lar leakage had an increment threshold sensitivity loss similar to that seen in the four patients with IDDM with preproliferative retinopathy, who showed normal macular fluorescein angiography.

In patients with IDDM with or without retinopathy, curves mainly shifted upward with a statistically significant difference, suggesting that the cause was not a change in preretal screening (e.g., yellowing of the lens) but was intrinsic retinal damage, possibly the result of metabolic change.

The probe-flash technique is a sensitive method for assessing changes in visual function as opposed to clinical hue discrimination tests, including the FM 100-hue test. Some patients with IDDM without retinopathy in this study showed minimal abnormality in the hue discrimination tests, although previous studies reported decreased hue discrimination using FM 100-hue test in patients without retinopathy. However, hue discrimination scores do not correlate with the level of early retinopathy. It is difficult to differentiate retinal sensitivity changes from the age-related change of the optic media using hue discrimination tests. However, S-cone sensitivity losses seen in the probe threshold versus flash intensity curves seen in the patients with IDDM cannot be the result of preretal screening. Thus, our findings suggest that patients with IDDM without retinopathy already suffer from functional disturbances from metabolic changes secondary to diabetes.

**Key Words**

insulin-dependent diabetes mellitus, noninsulin-dependent diabetes mellitus, retinopathy, S-cone pathway, sensitivity loss

**References**


**Serial Administration of Adrenergic Antagonist and Agonist (‘Pulsatile Therapy’) Reduces the Incidence of Long-Term Drift to Timolol in Humans**

**Stefano A. Gandolfi and Marco Vecchi**

**Purpose.** To test whether the incidence of long-term drift to timolol can be reduced by a “pulsatile” treatment (6 months timolol–2 months dipivefrin).

**Methods.** In a randomized clinical trial, 100 consecutive subjects with ocular hypertension or high-tension primary open angle glaucoma in at least one eye were randomly assigned to either group A, which was administered timolol 0.5% twice a day (b.i.d.), or to group B, which was administered timolol 0.5% b.i.d. (6 months) alternated with 0.1% dipivefrin b.i.d. (2 months). Diurnal intraocular pressure (IOP) was measured at recruitment, 1 month later during timolol administration (“reference value”), and every 6 months in group A or at the end of each pulse in group B. In bilateral cases, the right eye only was considered for the analysis. Length of follow-up was 54 months. Long-term drift was
The effect of beta blockers on intraocular pressure can vanish with time. This phenomenon occurs in two phases, named by Boger as “short-term escape” and “long-term drift.” The former takes place between the third and fourth weeks of treatment whereas the latter starts more insidiously after intraocular pressure (IOP) has leveled off; in most cases, it becomes detectable after 1 year of treatment with a beta-blocker.

In a previous pilot study, a group of glaucomatous eyes showing long-term drift were scheduled for a 60-day withdrawal of timolol (timolol “holiday”). During this phase, the sensitivity to the beta blocker was somehow restored because reinitiation of timolol at the end of the holiday was followed by a significant decrease in pressure. The IOP decrease was more marked and longer lasting in those eyes exposed during the holiday to the adrenergic agonist dipivefrin. It has been reported that prolonged in vitro exposure to a beta-agonist is paralleled by a decrease in the number and efficacy of beta-receptors in the tested tissue and that a short course of beta-blocker increases the number of beta-receptors in the exposed tissue in vitro. This mechanism has been claimed to explain the occurrence of a rapid loss of sensitivity to timolol (the short-term escape), but thus far no experimental evidence is available to extend this explanation to the later-occurring phenomenon (the long-term drift).2

Our working hypothesis was that by alternating a beta-blocker with a beta-agonist (“pulsatile schedule”), we might decrease the incidence of late-occurring tolerance phenomena (long-term drift) to the beta-blockade. The current randomized clinical trial was designed to test this hypothesis.

METHODS. Patients were recruited from those referred to the Glaucoma Service of our Institute. One hundred consecutive subjects affected by either high-tension primary open angle glaucoma or ocular hypertension in at least one eye, meeting the eligibility criteria and willing to participate, were enrolled. The eligibility criteria are listed in Table 1. Each patient was informed fully of the aim of the study and of the details of the procedure, and informed consent was obtained. The research protocol was prepared according to the tenets of the Declaration of Helsinki.

Diurnal IOP (8 AM to 6 PM; six readings, one reading every 2 hours) was measured by applanation tonometry. The average of the two highest values recorded in the affected eye (or, in bilateral cases, in the right eye) was considered to determine eligibility (“baseline value”). Then two computerized visual field analyses (Octopus, G1; Interzeag, Schlieren, Switzerland) were performed at a 3-day interval to separate those patients with primary glaucoma from those with ocular hypertension. The former field was discarded, and the latter was considered for the study. A field was labeled as pathologic if it showed ≥2 adjacent points of ≥5 dB loss each, ≥1 adjacent point of ≥10 dB each, or difference of ≥5 dB across nasal horizontal meridian at ≥2 adjacent points.

