**Commentary**

**β Blockers and the elderly with glaucoma: are we adding insult to injury?**

Many elderly people tend not to complain in the face of often serious disease but stoically accept 'every tatter in their mortal dress' as the inevitable price of aging. We, their carers, may not listen or question sufficiently.

This is well illustrated by an important recent paper in the *Lancet* which should cause a ripple of concern among all those involved in glaucoma management. Entitled 'Avoiding unsuspected respiratory side-effects of topical timolol...', the authors Diggory and colleagues are to be complimented on bringing to our attention the alarming scale of potential respiratory compromise associated with topical timolol use by the elderly with glaucoma. Spirometric investigations were performed on an elderly glaucomatous population with no history of airways disease whose treatment was changed from a non-selective (timolol) to a relatively cardioselective β antagonist (betaxolol) or a sympathomimetic agent (dipivefrine) in a well designed, randomised, crossover study. More than a quarter of the study population had undiagnosed obstructive airways disease as revealed by improved respiratory function on change of therapy.

Studies in respiratory and geriatric medicine also reveal a similar high level even in untreated subjects. A recent well designed epidemiological study of a large, predominantly white, inner city population in the north of England found a 37% prevalence of airways obstruction in the over 65 year age group; the majority of these (86%) had lability such that function could be expected to deteriorate with β antagonist therapy. The scale of β blocker use is enormous. Graft *et al* report that 1-4% of patients in all ages were prescribed oral or topical β blockers in a 1 year period, that the frequency of β blocker prescriptions increased with patient age, and 8-9% of asthmatic patients aged 60-69 had received β blockers.

Diggory and colleagues' paper serves to remind us of the perils of long term treatment with topical β blockers, dangerous systemic effects being mediated through nasal mucosal absorption and avoidance of first pass liver clearance. Most ophthalmologists will recall individual patients treated with topical β blockers who experience respiratory and other systemic side effects, but few would have suspected the scale of the problem suggested by these recent studies. Given that ophthalmic β blockers have been in use for almost two decades, the paucity of literature specifically addressing the scale of these side effects in the elderly population is, to say the least, surprising.

While Diggory and colleagues' study is important and well designed with some serious implications for ophthalmic practice, a number of points require comment. Expressing spirometric values as absolute rather than percentage of predicted norms may be acceptable but comparing change on the basis of absolute values is controversial. The astute reader will note that baseline spirometric values before commencement of the study may be somewhat lower than expected for this age group; whether this reflects the impact of long term β2 blockade or whether subjects had pre-existing respiratory disease (which might have precluded use of β blocker therapy?) is unclear and illustrates the need in future studies for adequately controlled, prospective comparative trials from the initiation of treatment. An important consideration, not addressed by the authors, is that reversibility should be assessed with the knowledge of baseline airway function, as there is likely to be greater reversibility in the more obstructed patient. The ratio forced expiratory volume in one second/forced vital capacity (FEV1/FVC) is perhaps the most robust spirometric index of respiratory status and the reader will note that while the p values may be impressive, the raw data in Table 3 show rather modest differences. The small differences in walk distance, while statistically significant, remain close to the expected learning effect anticipated for this group and it is well recognised that walk distance is unrelated to FEV1 in young and elderly subjects.

It will be argued – perhaps with justification – that timolol, as the ocular β blocker in longest and most frequent use, will inevitably have the largest number of adverse effect reports and that alternative β blockers will require a similar degree of scrutiny to justify alleged supremacy. It might also be said that a single study does not justify mandatory change in prescribing habits and that 74% of Diggory *et al*’s population did not show significant improvement in respiratory function when changed to betaxolol or dipivefrine. Of the 21 patients (26%) shown to have reversible airways obstruction, in 13 this was associated with change to a sympathomimetic agent which could have positive impact on respiratory function. Dipivefrine has limited value as first line glaucoma therapy and there is concern that long term use may compromise success of subsequent filtration surgery.

**Implications for current practice**

That non-selective β blockers should not be used in patients with obstructive airways disease is beyond debate. Diggory and colleague's paper adds to a growing awareness that there is a high prevalence of undiagnosed respiratory disease in the elderly population and that great vigilance is required to avoid inappropriate treatment of this group.

Will use of questionnaires prevent this problem? Less than 10% of Spaeth and Birbilis's glaucoma patients admitted adverse drug effects in response to a general question (that is, presence or absence?) however, this increased to over 30% when they were asked specific questions about common side effects. However, Spaeth and Birbilis's study was not confined to respiratory adverse reactions and it must be recognised that the use of respiratory function questionnaires is a poor predictor of lung function in old age as elderly subjects have impaired perception of acute bronchoconstriction. The frequency of symptoms in severe asthmatics decreases with age as does the frequency of asthmatic patients consulting their doctor. Although a combination of symptoms, known as the bronchial irritability syndrome (BIS) is highly suggestive of asthma in young patients, this is not the case in the elderly.
Therefore, a more realistic approach to patients should include spirometric evaluation; ideal practice should include peak flow and FEV1/FVC ratios. Adequate follow up must be given to monitor the impact of therapy. Elderly patients should be aware that respiratory tract infection can tip an often delicate balance. A recent review has shown that 17 of 24 cases with serious respiratory side effects associated with timolol had used the drug for 5 or more years before these respiratory symptoms became obvious; no previous history of respiratory disease could be elicited in 14 of these 17 patients. Clearly, long term vigilance must be maintained.

