ten normal eyes received no treatment.

The "active" drops were 5 per cent. guanethidine in methylcellulose with an appropriate buffering agent to maintain pH; guanethidine was omitted from the inactive drops. The duration of the trial was 8 weeks, but inactive drops were instilled in thirteen abnormal eyes in a dosage of 2 drops twice daily, and subsequently the dosage was reduced every 2 weeks to 1 drop twice daily, 1 drop daily, and finally 1 drop on alternate days.

At the end of each 2-week period, the symptoms and signs in the treated and untreated eyes were assessed. Record was made of:

- (1) Change in eye symptoms
- (2) Effect of drops on the mouth, bowel and micturition habit, and standing blood pressure
- (3) Appearance of conjunctiva, cornea, and periorbital tissues
- (4) Visual acuity at 6 m. and 18 in.
- (5) Pupil diameter in mm. and pupil reactivity to light and convergence
- (6) Lid-lag, assessed approximately by the maximum amount of sclera visible on slow downward gaze
- (7) Palpebral width, measured directly with a perspex mm. rule under standard conditions of lighting, position of head, and direction of gaze
- (8) Exophthalmos in mm., using the Copper orbitometer
- (9) Intraocular pressure in mm. Hg, using applanation tonometry
- (10) Retrobulbar resistance, using the Copper orbitometer to measure the decrease in globe protrusion resulting from pushing it backwards by increase in weight from 100 to 400 g. on the anterior globe (Copper, 1948)
- (11) Close-up photograph of both eyes under standard conditions.

Results

Thirteen of the 21 patients completed the trial. Of the eight who failed to complete the trial, two developed a severe conjunctival reaction to Guanethidine drops, two were admitted to other hospitals with severe abdominal pain, two were admitted for routine thyroidectomy, and two defaulted for unknown reasons.

(1) EYE SYMPTOMS

All patients using Guanethidine drops noticed a transient stinging in the treated eye immediately after instillation of drops. Of the 21 patients receiving Guanethidine drops, eye soreness and watering improved in eight, became worse in four, and were unchanged in nine. Of the ten patients using inactive drops, symptoms improved in four, became worse in one, and were unchanged in five.

(2) GENERAL SIDE-EFFECTS

Eleven of 21 patients receiving Guanethidine drops complained of an unpleasant taste after instillation. An attack of abdominal pain severe enough to warrant emergency admission to hospital occurred in two patients, with diarrhoea in one of these. The pain occurred after 2 and 3 weeks respectively on active drops, and lasted for 30 min. and 24 hrs respectively.

No other cause was found for the pain. No other effects on bowel, micturition, or standing blood pressure were noted.

(3) APPEARANCE OF CONJUNCTIVA, CORNEA, AND PERIORBITAL TISSUES

Of the 23 eyes treated with Guanethidine drops, sixteen had a conjunctival lesion before starting treatment. The usual lesion was oedema and vascular dilatation, mainly at the outer canthus. This was improved by treatment in seven eyes, became worse in five, and was unchanged in four. After treatment with active drops, the vascular dilatation tended to become more generalized. Eight of the thirteen eyes treated initially with inactive drops had conjunctival lesions and these improved in three eyes, became worse in two, and were unchanged in three. Conjunctival vascular dilatation occurred for the first time after treatment in three eyes on active drops and one on inactive drops.

Two patients developed a severe local conjunctival vascular reaction with periorbital oedema in the treated eye 1 week and 5 weeks respectively after starting Guanethidine eye drops. The former patient had received a 2-week course of 10 per cent. Guanethidine eye drops to the same eye 9 months earlier.

Two of the nineteen untreated eyes developed conjunctival vascular dilatation and oedema during the trial.

No pre- or post-treatment corneal lesions were recorded.

(4) VISUAL ACUITY

No change was observed during the trial.

(5) PUPIL DIAMETER AND REACTIVITY

All patients receiving Guanethidine drops developed meiosis with reduced or absent pupil dilatation to shade.

