

A 7 year prospective comparative study of three topical β blockers in the management of primary open angle glaucoma

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Abstract

Aim—To determine the long term efficacy of monotherapy with topically applied β blocking agents and to determine whether selective β blockers were able to preserve the visual field more effectively than non-selective agents.

Method—A prospective randomised, open, comparative study of three topically applied β blockers—timolol, betaxolol, and carteolol—was carried out on 153 patients (280 eyes) with newly diagnosed open angle glaucoma. Those patients who were not withdrawn were followed by the same observers for a minimum of 2 years and a maximum of 7 years, with clinical observations, Goldmann tonometry and 24.2 Humphrey visual field analysis.

Results—All three drugs lowered the IOP significantly from untreated levels but betaxolol took up to 12 months in some instances to reach the maximum pressure reduction. After 7 years only 43% of the eyes begun on timolol, 34% of those started on carteolol, and 29% of those on betaxolol were still being treated with these medications alone. Visual fields were analysed throughout the trial by CPSD and MD and at the end by linear regression analysis (PROGRESSOR). The visual fields remained the same without apparent improvement or deterioration throughout the period of follow up. Eight patients (11 eyes) were withdrawn because of continuing field loss in spite of reduction in IOP (six using carteolol and five using betaxolol).

Conclusions—Analysis shows that less than half the eyes initially treated with topical β blockers might be expected to still be being treated with their original medication after 5 years. The rest required either additional medication or trabeculectomy. There was no statistically significant improvement or deterioration in the visual fields over a 7 year period. On the evidence of this trial there are no particular advantages in using selective β blockers.

(Br J Ophthalmol 2001;85:962-968)

Topically applied β blockers have been in clinical use for the reduction of intraocular pressure in patients with hypertensive open angle glaucoma for 20 years. They have been very successful in this. They are inexpensive so provided there is no contraindication to their use

they have until recently been almost universally used as the initial treatment for this condition.

These β blockers act by competitively inhibiting the binding of the catecholamines at the β adrenoreceptors in the ciliary epithelium. Aqueous production is decreased by interference with ion transport and by the blocking of the chloride channel in the non-pigmented ciliary epithelium. The commercially available ocular β blockers have different modes of actions. The non-selective β blockers available at the time this investigation started were timolol and carteolol. These drugs block both β_1 and β_2 adrenoreceptors. As there is a significant systemic absorption of locally applied medication and as β_1 receptors are present in the heart, heart block and bradycardia, or even cardiac failure, can occur. The β_2 receptors are present in pulmonary tissue so that blockade of these receptors can cause bronchospasm and dyspnoea. β_2 Receptors have been found on receptors in the choroidal vasculature¹ and in retinal arteries and veins.² Blockade of these vessels would lead to vasoconstriction and consequent reduction in circulation of the adjacent tissues.³ If prolonged this could lead to tissue damage and loss of function. A relatively selective β_1 blocker such as betaxolol should have less effect on these vulnerable vessels and should therefore protect the tissues from damage and preserve the visual field.

Carteolol has intrinsic sympathomimetic activity (ISA) and thus only partial β blockade. This drug should, theoretically, reduce the likelihood of bronchospasm and reduction of pulse rate and should have a beneficial effect on the perfusion of the optic nerve.

Early, short term 3 and 6 month studies had shown that the intraocular pressure (IOP) was reduced to a target level by each of the drugs available at that time.⁴⁻⁶ However, there was no conclusive evidence of added value from ISA or a selective β blocker.⁷ This study was therefore undertaken to determine what proportion of patients put on topical β blockade for newly diagnosed open angle glaucoma could continue on this medication for a prolonged period and, by continuing the study, it would also be possible to determine if there were long term systemic or local side effects of the drugs; finally, and most importantly, whether the selective β blockers are able to protect the visual field from progressive damage.

