Timolol 0.5%/dorzolamide 2% fixed combination versus timolol 0.5%/pilocarpine 2% fixed combination in primary open-angle glaucoma or ocular hypertensive patients

Jakub J. Kałużny,1 Jerzy Szaflik,2 Krystyna Czechowicz-Janicka,3 Józef Kałużny,1 Alicja Orzalkiewicz,1 Anna Zaleska,2 Małgorzata Krajewska,3 Jeanette A. Stewart,4 Jessica N. Leech4 and William C. Stewart4,5

1Klinika Okulistyki, Bydgoszcz, Poland
2Samodzielny Publiczny Okulistyczny Szpital Kliniczny, Warsaw, Poland
3Centrum Medyczne Kształcenia Podyplomowego, Warsaw, Poland
4Pharmaceutical Research Network, Limited Liability Company, Charleston, South Carolina, USA
5Department of Ophthalmology, University of South Carolina, Columbia, South Carolina, USA

ABSTRACT.

Purpose: To establish the efficacy and safety of timolol maleate/dorzolamide fixed combination (TDFC) versus timolol maleate/pilocarpine fixed combination (TPFC), each given twice daily, in primary open-angle glaucoma or ocular hypertensive patients.

Methods: In this prospective, multicentred, double-masked trial, 37 patients were treated twice daily with timolol for 4 weeks. They were then randomized to one of the treatment medications for 6 weeks, after which they were treated with timolol again for 2 weeks before being placed on the opposite treatment medication for 6 weeks.

Results: A total of 36 patients completed the trial. Their mean baseline intraocular pressure (IOP) was 22.3 ± 3.7 mmHg. Following 6 weeks of treatment, the mean trough (08.00 hours) IOP was 18.0 ± 2.2 mmHg for TDFC and 17.4 ± 2.0 mmHg for TPFC (p = 0.22). The mean diurnal curve IOP was 18.1 ± 2.2 mmHg for TDFC and 16.7 ± 1.9 mmHg for TPFC (p = 0.0007). At the remaining time-points (10.00, 18.00 and 20.00 hours), TPFC IOPs were statistically lower than TDFC IOPs (p < 0.03). There were statistically more unsolicited reports of vision change and ocular pain associated with TPFC (p = 0.04). Six patients were discontinued early from TPFC therapy (17%) versus two from TDFC (6%) (p = 0.13).

Conclusions: This study suggests that TPFC can provide at least a similar efficacious reduction in IOP as TDFC in patients with primary open-angle glaucoma or ocular hypertension.
Introduction

The cornerstone of therapy for patients with primary open-angle glaucoma is the reduction of intraocular pressure (IOP). Recent studies have shown that IOP should be reduced to ≤18 mmHg to prevent longterm glaucomatous damage (Stewart et al. 1993; Mao et al. 1991; AGIS 2000; Stewart et al. 2000a). More than one medication is often required to control IOP in glaucoma patients. Because of the inconvenience and possible confusion caused by multiple bottles for patients using adjunctive therapy, fixed combination products have been introduced over the past several years. Among the first of these products was timolol maleate 0.5%/pilocarpine 2% or 4% (TimPilo™, Merck Inc., Bluebell, Pennsylvania, USA). Later, a timolol maleate 0.5%/dorzolamide 2% fixed combination (Cosopt™, Merck Inc., Bluebell, Pennsylvania, USA) became available.

Several previous studies have compared the fixed combination of timolol maleate/dorzolamide 2% to concomitant timolol maleate 0.5% and pilocarpine 2% given four times daily (Laibovitz et al. 1995; Strahlman et al. 1996a; Sverrisson et al. 1999). In these studies, the trough IOP was equal between groups. However, patients overwhelmingly (ratio 4–7:1) preferred the timolol/dorzolamide fixed combination to the timolol maleate/pilocarpine concomitant therapy because it caused fewer visual changes and less brow ache (Laibovitz et al. 1995; Sverrisson et al. 1999). In contrast, the pilocarpine-based fixed combination is dosed twice daily and might demonstrate fewer adverse events than the two components administered concomitantly. Unfortunately, little information is available comparing the dorzolamide and pilocarpine-based fixed combinations.