(6) LID-LAG

This was reduced in all eyes receiving Guanethidine drops.

(7) PALPEBRAL WIDTH

The pre-treatment mean in the treated eyes was 15 ± 3.3 (S.D.) mm., and in the untreated eyes 11.7 ± 4.4 mm. The changes in palpebral width during the trial are summarized in Table II and Table III. Reduction in palpebral width was obtained with both active and inactive drops, but the former produced a significantly greater reduction, the degree of mean reduction in palpebral width with active drops being dependent on dosage. No significant change in palpebral width was found in the untreated eyes.

(8) EXOPHTHALMOS

The pre-treatment mean in the treated eyes was 18.1 ± 4.85 mm., and in the untreated eyes 16.1 ± 4.84 mm. Table II and Table III show the changes in exophthalmos during the trial. A significant mean reduction in exophthalmos was obtained only in those eyes treated with Guanethidine drops, and this reduction seemed more dependent on duration of treatment than dosage.

Table II Mean change in palpebral width, exophthalmos, ocular tension, and retrobulbar resistance in treated eyes (untreated eyes in brackets)

Treatment	Inactive drops	5 per cent. Guanethidine drops			
		2 twice daily	1 twice daily	1 daily	1 on alternate days
Palpebral width (mm.)	-1.23* (+0.69)	-1.85* (+0.21)	-1.95* (+0.18)	-1.5* (+0.14)	-0.95 (+0.35)
Exophthalmos (mm.)	-0.5 (+0.57)	-1.04 (-0.8)	-1.35* (-0.68)	-1.82* (-1.37)	-2.03* (-1.22)
Ocular tension (mm. Hg)	-0.73 (-1.57)	-1.15 (-1.93)	-0.63 (+0.07)	-1.68 (-1.55)	+0.63 (-1.0)
Retrobulbar resistance (mm.)	-0.77 (-0.71)	+0.19 (-0.19)	+0.14 (-0.33)	-0.09 (+0.14)	-0.13 (-1.06)*

* P 0.05

Table III Changes seen in palpebral width, exophthalmos, ocular tension, and retrobulbar resistance in treated eyes (untreated eyes in brackets)

No. of eyes		Inactive drops	5 per cent. Guanethidine			
			2 twice daily	1 twice daily	1 daily	1 on alternate days
Total		13 (7)	23 (19)	20 (16)	17 (13)	15 (11)
Palpebral width:	Decreased	8 (0)	17 (6)	15 (4)	13 (6)	12 (4)
	Unchanged	2 (4)	4 (7)	2 (7)	0 (2)	1 (3)
	Increased	3 (3)	2 (6)	3 (5)	4 (5)	2 (4)
Exophthalmos:	Decreased	8 (3)	15 (9)	12 (8)	12 (8)	12 (8)
	Unchanged	1 (0)	1 (6)	3 (2)	3 (1)	1 (1)
	Increased	4 (4)	7 (4)	5 (6)	2 (4)	2 (2)
Ocular tension:	Decreased	7 (4)	13 (8)	11 (5)	12 (6)	7 (4)
	Unchanged	3 (2)	3 (7)	4 (6)	3 (3)	0 (1)
	Increased	3 (1)	7 (4)	5 (5)	2 (4)	8 (6)
Retrobulbar resistance:	Decreased	6 (2)	9 (5)	8 (6)	6 (3)	5 (2)
	Unchanged	1 (0)	3 (5)	6 (2)	4 (4)	2 (2)
	Increased	6 (5)	11 (9)	6 (8)	7 (6)	8 (7)

(9) INTRAOCULAR PRESSURE

The pre-treatment means were 17.1 ± 3.53 mm. Hg in the treated eyes and 15.6 ± 3.44 mm. Hg in the untreated eyes.

Changes during the trial are shown in Table II and Table III. No significant mean change was obtained.