Patients and methods

One hundred and fifty three patients (280 eyes) with newly diagnosed primary open angle

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Accepted for publication
12 March 2001

Table 1 Comparability of patients at the start of therapy

	Drug allocated (n = no of patients)		
	Timolol (n=51)	Betaxolol (n = 54)	Carteolol (n = 48)
% male	52.9	50.0	64.6
% with family history of glaucoma	31.4	39.0	52.1
% with previous history of IOP raised	2.0	1.9	8.3
% with vascular disease	11.8	13.0	12.5
% with diabetes	0	3.7	8.3
Mean age (years) (SE)	67.4 (1.7)	68.9 (1.4)	68.1 (1.6)
Mean BP systolic (SE)	152.7 (3.8)	154.8 (3.6)	156.5 (3.2)
Mean BP diastolic (SE)	89.6 (1.9)	88.9 (1.9)	89.7 (1.5)
Mean pulse rate (SE)	73.7 (1.3)	75.1 (1.3)	71.8 (1.4)

Table 2 Comparability of eyes at the start of therapy

	Drug allocated (n = no of eyes)		
	Timolol (n = 96)	Betaxolol (n = 96)	Carteolol (n = 88)
% left side	51	49	45.5
Mean disc grading* ratio (SE)	0.57 (0.015)	0.55 (0.016)	0.54 (0.015)
Mean IOP mm Hg (SE)	27.74 (0.48)	27.90 (0.43)	27.78 (0.46)
Mean visual acuity† (SE)	2.64 (0.15)	2.66 (0.15)	2.47 (0.16)
Mean field loss grade (SE)‡	1.11 (0.14)	1.07 (0.14)	0.87 (0.13)
Mean MD (SE)	-4.91 (0.63)	-4.33 (0.67)	-3.76 (0.58)
Mean CPSD (SE)	3.57 (0.40)	3.87 (0.36)	3.34 (0.37)

*Cup to disc ratio.

†Visual acuity grading 1 = 6/5, 2 = 6/0, 3 = 6/9, 4 = 6/12, 5 = 6/18, etc.

‡Field loss grading 0–5 0 = none, 5 = severe.

glaucoma (POAG) were admitted to a prospective, randomised open label study comparing timolol (Timoptol, MSD) 0.25% (51 patients), carteolol (Teoptic, Ciba) 1% (48 patients), and betaxolol (Betoptic, Alcon) 0.5% (54 patients).

All the patients were fully informed about the purpose of the trial and the possible side effects of the medication. They signed a consent form according to the requirements and protocols of the ethics committee of Addenbrooke's Hospital, Cambridge.

ADMISSION TO TRIAL

All patients referred to the eye clinic who had IOP of 22 mm Hg in one or both eyes, together with a visual field and/or disc changes suggestive of a diagnosis of POAG, were considered for entry into the trial.

However, patients presenting with IOPs over 32 mm Hg together with a marked reduction of the visual field or a dense visual field defect within 10' of the fixation point which might threaten vision were offered immediate trabeculectomy.

The characteristics of the patients when first entered into the three arms of the study are presented in Table 1. The overall mean age was 68 years; 56% of the patients were male. There was no significant difference at the 5% level between any of the demographic variables; 41% of patients entered in the study gave a family history of glaucoma and, overall, 12% of patients gave a history of, or were found to have, vascular disease as determined by history or clinical examination. The mean blood pressure (BP) at recruitment was within normal limits for the age group at between 155 and 189 mm Hg, as was the mean pulse rate of 74.

Table 2 shows the initial characteristics of the eyes in the three arms of the trial. The mean overall disc grading was 0.55 (timolol

0.6, betaxolol 0.5, and carteolol 0.5) and the mean IOP was 27.8 mm Hg. Cataract was present in 7% of the timolol group, 9% of the betaxolol group, and 4.5% of the carteolol group.