The purpose of this trial was to compare the safety and efficacy of the timolol maleate/dorzolamide fixed combination (TDFC) (Cosopt™, Merck Inc., Bluebell, Pennsylvania, USA) and the timolol maleate/pilocarpine fixed combination (TPFC) (Fotil™, Santen Oy, Tampere, Finland), each given twice daily, in patients with primary open-angle glaucoma or ocular hypertension. The pilocarpine-based fixed combination remains an important treatment in many countries because of its efficacy and lower cost.

Material and Methods

Design

This was a prospective, multicentred, randomized, double-masked trial.

Patients

The study was performed in three sites in Poland: two in Warsaw and one in Bydgoszcz. We included patients with the following characteristics: 40 years of age or older; a clinical diagnosis of primary open-angle glaucoma, pigment dispersion glaucoma or ocular hypertension in at least one eye (the study eye); open anterior chamber angles of normal appearance; IOP of 21–34 mmHg in the study eye(s) on timolol maleate, and visual acuity (VA) of 5/50 or better in the study eye(s).

We excluded patients with the following characteristics: any abnormality preventing reliable applanation tonometry or adequate examination of the ocular fundus or anterior chamber; any concurrent infectious/non-infectious conjunctivitis, keratitis or uveitis; any history of allergic hypersensitivity or poor tolerance to any components of the study preparations including sulfa medications; pregnancy or lactation; any severe medical or psychiatric condition; any participation in an investigational trial within 30 days prior to the screening visit for this trial; any intraocular conventional surgery or laser surgery within the previous 2 months in the study eye(s); unacceptable risk of visual field or VA worsening as a possible consequence of participation in the trial; inability to understand the trial procedures; any anticipated change in systemic hypertension during the trial; progressive retinal or optic nerve disease apart from glaucoma; past history of bone marrow depression; contraindications to the use of β-blockers; ocular opacities in which pilocarpine therapy would be unsafe; patients with an untreated retinal hole; prior or current symptoms of a retinal detachment, and high myopia of more than –8 diopters.

Procedures

All patients signed an informed consent document approved by the Institutional Review Board before any procedures were performed. At Visit 1 (day 28), as well as at other visits in this trial, patients underwent Goldmann applanation tonometry, slit-lamp biomicroscopy, Snellen VA testing and adverse event collection. If patients met the inclusion/exclusion criteria they were prescribed timolol maleate 0.5% to be instilled at 08.00 and 20.00 hours. Patients were then asked to return in 4 weeks for Visit 2 (day 0, baseline visit).

At Visit 2, IOP was measured at 08.00 hours before dosing with timolol maleate. If IOP on timolol maleate in at least one eye was 21–34 mmHg, the patient was entered into the trial. In addition, an ocular symptom survey and a pupil diameter measurement were carried out (normal room light using a standard chart). Patients were then dosed and diurnal curve readings were recorded at 10.00, 18.00 and 20.00 hours. Afterwards, patients were given either timolol maleate/dorzolamide 2% (Cosopt™, Merck Inc., Bluebell, Pennsylvania, USA) or timolol maleate/pilocarpine 2% (Fotil™, Santen Oy, Tampere, Finland) fixed combinations, which were prescribed twice daily at 08.00 and 20.00 hours. The study medicine was masked to both the doctor and patient by replacing the label on the medicine bottle and concealing it in an opaque medicine vial. As differences in bottle shapes might have been observed, an unblinded dosing co-ordinator instilled drops during clinic visits.

Visit 3 (week 2) consisted of a safety evaluation. Visit 4 (week 6) represented an efficacy visit, when the pupil diameter measurement, ocular symptom survey and treated diurnal curve were performed again. The study medicine was dosed following the 08.00 hours trough pressure check.

