Unwanted pharmacological effects of local Guanethidine in the treatment of dysthyroid upper lid retraction

J. STANLEY CANT AND D. R. H. LEWIS

Tennent Institute of Ophthalmology, University of Glasgow

Adrenergic blocking agents have had an occasional and limited use in ophthalmology for several years but are now being used with increasing frequency in the treatment of glaucoma and of the eye signs of accompanying thyroid dysfunction. Several trials of the therapeutic uses of local adrenergic blocking agents have been made and these indicate that, of the agents tested (including Bethanidine, Guanethidine, Phentolamine, and Propanolol), Guanethidine is the most effective (Lee, Morimoto, Bronsky, and Waldstein, 1961; Gay and Wolkstein, 1966; Sneddon and Turner, 1966; Gay, Salmon, and Wolkstein, 1967).

Accordingly, with increasing interest in dysthyroid ophthalmopathy, trials have recently been made of the use of Guanethidine in treating upper lid retraction and exophthalmos and, as local toxic effects have been met in some of these trials, including a short-term trial with fourteen patients (Sneddon and Turner, 1966) and a long-term trial with twenty patients and an average duration of 16 weeks (Crombie and Lawson, 1967), 81 patients in a recent extended trial have been examined in detail to determine if local Guanethidine has any serious side-effects.

Method

There were 81 patients in the series, which was conducted to determine the most effective strength of drop and dosage schedule in the treatment of dysthyroid upper lid retraction with local Guanethidine, and to assess the effect of the therapy on exophthalmos. Most of these patients had originally been thyrotoxic but were euthyroid at the time of admission to the trial and either required no further specific anti-thyroid treatment or, having become hypothyroid following treatment, were maintained by therapy in the euthyroid state. The detailed results of this trial have been recorded elsewhere (Cant, Lewis, and Harrison, 1969) and this communication is confined to the side-effects of Guanethidine.

Since at the start of the trial no indication of the dose of Guanethidine required to abolish upper lid retraction was available, the patients were given varying strengths of drops at varying frequencies of dosage. At the outset, 10 per cent. drops were used, but it was found that this strength was unnecessary and eventually 5 and 2 per cent. drops were instituted.

Results

The results showed that 5 and 2 per cent. Guanethidine drops were almost equally effective in the treatment of upper lid retraction and that the required schedule of administration varied very much in accordance with the needs of the patient. The majority of patients in

this series were eventually maintained on 5 or 2 per cent. Guanethidine drops to both eyes twice daily, and a further group had 5 per cent. Guanethidine drops even less frequently. An initial group had one drop of 10 per cent. Guanethidine instilled hourly for 8 hours followed by the same concentration four times daily for a varying period. This initial high dosage schedule was given to the group of patients who were selected as having very marked upper lid retraction of long duration, as it was thought that they might be resistant to local treatment. Throughout the trial great care was taken to instruct each patient on the correct method of using eye drops. Only one drop was used at each instillation and the lower lacrimal canaliculus was occluded by finger pressure.

SYSTEMIC SIDE-EFFECTS

In none of the patients in this series were systemic side-effects noticed. The dose of Guanethidine drops by any schedule of administration is small (Table I). The patients at no time mentioned any of the systemic side-effects sometimes encountered when Guanethidine is taken orally (this includes orthostatic hypotension and gastrointestinal upsets).

Table I *Total daily dosage of Guanethidine (mg.) when instilled to both eyes*

Dosage schedule	Concentration		
	10 per cent.	5 per cent.	2 per cent.
Daily	5.72	2.86	1.14
Twice daily	11.44	5.72	2.29
3 times a day	17.16	8.58	3.43
4 times a day	22.88	11.44	4.58
Hrly for 8 hrs (i.e. 9 instillations)	51.48	25.74	10.30

Note: These figures are based on the trial bottles which deliver 35 drops/ml. solution. The commercially available 5 per cent. strength of drops is contained in bottles which deliver 45 drops/ml. solution.

In all of the initial group the blood pressure was taken erect and supine several times daily, but no variation was found. In the extended trial with the entire group of 81 patients over an average duration of 44 weeks, on a varying dosage and administration schedule, no systemic side-effects were found in any patient and in none was there any significant variation in blood pressure.

LOCAL SIDE-EFFECTS

The local side-effects encountered are indicated in Table II. In this series of 81 patients the drops had to be discontinued in only seven because of local side-effects. Very few patients made any spontaneous mention of these side-effects.