(10) RETROBULBAR RESISTANCE

The pre-treatment orbitometry means were 5.2 ± 1.63 mm. in the treated eyes and 5.3 ± 2.73 mm. in the untreated eyes. Tables II and III show the changes during the trial. No significant mean change was obtained.

(11) RELATIONSHIP OF RESPONSE TO DEGREE OF EXOPHTHALMOS

There was no significant difference in the mean change with treatment in palpebral width, exophthalmos, intraocular pressure, or retrobulbar resistance in the seven eyes with marked exophthalmos (initial exophthalmometry measurement greater than 22 mm., or 5 mm. more than fellow eye), as compared with the response in the other treated eyes. All seven eyes with marked exophthalmos had initial conjunctival lesions which were improved by treatment in only one case.

Discussion

The results of this investigation establish the usefulness of 5 per cent. Guanethidine eyedrops in reducing lid retraction and exophthalmos in dysthyroid eye disease. Previous trials have shown symptomatic improvement in over 90 per cent. of patients with dysthyroid eye disease using 10 per cent. Guanethidine drops (Gay and Wolkstein, 1966; Crombie and Lawson, 1967). In the present series symptomatic benefit was obtained by only 40 per cent. of patients using 5 per cent. drops, with similar results for inactive drops. This relatively low rate of symptomatic improvement is probably, to some extent, due to conjunctival irritation associated with the use of the Copper orbitometer in measuring exophthalmos and retrobulbar resistance involving instillation of local anaesthetic (1 per cent. decicaine) and application of contact shells. This explanation is supported by the fact that two of the nineteen untreated eyes developed marked conjunctival irritation during the trial. Least symptomatic benefit was obtained by those patients with marked exophthalmos.

The degree of reduction of palpebral width produced by 5 per cent. Guanethidine drops was directly related to dosage. One drop twice daily was the least required to produce an effect significantly greater than that of inactive drops. Reduction of exophthalmos was a long-term result of 5 per cent. Guanethidine instillation.

All but one of the patients in the present trial were euthyroid. There is evidence to suggest that Guanethidine eye drops may not be so effective in reducing dysthyroid eye signs in the presence of active hyperthyroidism (Gay and Wolkstein, 1966).

Increase in local conjunctival irritation occurred in 35 per cent. of eyes receiving 5 per cent. Guanethidine, in 23 per cent. of eyes receiving inactive drops, and in 11 per cent. untreated eyes. Again, part of this increased irritation is explained by the use of the orbitometer. Allowing for this, 5 per cent. Guanethidine drops produce increased conjunctival irritation less frequently than 10 per cent. drops. A severe local allergic reaction occurred

in two eyes receiving 5 per cent. drops. No case of punctate keratitis was recorded following the use of 5 per cent. drops, confirming the experience of Crombie and Lawson (1967).

Severe abdominal pain with diarrhoea has not previously been reported following the use of Guanethidine eye drops, though it is a not uncommon side-effect of the orally administered drug in much larger doses. Generalized skin rashes have been reported with 10 per cent. eye drops, but no cases were encountered in the present series.

No new deductions can be made from the present experiment as to the aetiology of dysthyroid eye disease or to the mode of action of Guanethidine eye drops. It seems that adrenergic mechanisms must play a part in the development or maintenance of dysthyroid lid retraction and exophthalmos, and hence in the development of the associated exposure conjunctival and corneal lesions.

Summary

The results of a trial of 5 per cent. Guanethidine eye drops in 21 patients with dysthyroid eye disease are reported. Guanethidine drops produced significant mean reductions in lid retraction and exophthalmos in the series as a whole. Only 40 per cent. of patients obtained symptomatic relief while using Guanethidine drops, and a similar proportion obtained relief using inactive drops. A possible explanation of this relatively low symptom-improvement rate is offered. Local side-effects due to 5 per cent. Guanethidine drops seem to be less frequent and less serious than those reported using 10 per cent. drops.

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