EXCLUSIONS

Patients were excluded from the trial if they had had significant cardiac disease, particularly atrioventricular block, cardiac failure or sinus bradycardia, a history of pulmonary disease, acute bronchial spasm, or hepatic or renal disease. Also excluded were patients who wore contact lenses, those with a history of ocular trauma or surgery, angle closure glaucoma, and any pregnant or nursing mother. Patients who were unable for any reason to perform automated visual fields were not considered for the trial. Patients with chronic progressive angle closure were excluded but those with narrow but open angles were admitted to the trial. No patient with secondary glaucoma or pseudoexfoliation was included.

CLINICAL ASSESSMENT

At presentation a full clinical assessment was undertaken, which included the present and past history, Snellen visual acuity measurements, slit lamp biomicroscopy, together with gonioscopy and an IOP measurement with Goldmann applanation tonometry of two separate readings to each eye. The patients also had resting pulse and blood pressure recorded, together with laboratory and other investigations, if indicated by their systemic condition.

DISC CHANGES

As the disc does not cup in a uniform or predictable manner (the normal pattern in glaucoma being of an initial vertical rather than a horizontal enlargement) each disc appearance was recorded as a vertical and a horizontal cup to disc ratio—for example, 0.5 vertical, 0.3 horizontal (average equivalent to Armaly ratio = 0.4).⁸ These changes were compared throughout the trial by the same observer (PGW). Appearance of neuroretinal rim, peripapillary haloes, baring vessels, and disc haemorrhages were also recorded. It was not practical to record disc changes photographically.

VISUAL FIELD CHANGES

The visual fields were assessed with the 24.2 threshold program on the Humphrey visual field analyser. Defects in the hemifield or an isolated dense scotoma in conjunction with disc and pressure changes were regarded as glaucomatous. Occasional confirmatory Goldmann fields were undertaken if there was doubt as to the diagnosis.

All visual fields were performed under uniform conditions. Patients who were unable to perform Humphrey perimetry 24.2 visual field testing after two training attempts or who produced inconsistent field reliability indices as determined by fixation losses and false negative and positive values of more than 20% were excluded from the study. The IOP mean deviation (MD) corrected pattern standard

Table 3 Reasons for withdrawal

Reason	Drug		
	Timolol	Betaxolol	Carteolol
<i>Ocular</i>	<i>Eyes</i>	<i>Eyes</i>	<i>Eyes</i>
No change or increase in IOP despite treatment	5	14	5
Initial fall IOP Rise to original level	2	5	1
Failure to achieve target IOP of < 21 mm Hg	16	17	12
Uncontrolled IOP (total eyes)	23	36	18
Average initial IOP	27.74 (0.48)	27.98 (0.43)	27.78 (0.46)
Average initial IOP of those withdrawn	30.4 (0.52)	30.70 (0.54)	30.75 (0.54)
Average IOP at withdrawal	27.1 (0.40)	28.5 (0.43)	26.78 (0.41)
<i>Other ocular</i>	<i>Eyes</i>	<i>Eyes</i>	<i>Eyes</i>
Visual field deterioration with satisfactory reduction in IOP	0	5	6
Visual disturbance	7	0	0
<i>Medical</i>	<i>Patients</i>	<i>Patients</i>	<i>Patients</i>
Bradycardia	1	2	1
Breathlessness	2	3	5
<i>Non-medical</i>			
Patient request for surgery (patients)	1	0	2
Moved away (patients)	3	4	3
Deceased (patients)	3	4	6
Other non-medical (patients)	2	4	2

