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The combination of guanethidine 3% and adrenaline 0·5% in 1 eyedrop (GA) in glaucoma treatment

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SUMMARY During a 7-month period 33 patients (20 with primary open-angle glaucoma and 13 with suspected glaucoma) were treated with guanethidine 3% and adrenaline 0·5% in 1 eyedrop twice daily. The previous therapy was discontinued and the aim of the trial was to treat the patients with GA alone. There was an average decrease in intraocular pressure of 10·8 mmHg or 37·5% for the whole group (including 5 patients with additional therapy). In eyes with an average IOP in a day-curve without medication equal to or higher than 28 mmHg we found a decrease in IOP of 44·6% or 14·4 mmHg, and in eyes with an average IOP without medication between 21 and 28 mmHg a decrease of 30·4% or 7·6 mmHg. With GA alone the IOP was 3·3 to 3·9 mmHg lower than on the previous therapy ($P < 0·05$); 46% of the eyes without additional therapy had all IOPs lower than 22 mmHg and 74% of the eyes had IOPs lower than 22 mmHg except 1 with a peak lower or equal to 25 mmHg 3 hours after application. This peak 3 hours after application indicates that GA has a biphasic action and was significant at the 0·5% level. Red eyes and slight ptosis were no problem for most patients. Patients found it very convenient to administer GA only twice daily.

During the last 10 years non-miotic therapy has taken a more important place in the treatment of glaucoma patients suspected of having glaucoma and primary open-angle glaucoma (POAG). One of the non-miotic preparations used is a combination of guanethidine and adrenaline. Stepanik (1961), Kutschera (1961), Küchle (1961), Oosterhuis (1962), and Bonomi and di Comite (1967) reported a fall in intraocular pressure (IOP) with guanethidine 10% alone in the treatment of patients with POAG. This fall was only temporary. Sears (1966) showed in studies on patients with Horner's syndrome 'that the outflow mechanism can be made supersensitive to topical epinephrine'. G. D. and G. Paterson (1972, 1974) pointed to the phenomenon of hypersensitivity of the receptor for sympathomimetic drugs during chemical denervation with guanethidine and to the necessity of applying adrenaline twice daily during the treatment with guanethidine. Long-term studies on guanethidine and adrenaline in patients with glaucoma have been done by Roth (1973), Etienne (1973), Crombie (1974), Gloster (1974), Romano (1974, 1977), Nagasubramanian *et al.* (1976), and Jones *et al.* (1977) with good results.

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The aim of the trial reported here was to investigate the possibility of stopping all previous therapy of patients known to have POAG or suspected of having glaucoma, to treat them only with guanethidine 3% and adrenaline 0·5% (GA) in 1 eyedrop, and to investigate the proper dosage of GA. New patients with POAG or new glaucoma suspects were, if possible, treated only with GA. Thus we obtained an impression of the efficacy of GA alone and its effect in relation to previous therapy.

Patients and methods

Thirty-three patients (23 male and 10 female) with either POAG or suspected glaucoma were admitted to the trial. They were divided into 20 patients with POAG (33 eyes, 2 eyes having been previously operated on) and 13 glaucoma suspects (26 eyes). The mean age of the patients was 60 years (range 25 to 84 years), and treatment lasted for an average of 7 months (range 1 to 11 months).

Our criteria for diagnosing primary open-angle glaucoma were visual field defect and/or disc

pathologically excavated and/or in a day-curve without medication 1 pressure higher than 36 mmHg, and with an open angle. Our criteria for glaucoma suspects were no visual field defect, normal disc, in the day-curve without medication at least 1 pressure higher than 25 mmHg and lower than 36 mmHg, and with an open angle. If a patient had one eye with glaucoma and the fellow eye showed only a raised IOP, both eyes were regarded as having POAG. These criteria are arbitrary. In our clinic we prefer to use the term glaucoma suspect instead of ocular hypertension.