Following the Period 1 efficacy visit, patients were treated again with timolol maleate twice daily for 2 weeks. At Visit 5 (week 8), they were started on the
opposite medication. Visit 6 (week 10) comprised a safety evaluation and Visit 7 (week 14) represented an efficacy visit. All procedures in Period 2 were performed as in Period 1.

Statistics
All data analyses were two-sided; an alpha level of 0.05 was used. The primary efficacy variable was represented by the difference in diurnal IOPs (average of the IOPs taken at the four individual time-points) recorded at Visits 4 and 7. This was analysed by a paired \( t \)-test for intragroup analysis (Book 1978). The standard deviation used to determine the power was 2.8 mmHg (Duff 1987; Mundorf et al. 1998). As 28 patients completed the trial, this study provides at least an 80% power that a 1.5 mmHg difference between groups can be excluded. An average eye, intent-to-treat analysis was used. The secondary efficacy variable, IOPs at individual time-points, was also analysed by a paired \( t \)-test (Book 1978). Safety parameters compared for intragroup analysis included: VA by a Wilcoxon sign rank test, adverse events and solicited symptom query by a McNemar test, and pupil diameter by a paired \( t \)-test (Siegel 1956; Book 1978).

Results
Patients
Of the 37 subjects enrolled in the study, 36 completed the trough IOP in both periods and 28 finished the diurnal curve in both periods. Their average age was 58.0 ± 9.2 years. All patients were white. They included 29 women and seven men. Thirty-three subjects had primary open-angle glaucoma and three had ocular hypertension. One patient was discontinued because of a protocol violation.

Intraocular pressure
At baseline on only timolol maleate twice daily therapy, the mean diurnal IOP was 22.3 ± 3.7 mmHg. The average baseline treated IOP at each time-point and for the diurnal curve is shown in Table 1 and the diurnal pressures for each treatment are demonstrated in Fig. 1.

The timolol maleate/dorzolamide fixed combination showed a mean diurnal pressure of 18.1 ± 2.2 mmHg and a morning trough (08.00 hours) pressure of 18.0 ± 2.2 mmHg. In contrast, the timolol maleate/pilocarpine fixed combination showed a diurnal pressure of 16.7 ± 1.9 mmHg (\( p = 0.0007 \)) and a trough pressure of 17.4 ± 2.0 mmHg (\( p = 0.22 \)). At each time-point in the diurnal curve after trough, at 10.00, 18.00 and 20.00 hours, there was a statistical difference between IOPs in patients treated with TDFC and IOPs in those treated with TPFC. Intraocular pressures for both medicines at each time-point after the diurnal curve showed a significant reduction from baseline.

Safety
Table 2 shows the adverse events noted in this study. There were a significantly greater number of visual complaints associated with TPFC compared with TDFC. One serious adverse event was reported, where a patient treated with the pilocarpine-based fixed combination was hospitalized to stabilize systemic hypertension. This adverse event was not believed to be related to the study medicine.

Discussion
The fixed combination of timolol maleate 0.5% and dorzolamide 2% was first released commercially in 1998. Soon afterwards, various studies found that, compared to timolol maleate alone, this fixed combination further reduced IOP another 1.2–1.3 mmHg at trough and 2.7–2.8 mmHg at peak (2 hours after dosing) (Chineschmidt et al. 1998; Boyle et al. 1999). In the latter study, the combination product was found to reduce IOP at morning trough from an untreated baseline by 7.7 mmHg (27%), compared to 4.6 mmHg for dorzolamide and 6.4 mmHg for timolol maleate alone (20 and 23%, respectively) (Boyle et al. 1999). Further, several studies have