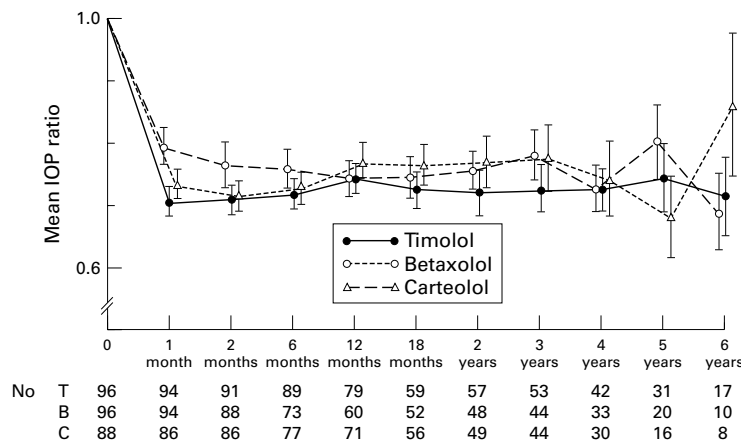


Figure 1 Mean ratios of measured IOP to the original value and the 95% confidence limits (CLs) at follow up visits. In this figure, measurements have been made up to and including the visit when the eye was withdrawn. These measurements contributed to the mean value. Visits beyond 6 years not included because of low numbers.

deviation (CPSD) were recorded and analysed. The aggregated results were also submitted to PROGRESSOR analysis.⁹

TREATMENT

If there were no contraindications to treatment with β blockers the patients were allocated to treatment with a specific agent by a computer generated random number selection. Thereafter all the patients in the trial were followed by one observer (MFB) to the end of the follow up period. As the trial was "open label" the observer was aware of the patient's medication. The medication was administered twice a day and the patients observed on average 3 hours after the last application of the eye drops. Unless there was an urgent requirement treatment was not started until a second visual field test had been performed.

FOLLOW UP

After the start of medication follow up examinations were carried out at 1, 3, and 6 months,

then every 6 months for 2 years and annually thereafter. Additional examinations were undertaken during the follow up period if the pressure was poorly controlled or it was felt necessary for any other reason.

At each follow up visit pulse, blood pressure and visual acuity were recorded. Patient compliance was carefully monitored by direct questioning to ensure that the medication was being taken as directed, that the drops were lasting the appropriate length of time, and to determine whether there were any local and systemic side effects from the medication. A measurement was taken of the IOP (3 hours (SD 30 minutes) after application of drops). The Humphrey 24.2 visual field was recorded.

The patients who were not withdrawn were followed for a maximum of 7 years and a minimum of 2 years after the first presentation at the glaucoma clinic.

WITHDRAWALS

Patients were withdrawn from the trial if they were unable to produce reliable Humphrey visual fields, if there was any deterioration in the visual field as judged by the Kratz criteria, or obvious deterioration in the optic disc, as judged by comparison with diagrams of the disc appearance at the start of the trial. If the IOP failed to fall, rose in spite of treatment, fell initially and then rose towards the original level, or did not fall below 21 mm Hg they were also withdrawn, as were patients who developed any persistent ocular or systemic side effects. Disc haemorrhages were noted but were not in themselves regarded as a reason for withdrawal. Some other patients were withdrawn for medical or other reasons (Table 3).

Results

INTRAOCULAR PRESSURE

Figure 1 shows the ratio of the IOP to the original value for each patient from the start of treatment to a follow up period of 6 years (visit 10). The initial IOP fell from an average of 27.8 (SD 0.3) mm Hg to an average of 20.6 (0.3) mm Hg after the fourth visit (12 months). Timolol and carteolol achieved a greater reduction of IOP than betaxolol initially and this low level was maintained through the whole follow up period. Figure 1 indicates that betaxolol produced a smaller fall in IOP initially but eventually achieved the same level of IOP after 12 months (visit 4). There was no difference in the initial measurements of IOP (timolol mean IOP 27.74 (SD 0.48) betaxolol mean IOP 27.98 (0.43) carteolol mean IOP 27.78 (0.46)) in the disc appearance or visual field scores between those originally given betaxolol or the other two medications. The IOP fall was the same in men and women.

VISUAL FIELDS AND VISUAL ACUITY

There was no change detectable in the CPSD of the full threshold Humphrey 24.2 visual field analysis throughout the follow up period.