The most common side-effect was dilatation of the vessels of the conjunctiva, but as the vaso-dilatation probably results from a reduction in sympathetic nervous control due to local adrenergic blockade, the redness of the conjunctiva caused by the instillation of Guanethidine drops must be considered as part of the pharmacological action of Guanethidine, as distinct from a "side-effect". Some degree of conjunctival vaso-dilatation was present in all patients in this series while on treatment with Guanethidine, although in eight

Table II Side-effects of Guanethidine in 81 patients

Miosis	81	Unilateral ptosis (both eyes treated)	4
Conjunctival congestion	81	Ptosis of contralateral eye (one eye treated)	3
Microscopic only	8	Nasal congestion (bilateral)	2
Minimal (<i>i.e.</i> evident on naked eye examination)	60	Rhinorrhoea (bilateral)	1
Cosmetic complaint	6	Burning on instillation	14
Discomfort (no corneal staining)	4	Itch on instillation	1
With superficial punctate keratitis	3	Exacerbation of viral keratoconjunctivitis	2
Conjunctival sensitivity	3	Effect on accommodation	0
Bilateral ptosis (both eyes treated)	1	Abnormal intraocular pressure	0

the vaso-dilatation could be seen only with the slit-lamp microscope. In the majority of cases (60) there was a slight conjunctival flush which was just apparent on naked eye examination but the patients did not complain about this. Six patients drew attention to their "red eyes" and a further four complained of local discomfort which they associated with the reddening of the eye; no other abnormality being present to account for ocular discomfort. Only three patients had superficial punctate keratitis associated with conjunctival congestion and they also mentioned ocular discomfort. This group of patients with corneal staining were all treated initially with 10 per cent. drops and the staining was reduced when 5 per cent. drops were used instead. Conjunctival congestion was more marked with the higher concentration of the drops and with increased frequency of instillation, but diminished proportionately after reducing both the concentration and the frequency of instillation.

Some degree of ptosis occurred in eight patients. In four of these (all of whom were treated with 5 per cent. Guanethidine drops) ptosis occurred in only one eye although the drops were being instilled into both eyes. Unilateral ptosis was not considered significant as there is frequently unequal retraction of the upper lid in dysthyroid eye disease and the initial response of the eyelid to treatment tends to vary according to the amount of upper lid retraction. This small group of patients who had unilateral ptosis had equal constriction of the pupils. In two of these patients the ptosis disappeared when the drops were stopped in that eye and as the upper lid retraction did not recur there was no need for further therapy to the affected eye. In the other two cases, upper lid retraction recurred on stopping the drops and therapy had to be reinstituted at a decreased frequency.

One patient had bilaterally equal ptosis and this was considered to be due to a simple overdosage as the upper lid retraction recurred some days after the drops were stopped but the ptosis did not recur on recommencing treatment at a decreased frequency.

Three patients who were using 5 per cent. drops in one eye only, had a transient ptosis of the contralateral eye which is difficult to explain. The possibility of systemic toxicity due to absorption of Guanethidine can almost certainly be excluded in view of the small quantities of Guanethidine used (Table I), and in the absence of any other evidence of systemic toxicity including constriction of the contralateral pupil. The more likely explanation is that some drops entered the opposite eye (although this was denied by the patient) and the absence of constriction of the pupil tends to be against this. The third possibility is that with the successful elimination of unilateral upper lid retraction by the use of Guanethidine a compensatory drooping may develop of the contralateral eyelid. In all three cases this drooping of the contralateral upper eyelid was transient and disappeared although the drops were not discontinued.

Three patients developed a marked sensitivity to Guanethidine drops after using them for several weeks, and this persisted in spite of reducing the strength of the drops (from 5 to 2 per cent. in all three cases). In these patients treatment had initially been successful in eliminating upper lid retraction and the sensitivity developed only after the lid retraction had been abolished and with the continuation of the therapy. The sensitivity took the form of an intense vaso-congestion of the conjunctiva extending throughout the conjunctiva and including the eyelid margins. This was accompanied by ocular discomfort, which was not, however, very marked. The possibility arose that the sensitivity could be due either to the drop vehicle (methyl cellulose) or to the preservative (benzalkonium chloride 0.02 per cent.), but in all three patients control drops of methyl cellulose alone and subsequently of methyl cellulose together with the preservative, did not produce any sensitivity yet this reappeared when Guanethidine drops were restarted, indicating that the sensitivity was to the Guanethidine itself.

Among other side-effects were nasal congestion, which occurred in two patients lasting for about an hour after instillation of the drops, and bilateral rhinorrhea in one patient which also lasted for about an hour after instillation of the drops. Fourteen patients complained of "burning" on instillation and one of a transient itch on instillation. During the period of this trial there was an epidemic of adenovirus 8 keratoconjunctivitis in the West of Scotland and two patients who were using 5 per cent. Guanethidine drops developed a particularly severe adenovirus 8 keratoconjunctivitis. It appeared that the use of Guanethidine exacerbated this condition, and when the drops were stopped in these patients considerable improvement took place.