Each eligible subject was assigned randomly to one of the following treatment groups: group A = timolol 0.5% twice a day (b.i.d.); group B = “pulsatile” schedule of timolol 0.5% b.i.d. (6 months)–dipivefrin 0.1% b.i.d. (2 months). Groups were matched for age, sex, IOP, and presence or absence of a glaucomatous field defect in the study eye (Table 2). The IOP (daily curve) was measured again 1 month later, and the value obtained was considered the reference value.

Follow-up visits were performed every 6 months in group A and at the end of each pulse in group B. Diurnal IOP (8 AM to 6 PM, six readings, one reading every 2 hours, average of the two highest values considered for the analysis) and visual field analysis (Octopus, G1; Interzeag) were obtained at each follow-up visit. Patients were instructed not to instill their scheduled eye drops the morning of the visit. At the begin-
TABLE 1. Eligibility Criteria

<table>
<thead>
<tr>
<th>Criterion</th>
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<tbody>
<tr>
<td>IOP &gt; 21 mm Hg in at least one eye (average of the two highest readings during the daily curve)</td>
</tr>
<tr>
<td>No current treatment with systemic beta-blockers or beta-agonists</td>
</tr>
<tr>
<td>No history of chronic obstructive pulmonary disease, diabetes, heart rate, and rhythm disorders</td>
</tr>
<tr>
<td>No previous bulbar surgery</td>
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<tr>
<td>Open angle by gonioscopy</td>
</tr>
<tr>
<td>Absence of pseudoexfoliative deposits and/or pigment deposits on the anterior chamber structures</td>
</tr>
<tr>
<td>No history of dry eye, chronic conjunctivitis, allergic eye disease</td>
</tr>
<tr>
<td>Mean defect (OCTOPUS, G1 program) &lt; 5 dB in the study eye</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure.

The IOP was measured by residents who were unaware of the study protocol. If a fellow eye was to be treated during follow-up, the same schedule was prescribed.

A drift was defined as an IOP increase of at least 5 mm Hg (average of the two highest readings of the daily curve) over the reference value in the study eye while on timolol, followed by a further increase of IOP of no more than 2 mm Hg 15 days after withdrawal of the beta blocker. In bilateral cases, the development of a long-term drift in the fellow eyes was not considered for analysis.

A subject was excluded during follow-up if a ≥5 mm Hg increase of IOP (average of the two highest readings of the daily curve) not caused by long-term drift was observed in the study eye during timolol therapy (i.e., any time in group A and during the timolol pulse in group B), if the study eye showed deterioration of the visual field (i.e., ≥10% worsening of either the mean defect or the corrected loss variance indexes of the Octopus G1 program on two consecutive examinations at a 3-month interval), or if clinically relevant cardiopulmonary side effects developed.

The sample size of this study was adjusted for a minimal expected difference in the rate of the event (i.e., the occurrence of a long-term drift) between the two groups = 25% with a type I error = 0.05 and a power = 95%. Statistical analysis was based on chi-square analysis when comparing proportions and on paired-sample Student’s t-test when comparing means.

RESULTS. Each patient had a decrease in IOP after 1 month of treatment with timolol. The reference value was comparable between the two groups (16.4 ± 1.2 in group A and 15.9 ± 1.7 in group B). Eleven patients (four in group A and seven in group B) showed a IOP increase ≥5 mm Hg in the study eye during follow-up, but the eye was still responsive to timolol (i.e., a 14-day withdrawal of the beta-blocker was followed by a >2 mm Hg increase of IOP). Because this event was outlined as an exclusion criterion (see Methods section), these 11 patients were dropped from the study.

After 54 months of treatment, 50% (25/50) of the patients in group A still responded to timolol compared to 80% (40/50) of the patients in group B (Fig. 1, P < 0.01, chi-square analysis). The percentage has been calculated on the original cohort (i.e., we also counted the 11 dropouts). If the analysis were performed on subjects who actually completed the study, the number of responders would have increased to 55% (25/46) in group A (timolol therapy) and 93% (40/43) in group B (pulsatile therapy). The incidence of long-term drift then would become 45% (21/46) in group A versus 7% (3/43) in group B.

We observed no unilateral drift in bilateral cases. In other words, when present, the tolerance to the beta-blockade developed in both eyes of each affected subject.

In group B (Fig. 2), IOP was always higher during the dipivefrin pulse than on timolol (paired-sample t-test, P < 0.01). However, dipivefrin proved more effective through follow-up; IOP was 21.1 ± 1.2 mm Hg at month 8 (first pulse) and 18.6 ± 0.95 mm Hg at month 48 (last pulse) (paired-sample t-test, P < 0.01).