After 2 years there is a suggestion that the mean deviation (MD) has returned closer to

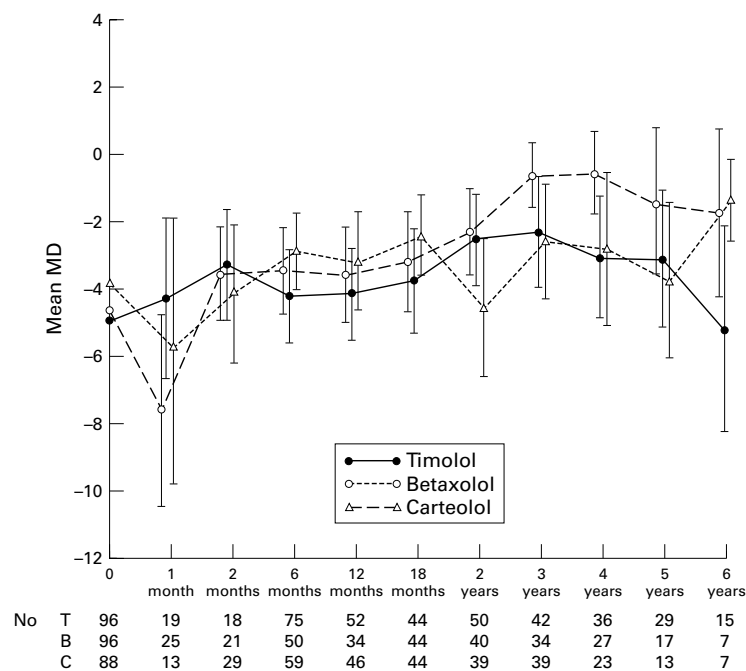


Figure 2 Mean MD values and 95% CLs at follow up visits.

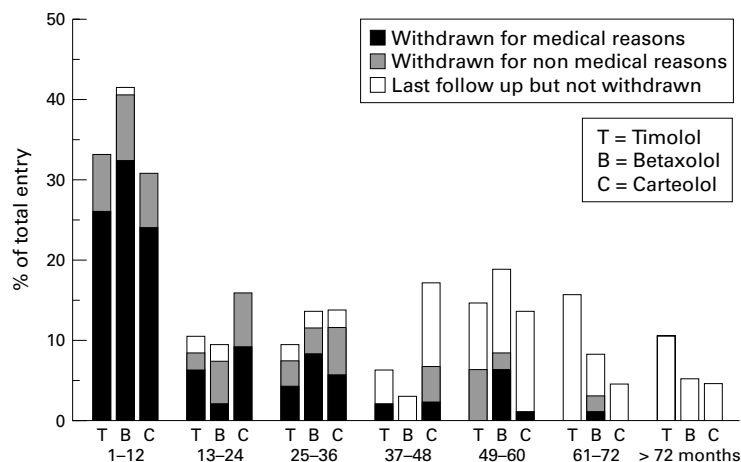


Figure 3 Reasons for withdrawal. Percentages are of total number of eyes entered in each group.

normal in patients on betaxolol but the apparent differences do not reach statistical significance (Fig 2). The visual acuity remained unchanged throughout the study period.

The changes detected by the Humphrey visual field analyser and the PROGRESSOR analysis were very similar. Only one eye in the timolol group showed some change on the PROGRESSOR which was not detected either by MD or CPSD. This patient had not been withdrawn from the trial. Two patients were withdrawn on the evidence of the MD and CPSD. PROGRESSOR detected change at one point only in both of these patients and was therefore graded one and would not have been withdrawn.

WITHDRAWALS

Table 3 shows the reason for withdrawal of patients from the trial. The majority of these withdrawals occurred during the first year of

treatment (Fig 3). More patients on betaxolol were withdrawn during this period than those who were given timolol or carteolol.