Before the patients were admitted to the trial they were evaluated. Visual acuity and refraction were tested, biomicroscopy with the Haag-Streit slit lamp, and gonioscopy with the 3-mirror contact lens of Goldmann were undertaken, and visual fields were tested on a Tübingen perimeter. Patients were taken off treatment 1 week before the trial if they had been on sympathomimetics and carbonic anhydrase inhibitors and 48 hours beforehand if on miotics. A day-curve without medication was then made. The IOP was taken with a Goldmann applanation tonometer mounted on a Haag-Streit slit lamp at 9 a.m. and 12 noon (0 to 3 hours) and 3 p.m. and 5 p.m. (6 to 8 hours). The previous therapy which was stopped in these patients is shown in Table 1.

Table 1 *Previous therapy of 20 patients with POAG and 13 with suspected glaucoma*

20 patients with POAG (n=33)	*No. of eyes*	*13 glaucoma suspects (n=26)*	*No. of eyes*
Pilocarpine 2% 4×d	14	Pilocarpine 1% 4×d	4
Aceclidine 2% 4×d	3	Pilocarpine 2% 4×d	10
Aceclidine 2% 2×d	2	Isoptocarpine 4×d	4
Aceclidine 2% + adrenaline 1% 2×d	5	Aceclidine 5×d	2
Eserine 0·25% 4×d	3	Eserine 0·25% 4×d	2
Carbachol 1·5% 3×d	2	Adrenaline borate 1 or 2×d	10
Adrenaline borate 1% 2×d	15	L-adrenaline bitartrate 2×d	2
Ismelin 5%	3	Ismelin 5% 2×d	2
Acetazolamide sustained release 1×d	4	2 or 3×0·5 Acetazolamide	6
Acetazolamide 0·250 2 or 3×d 0·5	4	None	4
None	5		

×d = times a day. Aceclidine = 3-acetoxyquinuclidine HCl.

After a day-curve without medication all patients started with GA twice daily at an interval of 12 hours (at 9 a.m. and 9 p.m.). The day-curves were repeated after treatment for 1 week, 1 month, 3 months, and 7 months, and then medication with GA was stopped for 2 weeks, when the day-curve was repeated. GA was given after the first pressure reading in the day-curve. Thus the first reading (at zero) gave the IOP 12 hours after the last application. Additional therapy was given to patients in whom the IOP was not sufficiently lowered. Every month during the trial the patients were examined at our polyclinic for a short control period when we checked visual acuity, refraction, and IOP, and looked for side effects. Visual fields were controlled during our trial, and we particularly looked for changes in the early defects.

In the group with 20 patients with POAG 2 left the trial (1 patient died suddenly, and 1 left for personal reasons). Additional therapy in this group was needed in 4 patients. One patient needed acetazolamide once daily plus pilocarpine 2% 4 times daily. One (who died suddenly) needed acetazolamide once daily. One needed acetazolamide once daily and carbachol 1·5% 3 times daily. And 1 patient received only pilocarpine 2% twice daily. The rest of the group was controlled with GA twice daily only.

In the group with suspected glaucoma 1 patient was taken off medication with GA because of transient serous maculopathy. She was known to have had maculopathy previously. One patient needed additional therapy with pilocarpine 1% twice daily. The rest of the group was controlled with GA twice a day only.

Our results were statistically evaluated by Student's *t* test.

Results

Fig. 1 and Table 2 show the combined results of all patients treated with GA for about 7 months. The average decrease in IOP for all patients (patients with additional therapy included) was 10·8 mmHg or 37·5%, with a reduction in fall of IOP to 7·4 mmHg or 26·7% after 3 hours. After 7 months' treatment the fall in IOP was still continuing and no adaptation was seen.

We have selected the eyes of patients who had no additional therapy in 2 groups. The first group with 22 eyes had an average IOP in a day-curve without medication higher than or equal to 28 mmHg. In the second group 25 eyes had an average IOP in a day-curve without medication between or equal to 21 and 28 mmHg (28 mmHg is about the median IOP of the averaged IOPs of the individual day-

