Additivity of Bimatoprost or Travoprost to Latanoprost in Glaucomatous Monkey Eyes

Donna J. Gagliuso, MD; Rong-Fang Wang, MD; Thomas W. Mittag, PhD; Steven M. Podos, MD

Objective: To compare the ocular hypotensive effect of the commercially available preparations of bimatoprost or travoprost added to latanoprost in monkey eyes with laser-induced unilateral glaucoma.

Methods: Four monkeys with unilateral laser-induced glaucoma were used in each treatment group and received drops in the glaucomatous eye only. Intraocular pressure (IOP) was measured hourly for 6 hours, beginning at 9:30 AM on day 1 (untreated baseline), days 6 and 7 (single-agent therapy), and days 13 and 14 (2-drug combination therapy). On days 2 through 7, 1 drop of the scheduled single agent was given immediately after the 9:30 AM IOP measurement, and on days 8 through 14, the second scheduled drug was given 5 minutes after the first. The following 5 different dosing protocols were studied: latanoprost with bimatoprost added, bimatoprost with latanoprost added, latanoprost with travoprost added, travoprost with latanoprost added, and latanoprost with a second dose of latanoprost added.

Results: There were no statistically significant (P = .95) differences among the mean baseline IOPs in any of the 5 treatment groups. When applied as single agents, latanoprost, bimatoprost, and travoprost all produced significant (P < .05) and equivalent (P = .98) reductions in IOP. The mean ±SEM maximum reduction (P < .05) from baseline IOP was 7.0 ± 0.4 mm Hg (20% reduction) with travoprost alone, 6.5 ± 1.6 mm Hg (18%) with bimatoprost alone, and 7.5 ± 1.0 mm Hg (22%) with latanoprost alone. The mean ±SEM maximum additive reductions in IOP were 3.0 ± 0.6 mm Hg (P < .05) for travoprost added to latanoprost; 2.0 ± 0.4 mm Hg (P < .05) for latanoprost added to travoprost; 4.8 ± 1.3 mm Hg (P < .05) for bimatoprost added to latanoprost; 4.3 ± 0.6 mm Hg (P < .05) for latanoprost added to bimatoprost; and 0.3 ± 0.5 mm Hg (P > .60) for latanoprost added to itself. The combination of bimatoprost and latanoprost produced a greater (P < .05) lowering of IOP at trough and peak than the combination of travoprost and latanoprost.

Conclusions: Latanoprost, bimatoprost, and travoprost used as monotherapy produced significant and equivalent reductions in IOP in glaucomatous monkey eyes. The IOP effects of the commercial concentrations of bimatoprost or travoprost were additive to that of latanoprost, with bimatoprost showing a greater additive response than travoprost.

Clinical Relevance: Because treatment with multiple medications is common among patients with glaucoma, determining which glaucoma medications produce an additive ocular hypotensive response when used in combination has practical implications for clinicians.

Arch Ophthalmol. 2004;122:1342-1347

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Table 1. Comparison of Baseline IOP in the 5 Treatment Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>IOP, Mean ± SEM, mm Hg</th>
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<tbody>
<tr>
<td></td>
<td>0 h</td>
</tr>
<tr>
<td>Latanoprost + bimatoprost</td>
<td>34.0 ± 1.1</td>
</tr>
<tr>
<td>Bimatoprost + latanoprost</td>
<td>32.5 ± 1.8</td>
</tr>
<tr>
<td>Latanoprost + travoprost</td>
<td>33.5 ± 1.8</td>
</tr>
<tr>
<td>Bimatoprost + latanoprost</td>
<td>32.5 ± 2.3</td>
</tr>
<tr>
<td>Latanoprost + latanoprost</td>
<td>32.8 ± 0.6</td>
</tr>
</tbody>
</table>

Abbreviation: IOP, intraocular pressure.
*Second drug indicates additive therapy. Each group consisted of 4 monkeys with laser-induced glaucoma.

RESULTS

The mean baseline IOPs of the 5 treatment groups were statistically (*P*=.95) similar (Table 1). When applied as single agents, latanoprost, bimatoprost, and travoprost all produced significant (*P*<.05) reductions in IOP (Figure 1). The mean maximum reduction (*P*<.05) from baseline IOP was 7.0±0.4 mm Hg (20% reduction) with travoprost alone, 6.5±1.6 mm Hg (18%) with bimatoprost alone, and 7.5±1.0 mm Hg (22%) with latanoprost alone (Table 2). The differences in reduction of IOP from baseline comparing the 3 drugs were not statistically significant (*P*=.98) (Figure 1). There was no statistically significant difference in the mean values of the IOP among the 5 treatment groups at days 6 plus 7 at trough (*P*>.90) or at peak (*P*>.60).

