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# Beta-adrenergic antagonists in the treatment of glaucoma

*S.A. GANDOLFI, L. CIMINO*

Glaucoma Research and Care Center, University of Parma, Parma - Italy

PURPOSE. *Beta-blockers have been used since the late 1970's as 'first-choice' in the treatment for glaucoma. Since the introduction of new molecules in clinical routine, the current role of beta-blockers in glaucoma therapy has been rediscussed. In particular, concerns have been raised regarding their actual safety profile.*
METHODS. *This review will focus on the latest advances on the efficacy and safety profiles of non-selective beta-blockers.*
CONCLUSIONS. *The data provided will help to trace a more appropriate role for beta-blockers in glaucoma therapy.* Eur J Ophthalmol 2001; 11 (Suppl 2): S63-S66

KEY WORDS. *Beta-blockers, First choice treatment, Glaucoma, Intraocular pressure, Safety*

## INTRODUCTION

Beta-blockers have been used since the early 1980s for treating patients with glaucoma. In most countries, they are still recommended as the first choice of treatment in glaucoma (European Glaucoma Society guidelines) and can usually be prescribed without any limitations as unrestricted bene-fit from National Health Services. However, the efficacy and safety of long-term therapy with topical beta-blockers has recently been questioned. In particu-lar, concerns have been raised about the actual role of topical beta-blockers in glaucoma therapy.

This review will attempt to gather information to establish if beta-blockers still deserve to be considered as the "first choice" therapy for glaucoma at the dawn of this new millenium.

### The concept of a first choice therapy

The initial choice of a specific drug is generally based upon *"predefined goals of acceptable efficacy and limits of acceptable toxicity"* (1). In a long-term mostly symptom-free disease such as chronic glaucoma, the evaluation of the utility of a drug is not easy. It must be remembered that *"...the physician, the patient and the patient's family may have disparate opinions of the utility of a therapeutic regimen*" (1). In this case, the patients' opinions will be mostly dominated by the perception of having suffered therapy-related side effects (2). Therefore, the drug of first choice in a chronic symptom-free disease, such as glaucoma, has to be the safest one available. In particular, the safety profile of a selected drug must be established according to the ease of detecting drug-related adverse events, as well as the reversibility of the side effects upon discontinuation of the drug. If the drug fails to achieve the desired clinical effect, a more effective (often more toxic) one may be adopted. However, such changes in the treatment schedule are generally associated with the risk of decreased compliance and increased costs (3). Therefore, a first-choice therapy for glaucoma should offer good efficacy and safety profile in order to prevent the need for changes in treatment.

### Efficacy profile of the beta-blockers

Most patients with primary open-angle glaucoma initially respond to beta-blockers, but both short-term

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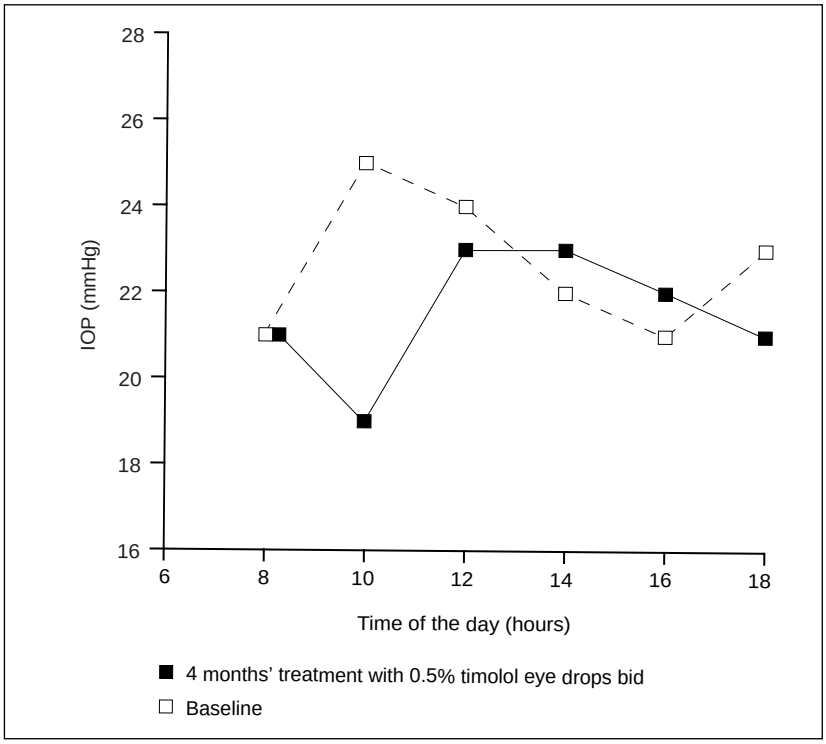


**Fig. 1 -** *Long-term drift: after 4 months of beta-blocker treatment, IOP is reduced by less than 10% compared with baseline.*

escape and long-term drift have been reported (4). Short-term escape refers to an acute partial loss of therapeutic effect on intraocular pressure (IOP) during the first few days of beta-blocker treatment. Other patients show a slow upward trend (long-term drift) in IOP after months of therapy (5). For each year of therapy, the incidence of loss of efficacy has been reported as 10% of patients in several long-term clinical trials (6, 7). This means that only one out of two patients, who are initiated on topical therapy with a non-selective beta-blocker, will show a clinically relevant response to the drug after 5 years.