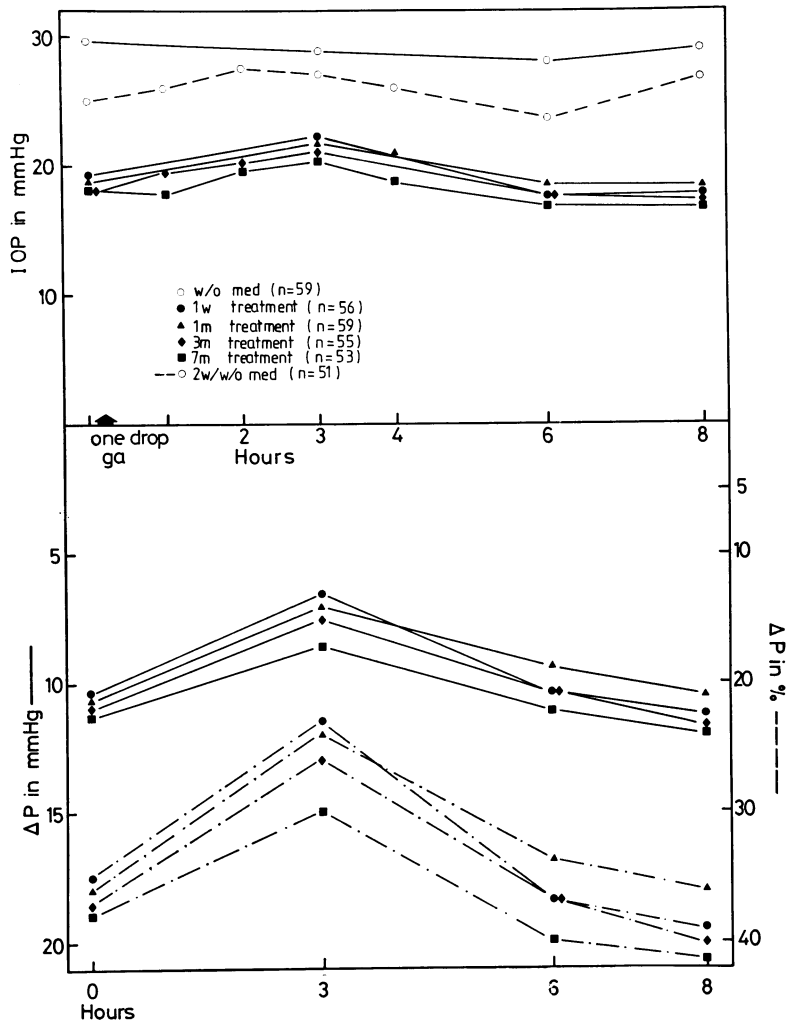

Fig. 1 Upper half: *Mean IOP day-curves of 33 patients with either POAG or suspected glaucoma during treatment (5 patients with additional therapy included).* Lower half: ΔP *in mmHg (solid line) and* ΔP *in percentages (dotted line)*

Table 2 *The results of treating 33 patients (59 eyes) with either POAG or suspected glaucoma (5 patients with additional therapy included), in mmHg* ± *standard error of mean*

	Hours			
	0	*3*	*6*	*8*
Mean IOP in mmHg without medication (n=59)	29·5±0·98	28·9±0·90	27·9±1·08	28·9±1·15
Mean IOP in mmHg after 7 days' treatment (n=56)	19·2±0·69	22·3±0·87	17·6±0·69	17·7±0·82
Mean IOP in mmHg after 1 month's treatment (n=59)	18·9±0·58	21·9±0·67	18·5±0·56	18·4±0·63
Mean IOP in mmHg after 3 months' treatment (n=55)	18·5±0·51	21·4±0·68	17·6±0·57	17·3±0·70
Mean IOP in mmHg after 7 months' treatment (n=53)	18·3±0·60	20·3±0·59	16·8±0·51	16·9±0·52
Mean IOP in mmHg after 2 weeks without medication (n=53)	25·0±0·63	26·9±0·81	23·7±0·78	26·7±0·98

± = standard error of mean.

