Effects of glaucoma medications on the cardiorespiratory and intraocular pressure status of newly diagnosed glaucoma patients

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Abstract

***Aims*—To evaluate the short term cardiovascular, respiratory, and intraocular pressure (IOP) effects of four glaucoma medications in newly diagnosed glaucoma patients.**

***Methods*—141 newly diagnosed glaucoma patients were recruited and underwent a full ocular, cardiovascular, and respiratory examination, including an electrocardiogram (ECG) and spirometry. They were prescribed one of four topical glaucoma medications and reviewed 3 months later. One eye of each patient was randomly chosen for analysis, performed using analysis of variance and the χ^2 test.**

***Results*—Latanoprost had the greatest mean IOP lowering effect in both the primary open angle glaucoma (POAG) ($p = 0.005$) and the "presumed" normal tension glaucoma (NTG) groups ($p = 0.33$), reducing the IOP by 8.9 mm Hg and 4.1 mm Hg respectively. Timolol was associated with lowered pulse rates and reductions in the spirometry measurements. 41% of patients using brimonidine complained of systemic side effects and over 55% of patients using betaxolol complained of ocular irritation. 28% of patients required an alteration in their glaucoma management.**

***Conclusions*—Latanoprost appears to be a useful primary treatment for glaucoma patients, in view of superior IOP control and a low incidence of local and systemic side effects. Timolol causes a reduction in measurements of respiratory function, a concern in view of the potential subclinical reversible airways disease in the elderly glaucoma population. Brimonidine is associated with substantial, unpredictable systemic side effects and betaxolol causes ocular irritation and weak IOP control. Spirometry is advised in all patients receiving topical β blocker therapy to control their glaucoma.**

(*Br J Ophthalmol* 2000;**84**:710–713)

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Accepted for publication
24 February 2000

Glaucoma is a common disease within the elderly population, affecting over 5% of those older than 75 years.[1] The current management of these patients, whether the open angle (POAG) or the normal tension (NTG) form, is to lower the intraocular pressure (IOP). The most frequently used medical treatment is a topical non-selective β blocker, such as timolol. However, a sufficient amount of this agent can be absorbed through the nasopharyngeal mucosa into the systemic circulation,[2] thereby potentially causing bradycardia and respiratory impairment. These changes, in particular the bronchospasm, may be of clinical significance in the elderly,[3 4] who commonly have undiagnosed reversible airway obstruction.[5 6]

In a previous retrospective audit of the practice within a district general ophthalmology department, a number of otherwise healthy patients being prescribed topical β blockers for their glaucoma were documented to be reporting breathlessness on initiating this treatment. Furthermore, some were being diagnosed with acute cardiovascular or respiratory impairment on admission to the accident and emergency department. As a consequence of this audit's findings, it was recommended that an electrocardiogram (ECG) and spirometry should be performed on all new glaucoma patients who were about to start topical β blocker therapy, thereby identifying previously undiagnosed cardiovascular or respiratory illness.

More recently, several new topical glaucoma medications have become available including the α_2 agonist brimonidine (Alphagan, Allergan) and the prostaglandin analogue latanoprost (Xalatan, Pharmacia and Upjohn). These agents allow the ophthalmologist to prescribe alternative first line topical medications to the traditional β blocker to their newly diagnosed glaucoma patients. In an attempt to clarify and consolidate current clinical practice, this prospective clinical interventional study was undertaken to evaluate the short term effects of four topical glaucoma medications on the respiratory and cardiovascular status of newly diagnosed glaucoma patients, as well as the control of their IOP.

Materials and methods

In this prospective 12 month study, newly diagnosed POAG or "presumed" NTG patients were immediately recruited from the eye outpatient department at Torbay Hospital. Patients were given an ocular, cardiovascular, and respiratory examination performed by one examiner (AW), after which they were prescribed one of four glaucoma medications. Following advice from the local ethics committee, a placebo control group was not recruited. The patients were subsequently reviewed 3 months later, before returning to their original glaucoma clinics for the future management of their glaucoma.

In the ocular examination, a mean of three IOP readings were obtained for each eye using Goldmann applanation tonometry. The

Table 1 Mean (SD) values for spirometry before topical medication

	PF (l/min) Mean (SD)	*FEV_1 (litres) Mean (SD)*	*FVC (litres) Mean (SD)*	*FEV_1/FVC (%) Mean (SD)*
Betaxolol (n = 34)	277 (117)	1.82 (0.71)	2.38 (0.97)	77 (11)
Brimonidine (n = 34)	315 (121)	2.04 (0.71)	2.76 (0.96)	74 (10)
Latanoprost (n = 33)	297 (133)	1.98 (0.82)	2.69 (1.04)	73 (13)
Timolol (n = 33)	355 (132)	2.26 (0.78)	2.80 (0.88)	81 (9)