The development of long-term drift may not be easy to detect. Figure I shows data from a 4-month, crossover study performed on patients affected by ocular hypertension who had never been treated previously. The six readings (one every 2 hours, from 8:00 AM until 6:00 PM) are inclusive of the trough and peak measures. Timolol was administered by the investigator just after the 8:00 AM reading. Assuming that the average of the two highest readings of the diurnal phasing is the most accurate indicator of the IOP-related risk in the individual eye, the patient shows a timolol-induced reduction from 24.5 mmHg to 23 mmHg (less than 10% reduction *vs* baseline). Conversely, if the average of the peak and trough readings is adopted as an indicator for efficacy (as reported in several clinical trials), the patient would show up as a responder to timolol with the IOP being reduced from 24.5 mmHg to 20 mmHg (approximately 20% reduction *vs* baseline).

The data collected in this study (the average of the two highest readings of the diurnal IOP phasing) showed a 20%–25% incidence of non-responders to timolol (i.e. patients showing a <15% IOP decrease over baseline) as early as 4 months after starting treatment. These data, collected by performing a diurnal IOP measurement, are consistent with recently reported studies in which up to 24-hour IOP phasing was adopted (8, 9).

Furthermore, there are studies that show that the effect of beta-blockers on aqueous humor production is negligible during sleep (10, 11). Therefore, even in a treated patient, the IOP will not alter for 6–8 hours each day. It is also well known that the supine position is often associated with a relevant increase in IOP in glaucomatous patients (12). Assuming that most of the time spent in the supine position occurs during sleep, these patients are not likely to be fully protected by beta-blockers. Therefore, based on the above evidence:

- The effect of beta-blockers on IOP is difficult to establish, the physician needs several visits to determine whether the therapy is effective or not in the patient.
- The proportion of patients who show a decrease in their response to beta-blockers (i.e. lose their initial efficacy) over time is clinically relevant (10% incidence for each year of treatment).
- The development of a long-term drift is subtle, occurring early in the course of therapy and may run undetected in the absence of an accurate assessment of the IOP (i.e. proper phasing).
- Beta-blockers cannot guarantee 24-hour control of the IOP, as their effect may be negligible during sleep.

### Safety profile of the beta-blockers

Non-selective topical beta-blockers can affect the cardiovascular, pulmonary and central nervous systems (14). The extent of these systemic side effects may be related to the frequency of administration of the drug rather than to the length of time spent by the drug in the conjunctival sac (before being cleared by the tears into the naso-lacrimal duct) (13).

Cardiovascular effects of topical beta-blockers can lead to a reduction in pulse rate and blood pressure. Both events can be easily detected and, once the therapy is discontinued, reversed (14).

Antagonism of beta-2 receptors in bronchi and bronchioles results in the contraction of smooth muscle. This can cause increased airway resistance, especially in patients with reactive forms of asthma or chronic obstructive pulmonary disease. Respiratory failure has been documented with topical beta-blocker therapy, and these drugs should not be used in patients with severe respiratory disease. Topical timolol therapy may adversely affect respiratory function in elderly patients who do not have a history of known airway disease (15). In a recent randomized, controlled clinical trial with 3-year therapy with topical timolol, it could be shown that the bronchial reactivity in otherwise symptom-free young individuals who had no previous history of airway disease increased after administration of timolol. This increased reactivity proved reversible, upon withdrawal of the drug, in less than 50% of the affected patients only (16).

Thus, pulmonary adverse events, without the occurrence of lung-related symptoms, can develop with the use of topical non-selective beta-blocker therapy in previously healthy subjects. Therefore, beta-blocker–related pulmonary side effects may run undetected until the lung function worsens enough to induce symptoms in the individual patient. Moreover, discontinuation of the therapy, even at a very early stage of the adverse event, does not always restore the lung function to the pre-treatment level. Therefore, based on the above evidence:

- Pulmonary adverse events, induced by long-term treatment with topical beta-blockers, may run undetected in the absence of proper diagnostic evaluation.
- These pulmonary side effects may not be fully reversible in every affected patient upon withdrawal of the therapy.

## CONCLUSIONS

The data discussed in this mini-review suggest that the role of beta-blockers in glaucoma therapy needs to be reconsidered. Beta-blockers can induce clinically undetectable systemic side effects, and their initial efficacy on IOP can decrease with time in a considerable percentage of patients. Moreover, their efficacy (when present) is greatly reduced when the patient is sleeping).

Therefore, when choosing a therapy for the first time for a patient with glaucoma, each individual patient should be monitored thoroughly according to:

- The systemic safety profile of the available drugs.
- The target IOP reduction to be achieved and maintained with time.
- The tolerability and feasibility of the treatment schedule.

Beta-blockers, instead of being considered as "*one-above-the-others",* will then find their place as *"one-among-the-others"*.

Reprint requests to:
Stefano Gandolfi, MD
Istituto di Oftalmologia
Via Gramsci, 14
43100 Parma, Italy
s.gandolfi@rsadvnet.it

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