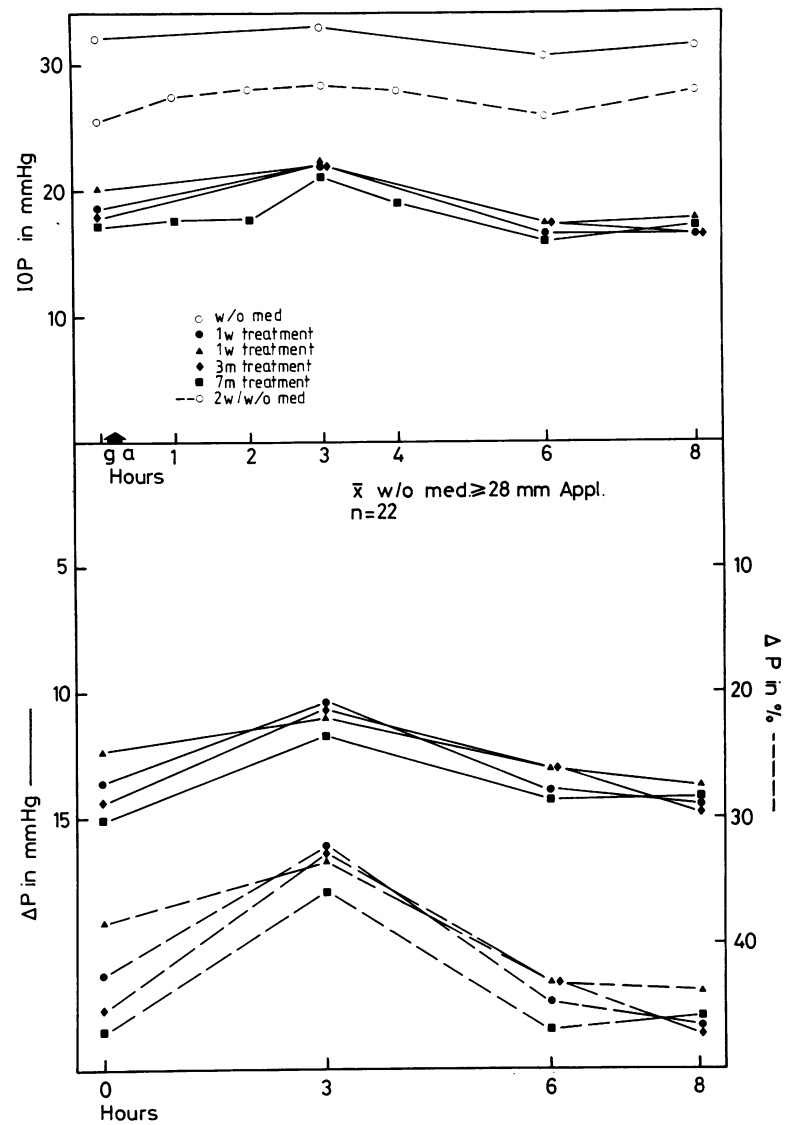

Fig. 2 Upper half: *Mean IOP day-curves of 22 eyes treated only with GA with an average IOP in the day-curve without medication equal to or higher than 28 mmHg.* Lower half: *ΔP in mmHg (solid line) and ΔP in percentages (dotted line)*

curves without medication). Figs 2 and 3 show the results.

There was a striking difference in percentage decrease of IOP. It was 44·6% for the eyes belonging to the group with the higher IOPs and 30·4% for the eyes with the lower IOPs. In Fig. 2 there is a fall in IOP from 31·7 mmHg (average of day-curves without medication) to 17·3 mmHg (average basal level with GA), and in Fig. 3 there is a fall from 24·8 mmHg (average of the day-curves without medication) to 17·2 mmHg (average basal level with GA).

It is interesting to note that, whatever the initial mean IOP was without medication, 24·8 or 31·7 mmHg, there seemed to be a decrease in IOP to a basal limit of 17 mmHg. We do not know the reason for this phenomenon.