Table 2 Mean (SD) values for the IOP before and during treatment

	Pretreatment IOP Mean (SD)	*IOP on treatment Mean (SD)*	*Change in IOP Mean (SD)*
POAG eyes:			
Betaxolol (n = 19)	24.1 (2.5)	18.5 (4.0)	5.6 (4.2)
Brimonidine (n = 17)	23.6 (1.3)	18.0 (2.4)	5.6 (2.4)
Latanoprost (n = 18)	25.6 (3.2)	16.7 (3.0)	8.9 (2.6)
Timolol (n = 18	25.2 (3.6)	17.4 (3.4)	7.8 (3.2)
NTG eyes:			
Betaxolol (n = 15)	17.3 (1.7)	14.5 (2.0)	2.8 (2.3)
Brimonidine (n = 17)	17.2 (2.1)	13.4 (2.8)	3.8 (2.6)
Latanoprost (n = 15)	16.6 (2.3)	12.5 (2.5)	4.1 (2.6)
Timolol (n = 15)	17.7 (2.4)	15.0 (2.6)	2.7 (2.8)

Table 3 Systemic side effects attributed to the topical medication

	Short of breath	*Headache*	*Dizzy*	*Drowsy*	*Low mood*	*No of patients*
Betaxolol (n = 34)	1	2	0	2	0	5
Brimonidine (n = 34)	5	3	4	7	1	14
Latanoprost (n = 33)	0	1	0	0	0	1
Timolol (n = 33)	5	1	2	3	1	8

diagnosis of POAG was based upon two sets of IOP readings over 21 mm Hg on separate occasions, along with the presence of open angles, pathologically cupped optic discs, and the presence of glaucomatous visual field defects. The diagnosis of "presumed" NTG was based upon the same criteria as above, with the exception that there were two sets of IOP readings of 21 mm Hg or less on separate occasions taken at different times of the day. This was considered to be a practical and ethical approach to the diagnosis and subsequent management of this condition, although the presumed reflects an acceptance that disease progression is required to distinguish this optic neuropathy from an isolated ischaemic insult to the optic nerve head.[7]

In the systemic examination, the resting pulse and blood pressure (BP) (Korotkoff phase V) were measured, along with an auscultation of the chest. The patients all underwent a 12 lead ECG recording and had spirometry using the Escort pocket size spirometer (Vitalograph Ltd, Buckingham) under the instruction of a staff nurse (JS) trained in performing this investigation. The best of three attempts for peak flow (PF), forced expiratory volume in one second (FEV_1), and forced vital capacity (FVC) were documented.

The patients were prescribed one of the following to both eyes: betaxolol (in suspension form) 0.25% (Betoptic, Alcon); brimonidine 0.2% (Alphagan); latanoprost 0.005% (Xalatan) or timolol 0.5% (Timoptol, MSD). Latanoprost was prescribed on a once a day regimen, while the others were a twice a day regimen. The choice of medication was allocated in a random fashion, assuming there was no contraindication to the use of the chosen treatment. The patients received the medication in an unmasked fashion and were informed of the accompanying manufacturers' leaflet outlining the potential side effects associated with their treatment.

As all newly diagnosed glaucoma patients within the 12 month period were recruited into this study, any patients with known or newly detected chronic obstructive pulmonary disease (COPD) were prescribed brimonidine or latanoprost, while those with significant congestive cardiac failure (CCF) were prescribed latanoprost. This was a decision based upon the recommendations from the original retrospective audit performed within the department, advising cautious use of topical β blockers in patients with substantial CCF. Any patient suffering from ischaemic heart disease (IHD), previous myocardial infarction (MI), or systemic hypertension was prescribed any of the four topical medications.

The patients were reassessed 3 months later by the same examiner (AW), who was blind to their specific treatment. A documented list of side effects covering all of the prescribed medications had been prepared and all patients were directly questioned about any ocular or systemic side effects experienced with their particular topical medication. A repeat ocular and systemic examination were performed including spirometry. This was supervised by the same staff nurse (JS) who was also blind to their medication. The patients' treatment was modified if there were significant side effects or inadequate IOP control.

The analysis of the data has been performed by randomly choosing one eye from each patient who completed the two examinations. The analysis of variance (ANOVA) determines any differences between measurement values of the treatment groups, while the χ^2 test evaluates differences in the proportions of observed and expected side effects in the treatment groups.

Results

One hundred and forty one patients were recruited during the 12 month period, of which 137 were reviewed 3 months after their initial visit. One patient was too ill to attend for the second visit and three others "did not attend" their follow up visit. On review, two patients had already had their treatment changed by their own general practitioners, while one patient had decided not to use the medication they had been prescribed at their initial visit. These seven patients were excluded from the evaluation.