| Table 1. Intraocular pressures, mean ± standard deviation (number of patients). |
|---------------------|----------|----------|----------|
|                     | TDFC     | TPFC     | p-value* |
| Trough had         | 23.4 ± 2.3| (36)     | 18.0 ± 2.2| (36) | 17.4 ± 2.0| (36) | 0.22 |
| + 2 hours          | 22.1 ± 3.4| (28)     | 17.3 ± 2.5| (28) | 15.9 ± 2.2| (28) | 0.03 |
| + 10 hours         | 21.5 ± 4.7| (28)     | 18.0 ± 2.4| (28) | 16.6 ± 2.4| (28) | 0.02 |
| + 12 hours         | 21.8 ± 4.6| (28)     | 18.6 ± 2.4| (28) | 17.0 ± 2.0| (28) | 0.009 |
| Diurnal            | 22.3 ± 3.7| (28)     | 18.1 ± 2.2| (28) | 16.7 ± 1.9| (28) | 0.0007 |
| Baseline: drug trough | 5.4 ± 2.4| (36)     | 6.0 ± 3.0| (36) | 0.13 |
| Baseline: drug + 2 hours | 4.8 ± 2.7| (28)     | 6.2 ± 3.1| (28) | 0.004 |
| Baseline: drug + 10 hours | 3.4 ± 3.8| (28)    | 4.9 ± 4.9| (28) | 0.009 |
| Baseline: drug + 12 hours | 3.2 ± 3.7| (28)     | 4.8 ± 4.6| (28) | 0.0005 |
| Diurnal            | 4.2 ± 2.8| (28)     | 5.6 ± 3.6| (28) | 0.0007 |

* p-values are for comparison between TDFC and TPFC.
TDFC = timolol maleate 0.5%/dorzolamide 2% fixed combination.
TPFC = timolol maleate 0.5%/pilocarpine 2% fixed combination.
indicated that the fixed combination has at least equal, if not improved, efficacy compared to the unfixed treatment of dorzolamide and timolol (Strohmaier et al. 1998; Choudhri et al. 2000).

The timolol maleate/dorzolamide fixed combination has been shown to be effective at other times during the day apart from morning trough. Two studies have demonstrated the fixed combination to be similar in efficacy to latanoprost in the late afternoon (Fechtner et al. 1999; Konstas et al. 2003); the latter study showed the fixed combination to have greater efficacy than latanoprost in the early night time hours.

The timolol maleate/pilocarpine fixed combination product (TimPilo™, Merck Inc., Bluebell, Pennsylvania, USA) was first introduced over a decade ago. Zadok et al. (1994) noted a further reduction of 1.7 mmHg in patients using the 4% pilocarpine-based fixed combination over those using timolol maleate twice daily monotherapy. Puustjarvi & Repo (1992) found that approximately 33% of patients needed to increase medication from the 2% timolol maleate/pilocarpine fixed combination to the 4% concentration in order to control IOP. In these patients, an additional 2.2 mmHg lowering of pressure was observed (Puustjarvi & Repo 1992). Several studies have shown that this pilocarpine-based combination reduces IOP from an untreated baseline by 5.8–9.2 mmHg (19–28%) (Söderström et al. 1989; Usitalo & Palkama 1994; Zadok et al. 1994; Demailly et al. 1995).

The timolol maleate 0.5%/pilocarpine 2% fixed combination made by Santen Oy has been compared to the Merck product (Usitalo & Palkama 1994). This study noted that the Santen product reduced IOP from untreated baseline by 32% and the Merck product reduced it by 27%. The primary differences in the two medications are firstly, that the Santen product has a slightly lower pH which improves stability but which may also increase ocular stinging, and secondly, that it contains hydroxy propyl methyl cellulose (HPMC) to increase viscosity (personal communication, Kari Lehmussaari, Santen Oy, Tampere, Finland). Despite the clinical importance of both the timolol maleate/dorzolamide and the timolol maleate/pilocarpine fixed combinations, little direct data comparing the safety and

