Randomised, controlled trial of spirometric changes in elderly people receiving timolol or betaxolol as initial treatment for glaucoma

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Abstract

***Aim*—To investigate respiratory and cardiovascular side effects in elderly people in the first 12 months after commencing topical β antagonists.**

***Methods*—40 patients (mean age 74 years) were recruited to a randomised, masked study. Spirometry, pulse, and blood pressure were recorded before, 1 month, and 12 months after starting topical therapy with either timolol 0.5% twice daily or betaxolol 0.5% twice daily.**

***Results*—After 1 month five of 20 patients allocated timolol and three of 20 given betaxolol had discontinued it for respiratory reasons, not always accompanied by symptoms. There were no significant differences in changes in mean values of spirometry, pulse, or blood pressure between groups. No further changes were made in therapy for respiratory reasons in the following year. One patient suffered a hypotensive stroke within 2 days of starting timolol.**

***Conclusions*—By performing spirometry before starting topical β antagonist therapy and repeating it after 1 month most patients at risk of respiratory impairment can be identified.**

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The treatment goal of chronic simple glaucoma is to lower intraocular pressure (IOP) and the most common form of treatment is medical therapy with β antagonists in the form of eye drops. However, significant systemic delivery of topically applied β antagonist eye drops occurs so that cardiac and respiratory side effects may result.[1] Elderly people form the majority of glaucoma suffers[2] yet most studies have concentrated on young patients. Chronic obstructive airflow limitation is common in old age; additionally, many people develop asthma as adults. Studies have found that much of this adult respiratory disease is unrecognised, untreated,[3 4] and that the elderly are especially vulnerable.[5 6] One study reviewed spirometry in a group of asymptomatic elderly patients, with no history of respiratory disease, who had been receiving non-selective β antagonist eye drops for more than a year.[7] It demonstrated that changing therapy improved lung function tests and that many patients experience clinically significant respiratory impairment when receiving topical β antagonists, despite not complaining of respiratory symptoms. Another study monitored prescriptions in the year after the commencement of topical β antagonists and found that many patients were subsequently given a new or increased prescription of bronchodilators.[8] This may be because elderly people are less likely than the young to notice deteriorating lung function[9] and, as airways disease develops insidiously, the condition remains undiagnosed and unsuspected. Frequently, respiratory impairment worsened by topical β antagonists may be asymptomatic. Or symptoms may not be associated with eye drops. This problem may become a serious one when a second factor, such as a chest infection, further impairs lung function.

The present study aimed to address the questions: can we avoid or identify early respiratory impairment due to topical β antagonists? Do changes in respiratory function develop with prolonged exposure? And is there any spirometric advantage from the prescription of cardioselective preparations? The study recruited apparently fit elderly patients, due to start treatment with β antagonists, to a randomised, double masked study reviewing spirometry performed before treatment, at 1 month, and 1 year.

Methods

After ethics committee approval, consecutive patients attending ophthalmology clinics at St James's University Hospital, Leeds were invited to participate in a study of changes in respiratory function when starting β antagonists. For ethical reasons a placebo control group was not recruited. The study protocol allocated patients to either the non-selective timolol[10] 0.5% twice daily or the relatively cardioselective β antagonist betaxolol[11] 0.5% twice daily to both eyes. Third party randomisation was performed by the pharmacy department using random number tables to allocate successive male and female patients into treatment groups. Double masked methodology with identical bottles for the first month was used. Study inclusion criteria were: over 55 years of age; a diagnosis of chronic simple glaucoma or ocular hypertension and treating ophthalmologist planning to start therapy with topical β antagonists; no evidence of cognitive impairment (defined as a mental test score of less than 8 out of 10[12]); mobile with no more than a single point stick. We excluded patients with a history of airways obstruction (though there were no spirometric exclusion criteria); those receiving bronchodilators or other β blockers; those with clinical evidence of heart failure, a

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Table 1 Numbers changing therapy and reasons at the end of 1 month

	Numbers changing		*Reasons for changing therapy*			
Group	*Total continuing*	*Total changing*	*Impaired spirometry +/− symptom*	*Stinging eyes*	*Cardiovascular side effects*	*Raised IOP*
Betaxolol	13	7	3	4	0	0
Timolol	13	7	5	1	1	0

