lar leakage had an incremental threshold sensitivity loss similar to that seen in the four patients with IDDM without 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 preretinal 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 preretinal 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 pulse than on timolol (paired-samples 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-samples t-test, P < 0.01).


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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, Sihleregen, 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>Criteria</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>
</tr>
<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.

TABLE 2. Study Population

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

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.

stress that dipivefrin, though less potent than timolol,\(^6\) 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.\(^7\) It is known that beta-receptors undergo a functional downregulation on prolonged stimulation\(^8\) 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.\(^9\) 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.\(^10\) 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.\(^11,12\) Moreover, it has been suggested that the deeper the glaucomatous field defects, the lower must the IOP be to stop progression;\(^13\) in our series, the eyes with glaucoma were bearing very subtle visual field defects (see Table 1 and the Methods section).

The efficacy of the pulsatile regimen does not mean that any supposed receptor-mediated mechanism does actually exist. Nevertheless, we would like to
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