Seventy two (54%) of the 134 patients were diagnosed as having POAG; 19 received betaxolol, 17 brimonidine, 18 latanoprost, and 18 timolol. In the NTG patients, 15 received betaxolol, 17 brimonidine, 15 latanoprost, and 15 timolol. The mean ages in years (SD) for the respective therapeutic groups were as follows: betaxolol 77 (8), brimonidine 74 (8), latanoprost 79 (10), and timolol 71 (12) ($p = 0.09$). The mean ages for the four NTG therapeutic groups were very similar at 75 years ($p = 0.99$). Nine POAG patients and six NTG patients had chronic obstructive pulmonary

Table 4 Ocular side effects attributed to the topical medication

	Burning	*Stinging*	*Itching*	*Blurred vision*	*Tearing*	*No of patients*
Betaxolol (n = 34)	7	12	1	2	2	19
Brimonidine (n = 34)	5	4	3	3	4	13
Latanoprost (n = 33)	1	4	3	3	1	9
Timolol (n = 33)	6	11	3	2	0	16

disease (COPD), while 14 patients had substantial CCF.

At the initial examination, 17 patients (13%) had ECG evidence of first degree heart block, seven were prescribed latanoprost, six with brimonidine, and four with betaxolol. One patient had previously undiagnosed second degree heart block and was immediately referred to the cardiology department for advice and management of their heart condition. Eight patients were found to have a respiratory wheeze, four were prescribed brimonidine and the other four latanoprost.

The mean values for the spirometry measurements before treatment for the whole patient group are given in Table 1. The mean PF, FEV_1, and FVC values are similar to those of previous studies[3 8 9] assessing a similar cohort of elderly glaucoma patients. The patients who were allocated timolol had better PF ($p = 0.08$) and a significantly greater FEV_1/FVC value ($p = 0.01$) before topical therapy. The mean visual acuities for the therapeutic groups were very compatible at 6/9 (Snellen chart) and there was no evidence of any uveitis or cystoid macular oedema. The pretreatment mean IOPs of the four therapeutic groups for the POAG eyes were similar ($p = 0.13$), as were those for the NTG eyes ($p = 0.59$) (see Table 2).

At the 3 month review, several systemic side effects were reported by the patients as a direct consequence of using the topical medications. Fourteen patients on brimonidine (41%) reported some form of systemic side effect ($p < 0.005$) (see Table 3), seven noticing drowsiness ($p < 0.05$). Five patients on timolol and five on brimonidine became aware of increased breathlessness on exertion, compared with one patient on betaxolol and no patients on latanoprost ($p < 0.05$). Nineteen patients on betaxolol (56%) and 16 on timolol complained of ocular problems, in particular stinging ($p < 0.05$) (see Table 4).

Table 5 Difference in cardiovascular factors while using topical medication

	Change in pulse rate (beats/min) Mean (SD)	*Change in systolic BP (mm Hg) Mean (SD)*	*Change in diastolic BP (mm Hg) Mean (SD)*
Betaxolol (n = 34)	−1.7 (6.7)	−4.3 (18)	−0.7 (8)
Brimonidine (n = 34)	+0.0 (4.6)	−2.8 (20)	+0.0 (9)
Latanoprost (n = 33)	−1.0 (8.8)	+2.4 (20)	−3.8 (10)
Timolol (n = 33)	−3.4 (7.0)	+1.4 (19)	+1.5 (9)

Table 6 Difference in spirometry measurements while using topical medication

	Change in PF (l/min) Mean (SD)	*Change in FEV_1 (litres) Mean (SD)*	*Change in FVC (litres) Mean (SD)*	*Change in FEV_1/FVC (%) Mean (SD)*
Betaxolol (n = 34)	−10.6 (67)	0.08 (0.40)	0.10 (0.56)	−0.14 (9.2)
Brimonidine (n = 34)	2.4 (96)	0.01 (0.39)	0.30 (0.64)	0.79 (7.7)
Latanoprost (n = 33)	1.4 (67)	0.01 (0.16)	0.03 (0.42)	0.03 (9.8)
Timolol (n = 33)	−26.2 (82)	−0.08 (0.34)	−0.02 (0.50)	−2.45 (8.7)

On the repeat systemic examination, the pulse rates were unchanged for three of the four groups (see Table 5), while those using timolol experienced a mean reduction of three beats per minute in their pulse rate ($p = 0.23$). The differences in the spirometry measurements during treatment are illustrated in Table 6. There was a mean PF reduction of 10.6 l/min (4% of the original value) for those on betaxolol and 26.2 l/min (7% of the original value) for those on timolol. The patients on timolol had a mean 0.08 litre reduction in FEV_1 (3% of the original value) ($p = 0.28$) with a subsequent 2.5% reduction in the mean FEV_1/FVC ratio ($p = 0.47$). Five patients using timolol demonstrated a 15% or more reduction in PF combined with a 15% or more reduction in FEV_1, only one of whom reported an increase in shortness of breath.