No significant cardiopulmonary side effects were reported by the study subjects throughout follow-up. Transient redness of the conjunctiva during the dipivefrin pulse often was reported. This phenomenon was annoying mainly in those patients undergoing

Table 2. Study Population

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 11</td>
<td>59 ± 12</td>
</tr>
<tr>
<td>Sex</td>
<td>34 females</td>
<td>30 females</td>
</tr>
<tr>
<td>IOP at recruitment (mm Hg)</td>
<td>26.8 ± 2.5</td>
<td>26.2 ± 1.9</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Primary glaucoma</td>
<td>16</td>
<td>19</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure.
FIGURE 1. Survival curve. The two lines represent the percentage of subjects showing an intraocular pressure (IOP) response to timolol. An eye was considered a responder if the IOP on timolol administration did not increase by 5 mm Hg or more over the reference value, with a ≤2 mm Hg increase 15 days after withdrawal of the beta-blocker. Dashed line = group A (timolol administration twice a day); solid line = group B (pulsatile schedule). The percentage was calculated on the total number of subjects enrolled in the study (see text for details). The difference between group B (80%) and group A (50%) at the end of follow-up was significant, with P < 0.01 (chi-square analysis).

treatment in one eye only. In no case was the treatment schedule reported as unattended by the patients.

DISCUSSION. Data collected in our study show that the efficacy of timolol on IOP is maintained for a longer time if the beta-blocker is pulsed with an adrenergic agonist. After 4 years, approximately one half of the cohort treated with timolol only showed a pressure response to the drug (i.e., an IOP within 5 mm Hg from the reference value). In 1980, Krieglstein7 described an insufficient pressure control in 25% of the eyes after 12.6 months of treatment with timolol. More recently, the Glaucoma Laser Trial8 reported that, after 2 years, only 30% of the subjects initially treated with timolol 0.5% b.i.d. remained controlled. Neither study differentiated whether the pressure increase was caused by a loss of timolol efficacy (i.e., an actual long-term drift) or to progression of the glaucoma. In addition, monitoring of compliance with the treatment regimen, when considered, was based on a subjective report informally obtained from each patient.8 Our study protocol included the administration of the scheduled eye drops by one of us (SAG) at the beginning of each visit. In this way, we were confident that the drugs were applied properly to the study eye at least when IOP (and, consequently, the efficacy of the treatment) was about to be measured.

The efficacy of the pulsatile regimen does not mean that any supposed receptor-mediated mechanism does actually exist. Nevertheless, we would like to stress that dipivefrin, though less potent than timolol,9 apparently becomes more effective through follow-up. Dipivefrin (a pro-drug of epinephrine) interacts with beta adrenoreceptors and triggers the adenylate cyclase that ultimately leads to an increase of cyclic adenosine monophosphate, which, in turn, alters cell shape to facilitate the passage of aqueous through the trabecular meshwork.10,11 It is known that beta-receptors undergo a functional downregulation on prolonged stimulation7 and that a morphologic counterpart of the phenomenon is represented by a surface membrane internalization, with an actual decrease of the number of receptors available on the cell surface.12 Alternating a stimulation with a blockade might allow the number of beta-receptors in the eye to reequilibrate, thereby allowing a better effect on IOP.

No subject was dropped from the study because of worsening of the visual field. Actually, the IOP was sometimes higher than what might have been expected for glaucoma not to progress.15 Sixty-five percent of the study population was composed of subjects with no defects in the visual field at recruitment (i.e., subjects with ocular hypertension). We know from two recently published multicenter clinical trials that fewer than 20% of those with ocular hypertension, if left untreated, will have glaucomatous field defects in 5 years.14,15 Moreover, it has been suggested that the deeper the glaucomatous field defects, the lower must the IOP be to stop progression;16 in our series, the eyes with glaucoma were bearing very subtle visual field defects (see Table 1 and the Methods section). Again, we want to point out that the analysis of stereophotographs of the optic nerve head and a black-and-white photograph of the nerve fiber layer (performed at our Glaucoma Service routinely) disclosed no reproducible and reliable papillary change in the study subjects during follow-up (data not presented).

FIGURE 2. Follow-up. Open circles = the mean intraocular pressure ± SD recorded in those subjects of group B (pulsed schedule) who completed the follow-up. □ = timolol pulse; ■ = dipivefrin pulse; * = recruitment; ** = reference value.
In conclusion, our results demonstrate that alternating beta-blockade with a beta-stimulation (pulsatile therapy) decreases the chances of producing tolerance to timolol in humans. This might be of particular clinical relevance in those patients showing high risk for ocular hypertension, who are considered suitable for a prophylactic reduction of IOP. The possibility that the molecular mechanism underlying the phenomenon might involve changes in the number of receptors deserves further study.

**Key Words**

adrenergic antagonists, beta-blockers, glaucoma medications, glaucoma pharmacology, receptors

**References**