---

**Table 2.** Adverse events (two or more events).

<table>
<thead>
<tr>
<th></th>
<th>TDFC</th>
<th>TPFC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular pain</td>
<td>2</td>
<td>8</td>
<td>0.11</td>
</tr>
<tr>
<td>Blurred/dim vision</td>
<td>1</td>
<td>8</td>
<td>0.04</td>
</tr>
<tr>
<td>Irritation</td>
<td>2</td>
<td>6</td>
<td>0.29</td>
</tr>
<tr>
<td>Tearing</td>
<td>2</td>
<td>3</td>
<td>1.00</td>
</tr>
<tr>
<td>Itching</td>
<td>1</td>
<td>3</td>
<td>0.63</td>
</tr>
<tr>
<td>Hyperaemia</td>
<td>5</td>
<td>0</td>
<td>0.07</td>
</tr>
</tbody>
</table>

TDFC = timolol maleate 0.5%/dorzolamide 2% fixed combination.
TPFC = timolol maleate 0.5%/pilocarpine 2% fixed combination.

**Table 3.** Trough Snellen visual acuity (in metres); (n = number of patients).

<table>
<thead>
<tr>
<th>Level</th>
<th>Baseline</th>
<th>TDFC</th>
<th>TPFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>31</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>5.5</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>6.5</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8.75</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Snellen visual acuity level: 5 = 5/5, 6 = 5/6, 5.5 = 5/5.5, 6.5 = 5/6.5, 8.75 = 5/8.75. TDFC = timolol maleate 0.5%/dorzolamide 2% fixed combination.
TPFC = timolol maleate 0.5%/pilocarpine 2% fixed combination.

---

Fig. 1. Mean IOP with timolol maleate twice daily (diamonds), timolol maleate/dorzolamide fixed combination (squares) and the timolol maleate/pilocarpine fixed combination (triangles) at each time-point and for the diurnal curve.
The efficacy of these medications is available.

The purpose of this trial was to compare the efficacy and safety of the timolol maleate/dorzolamide and timolol maleate/pilocarpine fixed combinations in patients with primary open-angle glaucoma or ocular hypertension. Pilocarpine is now seldom used in the USA and Western Europe, due mostly to the high number of associated adverse reactions and its four times a day dosing requirements, both of which are likely to decrease compliance. However, it remains an important product in Eastern Europe and other parts of the world because of its effectiveness and low cost.

This study found that both fixed combination products reduced IOP significantly from baseline for up to 12 hours after morning dosing at each time-point and for the diurnal curve. When both medications were compared, the trough IOP was statistically equal between groups. However, TPFC statistically reduced IOP more than TDFC at 10.00, 18.00 and 20.00 hours. In addition, the diurnal curve (an average of the four IOP readings taken throughout the day) was statistically lower with TPFC.

The difference in efficacy between the two fixed combinations may not be completely explainable. As timolol maleate is a component of both products included in this report, any divergence in efficacy would probably be explained by differences between the dorzolamide and pilocarpine. However, few data are available which directly compare these two products as monotherapy. Separate reports have shown that dorzolamide as a monotherapy agent given three times daily reduces diurnal pressure by 10–22% (Lippa et al. 1992; Wilkerson et al. 1993; Kitazawa et al. 1994). This medication has been demonstrated to reduce peak pressure by 11–23% and trough pressure by 9–22% (Lippa et al. 1992; Wilkerson et al. 1993; Kitazawa et al. 1994; Strahlman et al. 1995, 1996b; Stewart et al. 2000b).

Few clinical trials have been carried out on pilocarpine monotherapy. The 4% concentration given four times daily has been shown, in a small number of patients, to reduce IOP by 10–41% at unspecified times throughout the day by several investigators (Kroll & Newell 1964; Harris & Galin 1971). Pilocarpine has been shown to reduce IOP by 14–22% at peak (Harris & Galin 1970) and by 18% at trough (Drance et al. 1974).