Table 2 Numbers changing therapy and reasons at the end of 1 year

	Numbers changing		*Reasons for changing therapy*			
Group	*Total continuing*	*Total changing*	*Impaired spirometry +/− symptom*	*Stinging eyes*	*Cardiovascular side effects*	*Raised IOP*
Betaxolol	11*	8†	3	3	0	2
Timolol	13	7	5	1	1	0

*One patient underwent trabeculectomy in one eye because of raised IOP.
†One patient who had changed to timolol because of stinging eyes was lost to follow up.

resting pulse less than 60 beats per minute, or who had had a chest infection within the past 4 weeks; and those unable to self administer eye drops. We aimed to recruit 40 patients. Based on data from published work[7] this study was designed to have 80% power to detect a difference in mean forced expiratory volume in one second (FEV_1) of 0.2 litres at the 5% significance level.

After obtaining informed consent, outcome measures such as spirometry measured by a Micro Plus spirometer calibrated to plus or minus 2% for volume and timing (Micro Medical Ltd, Rochester, Kent)[13]; resting pulse and blood pressure (Korotkoff phase V); and IOP (by Goldmann applanation tonometry) were done. Patients were reviewed after 4 weeks, treatment unmasked, and subsequent therapy decided by their ophthalmologist. Patients were reviewed again after 1 year keeping researchers blind to treatment. On review, or if the patient withdrew from the study, outcome measures and a respiratory symptom inquiry were performed. Patients were asked if their breathing was "better, worse, or the same" and if there were local side effects. Reasons for changing therapy or withdrawal from the study were recorded. Patients demonstrating a greater than 15% change in FEV_1 and peak flow (PF) were deemed to have reversible airways obstruction[14] and β antagonists were discontinued. Because glaucoma therapy is given for many years and respiratory disease may develop gradually we were concerned that no patient with borderline changes in spirometry should continue long term β antagonists after completing the study. We therefore discontinued β antagonists in patients whose FEV_1 fell 10% if their PF had also fallen by more than 10%, they complained of increased breathlessness, or both. Analysis was by the intention to treat principle to address the primary concern of clinical practice.

Results

Twenty patients, eight male, mean age 75 years and mean height 1.66 metres, were allocated initial therapy with timolol. Twenty patients, eight males, mean age 72 years and mean height 1.62 metres were allocated betaxolol. Mean enrolment spirometric values were greater in the timolol than the betaxolol group. This may reflect the greater mean height of the patients in the timolol group. There was a higher enrolment mean FEV_1/FVC (forced vital capacity) ratio of 75% in the timolol group against 70% for the betaxolol group suggesting that the betaxolol group had a higher prevalence of patients with airways obstruction.

OUTCOME OF TIMOLOL GROUP

Of the 20 allocated timolol, 13 were still receiving it after 1 year. At the 1 month review two were changed to betaxolol because of greater than 15% fall in both PF and FEV_1 and with a fall of more than 200 ml in FEV_1. Only one was symptomatic. Three were changed to betaxolol because of a fall greater than 10% in FEV_1 and greater than 15% in PF, two were symptomatic. One was changed to betaxolol because of stinging eyes. One patient, with a history of hypertension controlled with diuretics and angiotensin converting enzyme (ACE) inhibitor, developed a hypotensive stroke and was changed to dipivefrine. Her blood pressure fell from 145/95 mm Hg with a resting pulse of 84 on enrolment, to 80/50 mm Hg and pulse of 66 two days after starting therapy. The blood pressure returned to 150/80 mm Hg on ceasing timolol and returning to previous medication. No further treatment changes were made between the 1 month and 1 year reviews (Tables 1 and 2). Satisfactory IOP control was achieved in all patients with medical therapy.

OUTCOME OF BETAXOLOL GROUP

Of the 20 allocated betaxolol 13 continued unchanged after review at 1 month but only 11 were still using it after 1 year. At 1 month two changed to dipifevrine and one underwent bilateral trabeculectomy because of respiratory symptoms coupled with a greater than 15% fall in PF and a 10–15% fall in FEV_1. Three were changed to timolol and one to pilocarpine because of stinging eyes. After 1 year two more had discontinued betaxolol because of poor IOP control (one of these was using it in one eye only having undergone a trabeculectomy in his other eye for the uncontrolled IOP). The patient changed to pilocarpine underwent bilateral trabeculectomy because of poor IOP control so, in total, three patients underwent bilateral and one a unilateral trabeculectomy because of failure of medical therapy. Of the three changed to timolol at 1 month, at 1 year one was lost to follow up and the others continued timolol and the two changed to dipifevrine continued using it at 1 year (Tables 1 and 2).