Diggory and colleagues’ paper presents evidence to suggest that the use of relatively selective agents may be a more desirable first line approach for glaucoma in the absence of effective alternatives to β blocker therapy but the data presented, though clearly food for thought, are as yet insufficient to promote this as a mandatory policy. Suggestions that betaxolol may be used in patients with obstructive airways disease should be treated with the utmost caution. The term ‘relatively selective’ should ideally replace ‘selective’ to remind us that betaxolol has significant, dose related, β2 blocking activity and has been associated with significant respiratory impairment.

Non-respiratory issues
Diggory and colleagues’ paper should cause reflection on possible underdiagnosis of other systemic adverse effects in the elderly. Further study is necessary to assess the scale of non-respiratory side effects of β blockers which may have serious cardiovascular side effects such as bradycardia, congestive cardiac failure, arrhythmia, syncope, etc with severe implications for quality of life. Suggestions that betaxolol may not have similar actions need confirmation.

Depression is more common with glaucoma than with other eye pathologies of comparable chronicity (such as diabetic retinopathy) with prevalence ranging from 15% to 80%. How much this relates to therapy is uncertain, but β blockers have a definite propensity to induce depression. Other reported neuropsychiatric effects of β blockers include hallucination, psychosis, confusion, insomnia, and fatigue and suggestions that betaxolol may have fewer central nervous system side effects require further confirmation.

Glynn et al concluded that the greatest single risk factor for falls in elderly patients with glaucoma is use of topical β blockers. (One year after a hip fracture one third of the elderly are non-ambulatory; one third are dead.)

One study revealing the negative effect of some ocular β blockers on serum lipid profiles concluded that such treatment translates into increased risk of myocardial infarction of up to 17%. Other areas of concern with ocular β blocker therapy will include diabetes masking, impotence, and the polypharmacy typical of old age with its potential for overlooking serious drug interactions such as augmentation of cardiac depressant drugs, etc.

Visual function issues
We have heard much in recent years of the link between vasospasm and some glaucomas; we must remember that we can also create vasospasm by blocking β2 receptors. Raynaud’s syndrome has been reported with the installation of timolol. It is possible that β blockers may exacerbate some glaucomas through vasoconstriction of optic nerve head. Various reports suggest that non-selective β blocking agents may have a deleterious effect on choroidal blood flow, but further work is necessary both to confirm this and to explore its significance in terms of glaucoma.

Studies utilising radioligand techniques imply that retinal vascular binding sites for vasoactive drugs are of β2 subtype; a comparison of five β blocking agents suggests that betaxolol had least receptor affinity and possibly less disturbance of vasoregulation. However, this is a single study and does not provide evidence for practical benefit in terms of long term visual field preservation. Emerging technology to measure accurately optic nerve head blood flow should enable future clarification of these issues in the clinical arena.

Every therapeutic intervention for glaucoma has some risk of adverse effect. More depressingly, the long term benefit of medical therapy, in terms of maintenance of visual fields, is less certain. In a well designed 6 year prospective study the Vancouver Group found no difference between treatment (timolol) and nontreatment of ocular hypertensions in terms of the development of glaucomatous field defects. We await a study of similar rigour for betaxolol.

Betaxolol may be slightly less effective than non-selective β blockers as an ocular hypotensive but some reports suggest better visual field preservation with betaxolol; however, functional differences and sample sizes in these ongoing studies are modest and the evidence, as yet, is unconvincing on close scrutiny.

Comment
The Diggory study should provoke considerable reflection on our prescribing habits. However, despite a veritable ‘Niagara’ of publications, many uncertainties remain on the relative merits of individual β blockers. Why is this so? Many published comparative drug studies have been short term trials on selected patients in relatively good general health; serious repercussions for the vulnerable older patient can clearly be overlooked. As many studies have lacked sufficient duration and statistical power to detect unequivocal differences between drugs there is an urgent need for further rigorously controlled, prospective, randomised studies to cover all potential adverse effects. Such studies should not be confined merely to respiratory function but should include peripheral vascular, cardiac, neurological, and neuropsychiatric effects in addition to visual field survival, impact on optic nerve head microrcirculation, and relevance to health economics. The necessary answers are attainable and overdue. Significant investment in this research by the major granting bodies is highly desirable. If such a study confirms the superiority of relatively selective β blockers in terms of safety (without sacrifice of efficacy) then such agents should have mandatory ‘preferred practice’ status whenever ocular β blocker therapy is indicated.

However, we may have to accept that long term therapy with β blockers is inappropriate for a significant proportion of elderly people. The term ‘dying with sight’ was coined some years ago by Roger Hitchings to remind us to take life expectancy into account and to avoid excessive intervention when forming a management plan for individual glaucoma patients; in the light of Diggory and colleagues’ paper this phrase has a disturbing resonance!

While unease regarding medication will provide more grist to the primary surgery mill, patients and those who care for them need to be fully informed of the relative risks and benefits of all medical, surgical, and laser therapies for glaucoma and that management which allows gradual field loss may be a legitimate individual patient choice in some cases.
Ophthalmology in the UK is dominated by the quick, clean allure of the cataract episode. Glaucoma does not fit this management model and has long been underfunded. There is an urgent need for provision of a more holistic approach to management of glaucoma patients with careful attention to changing status in terms not only of visual function but of general health, need for systemic medication, quality of life issues, adverse drug reactions, etc.

We will shortly witness the introduction of new alternatives to our present therapeutic armoury and this paper will remind us to maintain a cold, judicious eye on each new 'wonder drug'.

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EAMONN O‘DONOGHUE

Lister Centre,
Manchester Royal Eye Hospital,
Oxford Road, Manchester M13 9WH

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