The mean IOP values on treatment for the two glaucoma groups are illustrated in Table 2. Latanoprost produced the greatest IOP lowering effect with mean reduction values of 8.9 mm Hg for the POAG group ($p = 0.005$) and 4.1 mm Hg for the NTG group ($p = 0.33$). There was no change in the mean visual acuities for the four groups following the use of the treatment and no single patient experienced a loss in visual acuity. Following the use of the medication, three patients on latanoprost, two on betaxolol, and one on brimonidine had a definite increase in conjunctival injection. No eyes demonstrated any uveitis or clinical cystoid macular oedema.

Discussion

This study recruited all newly diagnosed glaucoma patients over a 12 month period, 46% of whom have been diagnosed as "presumed" NTG with a 2:1 female to male ratio, a trend which is becoming more common. In view of ethical considerations, no placebo control group was used. As a consequence, the timolol group is younger, probably reflecting the fact that they are the fittest group from the cardiorespiratory perspective. This may explain the lower pretreatment pulse rate and better respiratory function in this group.

This study has evaluated the short term effects of these agents. Latanoprost was the best IOP lowering agent in both glaucoma groups, causing a mean IOP reduction of 8.9 mm Hg for the POAG patients and 4.1 mm Hg for the NTG patients. Timolol was almost as effective in POAG patients, while brimonidine produced a similar IOP reduction as latanoprost in NTG patients. Betaxolol demonstrated relatively weak IOP lowering properties in both groups.

There was a high level of reporting of systemic and ocular side effects with all of

these topical agents. Although this is probably exaggerated by direct questioning, it does demonstrate the potency of these medications. Forty one per cent of patients on brimonidine experienced significant systemic side effects, most commonly drowsiness, while one quarter of those on timolol experienced systemic side effects, in particular shortness of breath. Betaxolol and timolol were notable for the degree of ocular irritation. As a consequence, 28% of patients required an alteration to their treatment regimen due either to inadequate IOP control or to intolerable side effects.

A major concern of previous studies[3 8–10] has been the adverse effect of topical β blockers on the general health of the elderly glaucomatous population, combined with evidence of "hidden" reversible respiratory airways disease.[8 11] This study confirms these findings in a clinical practice environment, illustrating both previously undiagnosed disease and the potential consequences of using topical β blockers. The pretreatment ECGs identified 17 patients (13%) with previously undiagnosed first degree heart block or bundle branch block and one patient with second degree heart block, the latter being a contraindication to the use of β blockers.

The patients using topical timolol demonstrated systemic β blockade and despite rigorous history taking, clinical examination, and lung function testing, the mean PF values fell in those patients using timolol and betaxolol. Arguably the most robust of spirometric variables, the FEV_1/FVC ratio,[12] was reduced in the timolol group, while five patients on timolol demonstrated a greater than 15% reduction in both their PF and FEV_1. Reversible airways obstruction is a cautionary indication to the use of β blockers and the aforementioned value has been deemed to necessitate a change in medication in previous studies.[9 13] Despite this reduction in respiratory "reserve" (mean PF reduction of 7% of original value), only five patients on timolol reported a noticeable shortness of breath on exertion, of which only one of these demonstrated this on spirometry. This suggests that there may be a degree of subclinical reversible airways disease within this population.

This study provides further evidence that topical timolol, and to a lesser extent betaxolol, can produce respiratory side effects as highlighted by previous papers.[3 6 8–11] In view of the potential severity of these effects,[8 9 13 14] along with the degree of "hidden" reversible airways disease that is present in the elderly population,[4 6 10] it would seem prudent to evaluate any new glaucoma patient who will be using a topical β blocker with spirometry. In agreement with previous advice,[9 15] small low cost, "easy to use" electronic spirometers are available[16] and can be used by suitably trained ophthalmic nurses to document respiratory function before and during treatment.

In conclusion, the evidence from this short term study suggests that latanoprost is a useful primary treatment for both new POAG and "presumed" NTG patients. This is based upon its substantial IOP lowering effects in both of these groups, in conjunction with its relatively "clean" side effect profile. The issues of conjunctival hyperaemia, iris colour change, and cost have not been evaluated. Topical β blockers do reduce the respiratory "reserve" of patients, whilst brimonidine appears to produce substantial and unpredictable systemic side effects in a significant number of patients. Finally, this study reiterates previous work advising the performance of spirometry on patients receiving topical β blockers for the control of their glaucoma.

We would like to thank the consultants of the ophthalmology department at Torbay for allowing us to perform this study.

The authors have no financial or proprietary interest in any of the medications evaluated in this study.

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