The significant (*P*<.05) mean maximum additional reductions in IOP were 3.0±0.6 mm Hg (10% reduction) when travoprost was added to latanoprost and 2.0±0.4 mm Hg (7%) when latanoprost was added to travoprost (Figure 2). There was no statistically significant difference (*P*>.90) in reduction of IOP when comparing travoprost added to latanoprost or latanoprost added to travoprost (Table 2 and Figure 2). The significant (*P*<.05) maximum additional reductions in IOP were 4.8±1.3 mm Hg (15%) when bimatoprost was added to latanoprost and 4.3±0.6 mm Hg (14%) when latanoprost was added to bimatoprost (Figure 3). There was no statistically significant difference (*P*>.90) in the reduction of IOP when comparing bimatoprost added to latanoprost or latanoprost added to bimatoprost (Table 2 and Figure 3). The maximum additive reduction in IOP, 0.3±0.5 mm Hg, was not significant (*P*>.60) when a second drop of latanoprost was added to latanoprost (Table 2 and Figure 4). The additional reduction in IOP when the second drug was added in the bimatoprost and latanoprost combination was greater (*P*<.05) than that in the latanoprost and travoprost combination, no matter which drug was given first for each drug combination (Table 2).

COMMENT

The results of this study demonstrate that latanoprost, bimatoprost, and travoprost produce significant and equivalent reductions in IOP when used as single agents.
Our finding that the ocular hypotensive effect of bimatoprost or travoprost, administered as a commercial preparation, is additive to that of latanoprost is somewhat unanticipated given that in most studies these 3 compounds have been shown to be agonists at the same prostaglandin-FP receptor.10-15 One study claims a different receptor profile and metabolism for bimatoprost.16 In addition, most studies report that all 3 drugs lower IOP primarily by the same mechanism of increased uveoscleral outflow.17-21 Despite these similarities, differences must exist in their mechanisms of action to account for the additivity that we have shown. Because we have demonstrated equivalent ocular hypotensive efficacy with monotherapy with all 3 commercial compounds, differences in drug distribution within the glaucomatous monkey eye, differences in prodrug metabolism, or a greater receptor affinity or intrinsic activity of bimatoprost or travoprost relative to latanoprost are unlikely to explain our additivity results. However, the drugs added to latanoprost in combination therapy may have an additional and distinct mechanism of action.

Thus, a possible explanation for the additivity of bimatoprost or travoprost to latanoprost is relative differences in their effects on trabecular and uveoscleral outflow. In studies performed in normotensive and ocular hypertensive human eyes, latanoprost was shown to lower IOP by increasing uveoscleral outflow without substantially altering aqueous flow or trabecular outflow facility.17 However, in another study, latanoprost substantially increased tonographically measured outflow facility in humans, in addition to its effect on uveoscleral outflow.18 The effects of travoprost on outflow facility have not been reported in humans, but in a study in normotensive and glaucomatous monkey eyes, travoprost significantly increased uveoscleral outflow in the normotensive eyes.19 An increase in uveoscleral outflow in the ocular hypertensive eyes at the indicated clinical dosage in glaucomatous monkey eyes. This finding appears consistent with those of some clinical studies in humans that have compared the effectiveness of these 3 drugs.1-8 A 3-way comparative study by Parrish and colleagues1 shows that latanoprost, bimatoprost, and travoprost are equivalent in lowering IOP in patients with glaucoma or ocular hypertension. Three other recent studies2-4 comparing bimatoprost or travoprost to latanoprost also demonstrate comparable efficacy when differences in baseline IOP are taken into account.6 In contrast, one study has found bimatoprost to be more effective than latanoprost in lowering IOP. However, as has been discussed elsewhere,2 the reduction in IOP from baseline with latanoprost is lower than expected, and the number of patients who were non-responders to latanoprost is higher than expected in this one study compared with data from most other published studies. These differences may, in part, explain the significantly lower IOP achieved by bimatoprost relative to latanoprost in this single study.