The eyes of patients who had uncontrolled IOP, visual field deterioration, and visual disturbance are listed in Table 3. They were withdrawn from the trial and given alternative treatment. The mean IOP of those withdrawn from the trial was 30.4 mm Hg for the timolol patients, 30.7 mm Hg for the betaxolol patients, and 30.5 mm Hg for the carteolol patients. No patients receiving timolol were withdrawn because of increasing field loss alone whereas six patients using carteolol ($p = 0.022$) and five using betaxolol ($p = 0.057$) had to be withdrawn for this reason. Seven patients receiving timolol had to be withdrawn because of blurring or similar disturbance of vision (timolol *v* betaxolol $p = 0.14$, timolol *v* carteolol = 0.019). A further three patients using timolol and five using betaxolol complained of blurring but this was not severe enough to necessitate withdrawal from the trial. In Table 3 those withdrawn for other reasons are listed as "patients." The most common medical reason for withdrawal was uncontrolled IOP, the highest number being withdrawn for this reason occurring in the betaxolol group. This is confirmed by Figure 4 which shows the "survival" curves for each arm of the trial. This shows the percentage of eyes remaining in the trial plotted against time after the commencement of treatment. Eyes withdrawn for non-medical reasons have been treated as "censored" at the time of their withdrawal. There is a tendency for eyes treated with betaxolol to do the least well, particularly during the first 18 months, but the overall differences are not statistically significant ($\chi^2 = 3.94$; 2 df; $p = 0.14$, $\chi^2 = 3.97$; 2 df; $p = 0.14$). Nevertheless, a test of timolol and carteolol combined against betaxolol achieves statistical significance ($p = 0.05$ for patients and $p = 0.04$ for eyes).

SIDE EFFECTS

The numbers and nature of side effects reported are shown in Table 4. The lowest number was reported in the carteolol group, the highest in the betaxolol group, mainly because these drops caused stinging in the eyes.

ANALYSIS

Statistical methods

"Survival" curves were calculated in two ways using the Kaplan-Meier method. The first was based on the numbers of patients in the trial, treatment being considered to have failed as soon as at least one eye has required a change in management. The second method was based on the number of eyes in the trial; treatment failure being counted for individual eyes (Fig 4). The comparison based on patients ignores cases where one eye required a change of treatment while the other eye continued to be satisfactorily treated with the originally allocated drug. Thus, some successes are ignored. In the comparison based on eyes, failures due to systemic effects, such as breathlessness, are

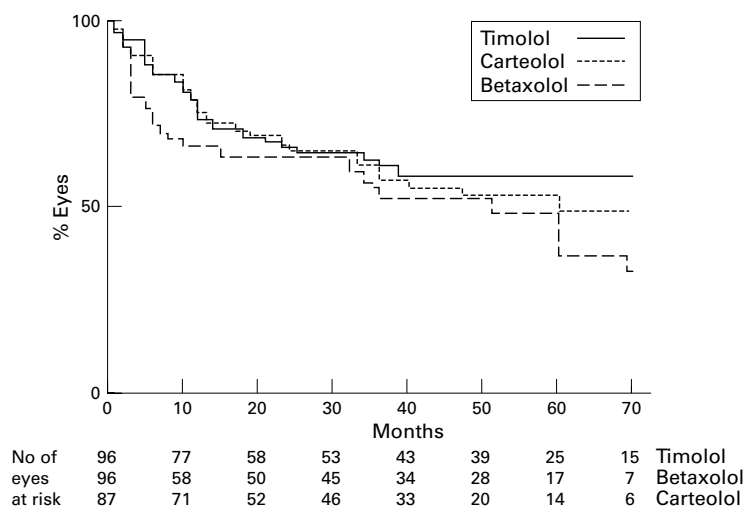


Figure 4 Survival curves. Percentages of eyes still being treated with the originally allocated drug.