The mean values of PF and FEV_1 fell both in the timolol and betaxolol groups on starting therapy but there were no significant differences in mean changes in spirometry between the groups, either at 1 month or 1 year. There was no significant difference in the mean changes in resting pulse and blood pressure between groups. Both groups demonstrated a similar fall in mean IOP. The groups differed in that all patients allocated timolol were

Table 3 Mean values of spirometry, blood, and IOP at 1 month and 1 year

	Treatment group	*Enrolment (SD)*	*1 Month (SD)*	*1 Year (SD)*	*Change from enrolment (95% CI)*	*Significance of difference between groups at 1 year*
Peak flow (l/min)	Timolol	336 (97)	305 (83)	321 (93)	−15.0 (−29.0, −0.9)	p=0.34
	Betaxolol	295 (121)	282 (114)	287 (132)	−6.3 (−16.3, 3.7)	
FEV_1 (litres)	Timolol	2.04 (0.50)	1.92 (0.51)	1.97 (0.51)	−0.07 (−0.12, −0.01)	p=0.29
	Betaxolol	1.68 (0.66)	1.65 (0.63)	1.65 (0.70)	−0.02 (−0.09, 0.05)	
FVC (litres)	Timolol	2.65 (0.73)	2.53 (0.73)	2.49 (0.62)	−0.17 (−0.30, −0.04)	p=0.42
	Betaxolol	2.34 (0.87)	2.24 (0.83)	2.23 (0.99)	−0.09 (−0.21, 0.02)	
FEV_1/FVC (% age)	Timolol	75 (8)	75 (8)	79 (6)	4.2 (1.3, 7.0)	p=0.99
	Betaxolol	70 (12)	72 (11)	74 (13)	4.1 (0.0, 8.2)	
Systolic BP (mm Hg)	Timolol	153 (24)	138 (23)	142 (22)	−10.5 (−23.0, 2.0)	p=0.82
	Betaxolol	141 (22)	135 (23)	134 (19)	−8.7 (−18.1, 0.7)	
Diastolic BP (mm Hg)	Timolol	93 (10)	84 (13)	88 (13)	−5.0 (−10.8, 0.8)	p=0.85
	Betaxolol	88 (14)	82 (11)	83 (12)	−5.8 (−11.8, 0.3)	
Pulse (beats/min)	Timolol	80 (11)	70 (10)	74 (11)	−5.6 (−9.2, −2.0)	p=0.07
	Betaxolol	82 (10)	78 (15)	83 (12)	+0.2 (−4.9, 5.3)	
IOP (mm Hg)	Timolol	25 (4)	19 (3)	19 (3)	−5.7 (−7.8, −3.6)	p=0.96
	Betaxolol	24 (4)	20 (4)	19 (3)	−5.6 (−7.8, −3.5)	

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.

maintained on medical treatment alone whereas four patients allocated betaxolol required a trabeculectomy to control IOP (Table 3).

Discussion

The study confirmed that significant amounts of topically applied eye drops reach the systemic circulation and that serious cardiovascular and/or respiratory side effects often result in elderly people, even if they are screened for cardiac and respiratory disease. Many elderly patients receive drugs for conditions other than glaucoma and the patient who developed a hypotensive stroke illustrates that topical β antagonists may interact with other therapy. All medication should be reviewed before commencing topical treatment and particular caution exercised with patients receiving systemic therapy for heart failure or hypertension, especially if treatment already includes β antagonists.

There were small falls in mean spirometry at both 1 month and 1 year in both groups. The fall was larger (and statistically significant compared with enrolment) in the timolol group. However, there were no significant differences in the mean changes in spirometry between the groups. Several patients developed respiratory impairment, sometimes without symptoms. This was more frequent and of larger magnitude in the timolol group but also occurred among those allocated betaxolol. The study illustrates that though the use of relatively cardioselective preparations reduces the frequency of respiratory side effects, they may still occur in a significant number of patients. That all cases of respiratory impairment and the hypotensive stroke occurred in the first 4 weeks of treatment and no further systemic adverse events occurred in the following year is reassuring. It suggests few patients will develop cardiorespiratory impairment with longer exposure to β antagonists.