All patients using the drops had miosis but this did not interfere with vision and no blurring of vision on reading was complained of. No patient was found to have decreased accommodation. No abnormal intraocular pressure readings were recorded (the intraocular pressures were taken regularly) and no patient complained of an unpleasant taste on using the drops although this has been described by previous observers (Crombie and Lawson, 1967; Oosterhuis, 1962).

The drops were stopped in only seven of this group of 81 patients because of unpleasant side-effects. In two patients the reason for discontinuing treatment was the development of a viral keratoconjunctivitis, and in two the appearance of superficial punctate keratitis. The two latter patients had initially been treated with 10 per cent. drops and the corneal staining decreased on reducing the concentration, but despite this it was felt wise to discontinue local treatment after causing initial corneal damage. Finally the drops had to be discontinued in the three patients who developed local sensitivity.

It was noticeable that very few patients with side-effects complained of them spontaneously and most preferred to continue with the drops in view of the benefit they brought about. Amongst those who requested to continue were three patients with acute sensitivity, those with ptosis, and those with conjunctival congestion associated with discomfort as they all considered the side-effects trivial compared with the comfort brought to the eyes by the elimination of the previously gritty feeling, and in view of what they all considered to be a marked improvement in their appearance; even those with noticeable conjunctival congestion preferred to continue with the drops as they thought that the elimination of the upper lid retraction and staring appearance far outweighed the cosmetic blemish of slightly pink conjunctivae. However, in the patients who developed the local sensitivity, it was considered advisable to refuse their request and to discontinue therapy.

Discussion

The striking feature in this series of 81 patients was the almost complete effectiveness of Guanethidine drops in abolishing, or at least reducing, dysthyroid upper lid retraction. Side-effects were encountered in very few patients and in only seven were the drops discontinued because of these. The most important point in regard to side-effects is the complete absence of any systemic toxicity in this large group of patients. The dose of Guanethidine delivered locally in the treatment of upper lid retraction (or in the treatment of chronic simple glaucoma) is small indeed, and would not be expected to produce any systemic toxicity, but the absence of systemic toxicity or unwanted pharmacological effects is an important observation.

Amongst the other "side-effects" listed in this communication, several are simply indications of the pharmacological action of the drug. Guanethidine can be considered to produce a modified and medically-induced Horner's syndrome, and in normal patients the drops produce miosis and ptosis although there is no true enophthalmos. Similarly in the dysthyroid patients there is a miosis and drooping of the upper eyelid although it is disappointing that there is no reduction in exophthalmos. Miosis is a true pharmacological effect and as it occurs after a single drop instillation, it can be taken to indicate that the drops are being used although, since a single drop is seldom effective in changing the position of the upper eyelid, it does not indicate effectively in this respect. A single drop of Guanethidine instilled into the eye may produce a transient mydriasis, but the pupil thereafter returns to normal size and becomes miotic within about an hour and continued administration of the drops thereafter produces a continuing miosis. This initial mydriasis is probably due to an initial release of catecholamines from the nerve ending storage sites. Miosis can in no sense be considered a side-effect and the pupil size produced with even 10 per cent. Guanethidine in the normal patient is not as small as that produced by 2 per cent. Pilocarpine drops. There is seldom any interference with vision and none of our patients complained of any reduction in visual acuity. With diminution in pupil size it might be anticipated that there would be reduction in visual acuity in a patient with central lens opacities, but none of our patients had this form of cataract which is relatively rare in the age group of patients dealt with. Previous accounts of the use of Guanethidine have mentioned accommodative upsets, but no difficulty in reading was experienced by the patients in this series, and indeed a relatively small pupil can be an advantage in near vision.

Conjunctival vaso-dilatation must also be considered part of Guanethidine's pharmacological action when used on the eye and it is not a true "side-effect". Conjunctival vaso-dilatation does not occur immediately on instillation but appears over a period of a few days and seldom increases thereafter, and in our series it was a constant finding. If the presence of miosis is taken to indicate that at least one drop has been instilled, the presence of conjunctival vaso-dilatation indicates that several drops have been instilled and indeed the absence of some degree of dilatation of the conjunctival vessels might be taken to indicate that the drops have not been instilled. The amount of vaso-dilatation varies from patient to patient but in the majority it amounts to a minimal flush of the conjunctiva. Although in a few patients the eyes appeared to be distinctly red, only the three patients who developed actual sensitivity to the drops had marked conjunctival congestion. Superficial punctate keratitis has been described in the past (Crombie and Lawson, 1967) but this does not occur without conjunctival vaso-dilatation or congestion. We encountered this finding much less than in previous series which were conducted largely with 10 per