Table 4 Number of patients reporting minor side effects not leading to withdrawal from the trial

Side effect	Drug reported side effects*			Total
	Timolol	Betaxolol	Carteolol	
Finger nail thickening	0	1	1	2
Libido loss	1	0	0	1
Hay fever	0	1	0	1
Travel sickness	0	0	1	1
Nausea, sweating	1	0	1	2
Cramp	0	2	1	3
Hay fever acquired	2	0	1	3
Skin irritation/rash	0	0	2	2
Arrhythmia/dizziness	3	3	1	7
Lassitude	1	2	1	4
Blurred VA/visual disturbance†	3	5	0	8
Drops sting	1	11	0	12
Epiphora	0	1	0	1
Fall in pulse rate	4	1	2	7
Headache	2	3	0	5
Asthma onset/wheeziness/breathlessness	4	2	6	12
Loss of sense of taste	0	1	0	1
Scleritis†	0	2	0	2
Cold hand and feet, circulatory problems	1	0	0	1
Facial pain	0	1	0	1
Total	28	41	20	89

*Could be more than one per patient. †Eyes.

counted as two events whereas they are not truly independent. As a result, a comparison of the curves using a standard statistical test may overestimate the significance of any difference.¹⁰ The curves in both types of analysis were compared using the log rank test.

Differences in percentage or numbers in Tables 1–3 were tested in 2×2 tables by χ^2 with Yates's correction or by Fisher's exact test when numbers in each cell were less than five. Differences between mean values were not considered to be significant if the difference was less than 1.96 its standard error.

VISUAL FIELDS

Changes in the visual field were analysed by two methods:

- (1) Changes in MD or CPSD on the Humphrey visual field as judged by two consistent consecutive readings and at successive visits.
- (2) Changes in linear progression analysis (PROGRESSOR visual field analysis system).

The results of the two first field tests were ignored to reduce errors induced through learning effects. If the third visual field was unreliable this reading was ignored or the patient was excluded from the trial.

Discussion

The loss of vision in open angle glaucoma is the result of a loss of retinal ganglion cells and their axons which has the effect of causing defects in the field of vision. The exact reason for the ganglion cell loss is at present unclear but the relative hypoxia induced by a chronic reduction of the choroidal and retinal circulation, particularly at the optic disc, together with a raised IOP, are the predominant abnormalities in all types of open angle glaucoma. In some patients vascular changes are paramount whereas in others the elevation of the IOP is apparently the major cause of the visual field loss.^{11–13} This has led to the concept of pressure related glaucoma and pressure unrelated glaucoma.¹⁴

Reduction of the IOP, whether by medical or surgical means, to a target level determined for each individual patient helps to preserve the visual field in most of those with hypertensive and normal tension open angle glaucoma.^{15–17} The exact effect of reduction of the IOP on the progression or regression of the visual field is still to be determined.^{18–23} However, prospective studies of various forms of therapy indicate that in all types of open angle glaucoma the greater the lowering of IOP the longer the visual field is preserved.^{24–28} Topically applied β blocking agents have been used to reduce the intra-ocular pressure for about 20 years. They have proved to be highly effective in IOP reduction and, provided there are no contraindications to their use, are the usual initial treatment in the management of hypertensive primary open angle glaucoma. However, there are apparent differences in the efficacy, side effects and also, possibly, on the ability to protect the visual fields from damage of the various β blocking agents. This depends on whether the agent is a non-selective β_1 and β_2 antagonist such as timolol, whether it had intrinsic sympathomimetic activity (ISA) such as carteolol, or whether it was a β_1 selective antagonist such as betaxolol. The trial was designed to show whether any clinically detectable differences could be found between the different types of β blockers after a long period of follow up.

This investigation required sufficient numbers of patients to produce a statistically clear cut result as all the previous trials had been with small numbers and over very short periods.^{4–6}

Apart from a small number of patients who had very severe glaucoma at presentation and who had an immediate trabeculectomy operation, all patients who presented to the glaucoma clinic were assessed for the treatment trial. One hundred and fifty three patients (280 eyes) were eventually selected. These patients were followed by one observer under strict conditions for a minimum of 2 years and a

maximum of 7 years. As with all trials of medication in which the drugs being investigated are not completely effective in achieving the required effect, there were a significant number of withdrawals from the trial. Even though the number of eyes entered into the trial was large, only 35% (99 eyes) were still being treated by the initially allocated single β blocker at the end of the follow up period (Fig 4); 76 eyes had to be withdrawn because of failure to control the IOP. The majority of these patients were withdrawn within 1 year of starting medication (Fig 3). They were either given additional medication or treated by trabeculectomy; 53 of these patients have since been treated with trabeculectomy.