This current study is also instructive because it showed that, when the 2% formulation is added to timolol maleate, it results in a statistical reduction over the daytime diurnal curve up to 12 hours after dosing. Maclure et al. (1989) demonstrated a 24-hour (six time-points) reduction in pressure in eight patients treated with the timolol/pilocarpine 2% fixed combination compared to timolol alone. Traditional thinking has dictated that pilocarpine should be given four times daily in order to maintain a consistent diurnal curve. However, this current study may not be applicable to pilocarpine monotherapy. For example, it has been noted that brimonidine dosed twice daily as monotherapy may not provide sufficient 12-hour daytime reduction of pressure, but when dosed twice daily with timolol maleate, brimonidine may provide a statistical reduction 12 hours after daytime dosing (Konstas et al. 2001; Stewart et al. 2001; Stewart JA, ARVO Abstract: 442, 2002). Consequently, pilocarpine as monotherapy still might require three or four times daily dosing to maintain diurnal control. Further research is required regarding the diurnal control and dosing frequency of pilocarpine monotherapy.

The only significant difference in adverse events between groups was a greater incidence of visual complaints generated by the pilocarpine-based combination. Accordingly, a reduced pupillary diameter was associated with pilocarpine therapy. However, over two-thirds of patients had resolution, by patient survey, of visual symptoms within 2 hours of dosing. Furthermore, no mean difference in VA at trough was observed between treatment groups. The frequency of side-effects caused by pilocarpine in our trial appeared less than that observed in a previous trial, when pilocarpine 2% was given four times daily concomitantly with timolol maleate (Laibovitz et al. 1995). It is possible that the twice daily dosing in our current study reduced the pilocarpine-related side-effects. In contrast, ocular hyperaemia was only noted by patients receiving the dorzolamide-based fixed combination (n = 5), although this was not quite significant (p = 0.07). Hyperaemia has been noted at a low frequency in previous studies evaluating dorzolamide (Clineschmidt et al. 1998; Boyle et al. 1999). Six patients were discontinued early from the timolol maleate/pilocarpine fixed combination (17%) versus two from the timolol maleate/dorzolamide fixed combination (6%).

This study suggests that the timolol maleate/pilocarpine fixed combination can provide at least a similar efficacious reduction in IOP as the timolol maleate/dorzolamide fixed combination in patients with primary open-angle glaucoma or ocular hypertension.

This study did not evaluate the 4% pilocarpine combination, which might alter the efficacy and safety characteristics. In addition, exfoliation patients were not used in this study because they have higher levels of IOP than primary open-angle glaucoma patients and might potentially generate different results with these two fixed combination preparations (Konstas et al. 1997).

Acknowledgement

This study was made possible by an unrestricted grant from Santen Oy, Tampere, Finland.

References


Konstas AGP, Stewart WC, Topouzis F, Tersis I, Holmes KT & Stangos NT (2001): Brimonidine 0.2% given twice or three times daily versus timolol maleate 0.5% in primary open-angle glaucoma. Am J Ophthalmol 131: 729–733.


Maclure GM, Vogel R, Sturm A & Binkowitz B (1989): Effect on the 24-hour diurnal curve of intraocular pressure of a fixed ratio combination of timolol 0.5% and pilocarpine 2% in patients with COAG not controlled on timolol 0.5%. Br J Ophthalmol 73: 827–831.


Mundorf TK, CatE SA, Sine CS, Otero DW, Stewart JA & Stewart WC (1998): The safety and efficacy of switching timolol maleate 0.5% solution to timolol hemihydrate 0.5% solution given twice daily. J Ocular Pharm Therap 14: 129–135.


Stewart WC, Day DG, Stewart JA, Schuur J & Latham KE (2001): The efficacy and safety of latanoprost 0.005% once daily versus brimonidine 0.2% twice daily in open-angle glaucoma or ocular hypertension. Am J Ophthalmol 131: 631–635.


Received on December 20th, 2002. Accepted on April 10th, 2003.

Correspondence:
William C. Stewart MD
Pharmaceutical Research Network LLC
1639 Tatum Street
Charleston
South Carolina 29412-2464
USA
Tel: +1 843 762 6500
Fax: +1 843 762 7444
Email: prnc@bellsouth.net