cent. drops. We found that two out of ten patients using 10 per cent. drops developed superficial punctate keratitis, which was reduced, but did not disappear on changing to 5 per cent. drops, but their corneae became clear when the drops were stopped completely. One out of 41 patients developed superficial punctate keratitis using 5 per cent. drops twice daily, and this disappeared on reducing the strength of drops to 2 per cent.; none out of 10 patients using 2 per cent. drops three times daily developed this sign. It appears that superficial punctate keratitis is associated with conjunctival vaso-dilatation and is directly connected with the strength of drops used. We feel that the relative absence of superficial punctate keratitis in our series is due partly to the majority of our patients being treated with 2 or 5 per cent. drops and partly, and possibly to a greater extent, to our patients being instructed to take great care in the instillation of the drops and only to use one drop at each instillation.

Nasal congestion may also be considered to be part of the pharmacological effect of Guanethidine and the two patients who experienced this said that they felt the drops passing to the nose on instillation. One of these patients was able to overcome her nasal congestion by occluding the lacrimal canaliculi with finger pressure but the other patient found this difficult. Both patients with this transient nasal congestion preferred to continue using the drops.

Of the true side-effects, the exacerbation of serious superficial ocular inflammation is the most important. Dilatation of the conjunctival vessels may be expected to exacerbate superficial ocular inflammation or infection and our experience of the exacerbation of kerato-conjunctivitis indicates that the drops should be temporarily suspended in the presence of such conditions. The three patients with sensitivity developed intensely injected bulbar and tarsal conjunctivae, although there was no conjunctival oedema (chemosis). The absence of this reaction to control drops containing the same base and preservative as the local drops, indicates that the sensitivity was to Guanethidine. This appears to be a true sensitivity with the substance possibly acting as a hapten antigen and as in all three cases the reaction was confined to the eyes, it is presumably mediated by some local immunological mechanism. It is interesting that no true generalized sensitivity to Guanethidine in tablet form has been authenticated. The rhinorrhoea which occurred in one case could possibly be taken to indicate a local sensitivity although there was no evidence of sensitivity in the eyes.

Fourteen patients mentioned a "burning" sensation on instilling the drops but this lasted for only a few seconds and was not troublesome and as the majority of our patients had no discomfort on instillation (and many of these commented on the fact that the drops did not "sting"), the complaint of burning may be a personal idiosyncrasy.

The use of local Guanethidine in glaucoma is well known but in this series no significant fall in intraocular pressure was found in any of the patients, who all had normal intraocular pressures before entering the trial.

Several communications previously made on the subject of Guanethidine eye drops have indicated that there is the distinct possibility of local side-effects. The present trial points to the great usefulness of local Guanethidine in the treatment of dysthyroid upper lid retraction and to the very low incidence of true side effects. The pharmacological effects which may be expected to occur in all cases increase with over-dosage and this indicates that Guanethidine drops should be used at the lowest strength and frequency to produce the greatest effect in lowering the upper lid. Systemic side-effects from the use of these drops in this extensive trial did not occur and the only true side-effect encountered was local sensitivity.

Summary

A series of 81 patients suffering from dysthyroid ophthalmopathy was treated with local Guanethidine for an average of 54 weeks.

None exhibited any systemic complication of this therapy during the trial.

Only seven patients developed local complications severe enough to warrant discontinuation of therapy. Three of these developed local sensitivity to Guanethidine, two developed superficial punctate keratitis, and in the remaining two cases the therapy produced an exacerbation of a viral keratoconjunctivitis.

These findings indicate that the long-term use of local Guanethidine in eyes produces only a low incidence of toxic effects of sufficient severity to necessitate discontinuance of the therapy.

We are grateful to Dr. A. K. Pittman and Dr. D. A. Richards of Ciba Laboratories Ltd. for making Guanethidine drops available to us and for help in the preparation of this paper.

References

- CANT, J. S., LEWIS, D. R. H., and HARRISON, M. T. H. (1969) *Brit. J. Ophthalm.*, **53**, 233
CROMBIE, A. L., and LAWSON, A. A. H. (1967) *Brit. med. J.*, **4**, 592
GAY, A. J., SALMON, M. L., and WOLKSTEIN, M. A. (1967) *Arch. Ophthalm. (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. Ophthalm. (Chicago)*, **67**, 802
SNEDDON, J. M., and TURNER, P. (1966) *Lancet*, **2**, 525