It has been reported previously that the reduction in IOP between timolol and carteolol was similar but that betaxolol had less IOP lowering effect than timolol in follow up periods of 3–6 months.⁴ This investigation confirms that the fall of IOP between timolol and carteolol was similar and the same as that reported in previous trials.⁵ In those patients who were able to continue on betaxolol therapy the maximum IOP lowering effect was not achieved for up to 12 months. More patients using betaxolol were withdrawn early either because there was little or no fall in the IOP or because the target IOP had not been achieved. This effect with time is difficult to explain but careful examination of the results revealed no evidence that those given betaxolol initially differed in any way from those given other medication and, specifically did not have “worse” glaucoma either in terms of the height of the IOP or of the severity of visual field loss. Apart from a failure to reduce the IOP to the level required for that particular patient, the most common medical reason for withdrawal of a patient from the trial was breathlessness (Tables 3 and 4). No one had been admitted to the trial if they had a history of asthma, chronic bronchitis, airways disease, or persistent breathlessness. This meant that the onset of breathlessness was important and caused by systemic absorption of the medication.

The groups were comparable in terms of age, sex, presenting IOP, degree of field loss, blood pressure, pulse rate, visual acuity, and the presence of cataracts (Tables 1 and 2). Patients' compliance with medication was similar for each of the drugs and tolerance of the regime was good in each of the groups. As has been found in other studies stinging and uncomfortable eyes were more commonly reported with betaxolol than with the other two drugs (Table 4).

A family history of confirmed glaucoma was present in 31% of those on timolol, 39% of those on betaxolol, and 52% of those on carteolol (41% of all the patients studied).

The main purpose of this study was to determine whether the visual field could be protected by substituting a drug with ISA activity (carteolol) or a selective β blocker (betaxolol) for the non-selective β blocker, timolol. This was to be achieved by examining a large number of patients who were to be examined under strictly controlled conditions

by the same observer with a long period of follow up.

The visual field was maintained, and to a certain extent improved, with all three medications although there was no change detectable in the CPSD throughout the follow up period. After 2 years of treatment there is a suggestion that the mean deviation had returned closer to the normal with those remaining on betaxolol than the other two medications. The criteria for withdrawal were the same in all three groups. The visual field analysis was not skewed by the early withdrawal of many of those on betaxolol because the visual field was found to deteriorate early in spite of good control of IOP in patients on betaxolol and carteolol but not in those on timolol (Table 3). In addition there were also more in the betaxolol group than in either of the other two groups who failed to achieve any fall in IOP or had an initial fall and a return to the previous level (Table 3). The apparent difference in MD (Fig 2) (confirmed by PROGRESSOR analysis)⁹ later in the trial did not reach statistical significance. We are therefore unable to confirm or refute the observation that there is an apparent dissociation between the pressure lowering effects of the β blocker²⁹ and the protection of the visual field noted by Drance³⁰ and Kaiser *et al.*³¹

All the β blocking agents tested were effective in reducing the IOP in new patients with open angle glaucoma of moderate severity. This trial shows that they do not necessarily act in the same way on individual patients and that they do have a significant number of side effects. Furthermore, it can be expected that almost half the patients started on a β blocker will need other medication during the succeeding 8 years. As most failures of treatment occur in the first year it is most important that patients are monitored carefully and frequently after starting medication.

We would like to thank Professor Fitzke for his time and trouble in performing the PROGRESSOR analysis.

We would like to acknowledge financial assistance from Ciba UK and Alcon UK during the conduct of this trial.

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