The results in the individual patients are shown in Table 3. Twenty-three eyes were well controlled and all had an IOP lower than or equal to 21 mmHg. Twenty-three eyes were controlled and had all IOPs lower than 22 mmHg except at least one peak pressure 3 hours after application in one of the day-curves during treatment. In 14 eyes this peak pressure was lower than or equal to 25 mmHg, and in 9 eyes there were peak pressures between 25 and

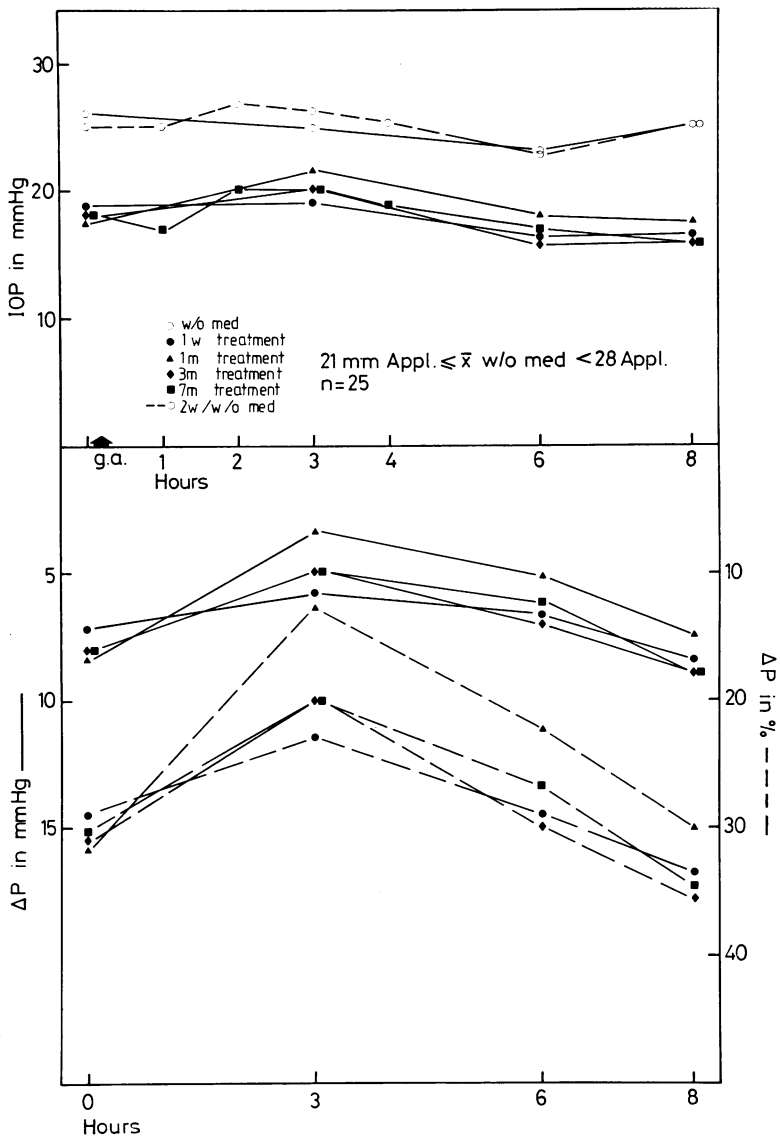

Fig. 3 Upper half: *Mean IOP day-curves of 25 eyes treated only with GA with an average IOP in the day-curve without medication equal to or greater than 21 mmHg and lower than 28 mmHg. The lower half shows ΔP in mmHg (solid line) and ΔP in percentages (dotted line)*

30 mmHg. Nine eyes were not controlled but had a good fall in IOP. In 2 patients (4 eyes) there was no response at all.

Among the patients who were treated with GA alone 46% of eyes had all IOPs lower than 22 mmHg during and after the 7-month period, and 74% had all IOPs lower than 22 mmHg with now and then a peak pressure in a day-curve but not higher than 25 mmHg. The patients who needed additional medication were included in the not well controlled group but with a good fall in IOP. The POAG patient with no response at all, had acetazolamide and pilocarpine 2% 4 times daily as additional therapy. The glaucoma suspect with no response had an initial good response on GA but tachyphylaxis developed.