Topical β antagonists remain first line medical therapy as they are proved, effective, inexpensive ocular hypotensives, and have few local side effects. Cholinergic and adrenergic alternatives, including brimonidine, may have local side effects. Dorzolamide is expensive, given three times daily as monotherapy, and is less effective at lowering IOP. Though latanoprost is as well tolerated and as potent an ocular hypotensive as timolol it is expensive and there are concerns as to its effects on iris melanocytes.

This study supports the conclusion of previous papers[7 8] that many people suffer unrecognised respiratory impairment when prescribed topical β antagonists. More care is needed to recognise systemic side effects. By performing spirometry before starting β antagonist therapy and repeating it after 1 month most patients developing respiratory impairment will be identified.

Topical β antagonist therapy often continues for many years, systemic therapy changes and patients' cardiorespiratory function is likely to deteriorate with time. Therefore, a patient may develop serious side effects only after many years of treatment with β antagonist eye drops. Small, easy to use, low cost electronic spirometers are available to measure PF, FEV_1, and FVC accurately.[13] Spirometry, resting pulse, and blood pressure could be performed by nursing staff, who already record visual acuity and, in many clinics IOP, before the patient is reviewed by the ophthalmologist. We recommend a policy of warning patients of possible respiratory and cardiovascular side effects, as well as recording spirometry, pulse, and blood pressure before and after starting elderly people on topical β antagonists and it would seem prudent practice to repeat the measurements at each visit. A fall of more than 10% in FEV_1 between clinic attendances, and the development of hypotension and/or bradycardia should caution against continued treatment with a topical β antagonist. Patients' health may change with time and both topical and systemic therapies should be reviewed together and not considered in isolation.

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1 Fraunfelder FT, Meyer SM. Systemic side effects of ophthalmic timolol and their prevention. *J Ocul Pharmacol* 1987;**3**:177–84.
2 Klein BEK, Klein R, Sponsel WE, *et al*. Prevalence of glaucoma: the Beaver dam eye study. *Ophthalmology* 1992; **9**:1499–504.
3 Bodner C, Ross S, Douglas G, *et al*. The prevalence of adult onset wheeze: longitudinal study. *BMJ* 1997;**314**:792–3.

4 Dodge RR, Burrows B. The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. *Am Rev Respir Dis* 1980;**122**:567–75.
5 Renwick DS, Connolly MJ. Prevalence and treatment of chronic airways obstruction in adults over the age of 45. *Thorax* 1996;**51**:164–8.
6 Banerjee DK, Lee GS, Malik SK, Daly S. Underdiagnosis of asthma in the elderly. *Br J Dis Chest* 1987;**81**:23–9.
7 Diggory P, Cassels-Brown A, Vail A, Abbey LA, Hillman JS. Avoiding unsuspected respiratory side-effects of topical timolol by using cardioselective or sympathomimetic agents. *Lancet* 1995;**345**:1604–6.
8 Avorn J, Glynn R, Gurwitz JH, *et al.* Pulmonary effects of beta blockers. *Glaucoma* 1993;**2**:158–65.
9 Connolly MJ, Crowley JJ, Neilson CP, Vestal RE. Reduced subjective awareness of bronchoconstriction provoked be methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. *Thorax* 1992;**47**: 410–3.
10 Zimmermen TJ, Kaufman HE. Timolol. A beta adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977;**95**:601–4.
11 Berrospi AR, Leibowitz HM. Betaxolol. A new beta-adrenergic blocking agent for treatment of glaucoma. *Arch Ophthalmol* 1982;**100**:943–5.
12 Hodkinson HM. Evaluation of a mental test score for assessment of mental impairment in the elderly. *Age Ageing* 1981;**1**:233–8.
13 Chowienczyk J, Lawson CP. A pocket sized device for measuring forced expiratory volume in one second and forced vital capacity. *BMJ* 1982;**285**:15–7.
14 Quanjer PH, Tammeling GH, Cotes JE, *et al*. Lung volumes and forced ventilatory flows. Report of the working party standardization of lung function tests European community for steel and coal. Official statement of the European Respiratory Society. *Eur Respir J* 1993;**6**(suppl 16):5-40.