We compared the results of 12 POAG patients and 9 glaucoma suspects, who were treated with GA alone, with the control level they showed on the previous therapy. The results are shown in Table 4. It indicates that in 18 patients (33 eyes) there was a lower controlling IOP level with GA alone than with previous therapy (3·3 to 3·92 mmHg; $P < 0.05$). In 1 POAG patient the level with GA alone

Table 3 *Number of eyes controlled by GA*

	POAG (n=33)	*Glaucoma suspects (n=26)*	*Total (n=59)*
Well controlled	12	11	23
Controlled	14	9	23
Uncontrolled but with decrease in IOP	5	4	9
No response	2	2	4

Table 4 *Mean individual differences in IOP of 21 patients (38 eyes) treated with GA alone with respect to their mean individual IOP on previous treatment; n = number of eyes. For POAG patients the mean number of measurements during previous medication is 12·5 and for glaucoma suspects 14*

	12 POAG	*9 Glaucoma suspects*
Mean lower IOP level in mmHg with GA	−3·92 (n=15)	−3·3 (n=18)
Equal mean IOP level with GA	(n=2)	—
Mean higher IOP level in mmHg with GA	+0·8 (n=3)	—

was the same and 2 POAG patients (3 eyes) had a higher pressure with GA alone (0·8 mmHg).

The number of measurements taken during the previous therapy were 12·5 (range 5 to 25) for the POAG patients and 14 (range 7 to 24) for glaucoma suspects. These were measurements taken during examinations at the polyclinic and not when day-curves were done.

SIDE EFFECTS

Only 2 patients found the drops unpleasant and had cosmetic objections. One of these had severe redness of the eye with chemosis and severe ptosis (more than 3 mm). The other had only moderate hyperaemia of the conjunctiva bulbi et tarsi. Fifteen patients with slight redness and 5 with moderate redness of the eyes had no objections to continuing treatment because of this. Transient or slight ptosis (1 to 2 mm) was found in 7 patients and moderate ptosis (2 to 3 mm) in 2. In 2 patients there was evidence of transient keratoepitheliopathy, but this did not lead to interruption of medication. Six patients had reading problems during the first hours after application. In 4 patients (4 eyes) early visual field defects disappeared and in 1 patient with an absolute visual field defect the defect progressed in spite of an excellent response on IOP. Tachyphylaxis was seen in 1 glaucoma suspect after 3 months' treatment. One patient showed serous maculopathy in 1 eye after 1 month's treatment, which disappeared 3 months later after GA was discontinued. She was known to have maculopathy previously. It was not regarded as a side effect but as progression of the underlying maculopathy.

Discussion

Guanethidine is thought to remove the stored noradrenaline in the granulated vesicles of the sympathetic nerve endings, to block the re-uptake, and to cause a depletion of noradrenaline at the nerve ending. As a result hypersensitivity for sympathomimetics develops at the receptor side. Since the Patersons started to use adrenaline in combination with guanethidine many studies on this subject have been done. Until now GA has not yet gained an important place in the treatment of glaucoma. This is partly owing to the side effects and partly owing to unfamiliarity with GA.

We have carried out this detailed study because we believe that more knowledge about its less well known properties was needed. We consider that we have in GA a potential mixture for lowering IOP, though there is some reduction of the effect on IOP 3 hours after application. This reduction is about 3·5 mmHg for the whole group ($P < 0·005$). A detailed analysis of this peak effect with GA 3 hours after application will be published elsewhere. The biphasic response during GA treatment has not been previously reported.

In comparison with previous therapy, all patients (except 2 with red eyes) found it pleasanter to administer the drops only twice daily. Hyperaemia of the conjunctivae and slight or moderate ptosis was acceptable to most patients. Visual acuity did not change except in 1 patient known to have progressing cataract. Refraction showed a slight increase in hypermetropia of $\frac{1}{2}$ to $\frac{3}{4}$ dioptre in 7 patients. After GA was stopped this disappeared. Relaxation of the ciliary muscle may be the cause of it. Reading problems during the first few hours after application of GA disappeared with $\frac{1}{2}$ dioptre stronger presbyopia correction for reading. We do not know whether this is due to widening of the pupil or a slight increase in hypermetropia. Reading problems were mainly in patients aged between 40 and 55. Patients who complained of dark vision with miotics lost these symptoms with GA. Widening of the pupil during the first hours after application was frequently seen.

Summarising, we find that with GA, despite red eyes and slight ptosis, we have an effective conservative treatment for patients with suspected glaucoma and POAG. Younger patients, who had many

problems with miotics, respond particularly well on GA. Operations may be delayed in patients who were not responding to previous therapy. Combinations with other conservative treatments are possible.

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