Our results also show that, regardless of which drug is used during the first week of the protocol, significant additional lowering of IOP occurs when bimatoprost or travoprost is used with latanoprost in the second week of therapy, strongly suggesting true additivity. The fact that no additional reduction of IOP takes place when we double the latanoprost dose in the second week of treatment implies that the single application of the drug is at or close to a maximum effective dose. To date, no published studies have examined whether combinations of these 3 drugs are additive in humans, although additivity studies with latanoprost and other prostaglandin derivatives have been performed. In 2 studies of unoprostone isopropyl ester and latanoprost in patients with glaucoma or ocular hypertension, no additional reduction of IOP was observed when unoprostone was added to latanoprost, although lowering was observed when latanoprost was added to unoprostone.7,8 Thus, latanoprost has greater efficacy to lower IOP than unoprostone, but the effects of the 2 drugs are not additive. In contrast, the IOP effects of latanoprost and 8-iso prostaglandin-E₂, an isoprostane, appear to be additive in glaucomatous monkey eyes, a finding possibly due in part to pharmacologically different mechanisms of action in lowering IOP related to the unique structure of 8-iso prostaglandin-E₂.9

**Figure 1.** Comparison of the mean±SEM reduction in intraocular pressure (IOP) in 4 glaucomatous monkey eyes after 1 week of monotherapy with latanoprost, bimatoprost, or travoprost. Values are the average of days 6 plus 7. Values for latanoprost in the upper and middle panels represent the results from monotherapy specific to each of the additivity experiments. None of the differences are statistically significant (P=.98).
was also measured but did not reach statistical significance. No significant alterations were found in aqueous flow or trabecular outflow facility in the normal or the glaucomatous eyes for travoprost. Similarly, in a study of aqueous humor dynamics in normal human eyes treated with bimatoprost, Brubaker and colleagues found a substantial increase in uveoscleral outflow, consistent with the effects on aqueous dynamics of latanoprost and travoprost. However, a statistically significant increase in tonographic facility of outflow compared with baseline was also measured. Although that study was performed in normotensive eyes only, an increase in both trabecular and uveoscleral outflow by bimatoprost may be consistent with our findings of additivity of bimatoprost and latanoprost, if latanoprost has no effect on traditional trabecular function.

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Table 2. Comparison of IOP Effects of Single- and Dual-Drug Therapy in the 5 Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Latanoprost + Travoprost</th>
<th>Travoprost + Latanoprost</th>
<th>Latanoprost + Bimatoprost</th>
<th>Bimatoprost + Latanoprost</th>
<th>Latanoprost + Latanoprost</th>
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<tbody>
<tr>
<td><strong>Trough (0 h)</strong></td>
<td></td>
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</tr>
<tr>
<td>Baseline (day 1)</td>
<td>33.5 ± 1.8</td>
<td>32.3 ± 2.3</td>
<td>34.0 ± 1.1</td>
<td>32.5 ± 1.8</td>
<td>32.8 ± 0.6</td>
</tr>
<tr>
<td>First drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>30.5 ± 1.9 (8%)†</td>
<td>30.8 ± 2.6 (5%)†</td>
<td>31.8 ± 0.6 (6%)†</td>
<td>30.0 ± 1.6 (7%)†</td>
<td>29.0 ± 0.4 (11%)†</td>
</tr>
<tr>
<td>Day 7</td>
<td>30.3 ± 1.7 (9%)†</td>
<td>29.8 ± 2.6 (8%)†</td>
<td>30.8 ± 0.9 (9%)†</td>
<td>30.0 ± 1.3 (7%)†</td>
<td>29.3 ± 0.9 (10%)†</td>
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<tr>
<td>Both drugs</td>
<td></td>
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<tr>
<td>Day 13</td>
<td>29.5 ± 1.0 (11%)†</td>
<td>29.8 ± 2.9 (8%)†</td>
<td>28.0 ± 0.8 (17%)‡</td>
<td>27.8 ± 1.3 (14%)‡</td>
<td>29.0 ± 1.4 (11%)†</td>
</tr>
<tr>
<td>Day 14</td>
<td>29.0 ± 2.0 (13%)†</td>
<td>29.0 ± 2.9 (10%)†</td>
<td>27.5 ± 1.2 (19%)‡</td>
<td>28.3 ± 1.5 (13%)‡</td>
<td>28.8 ± 1.1 (12%)†</td>
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<tr>
<td><strong>Peak (2 h)</strong></td>
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<td></td>
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<tr>
<td>Baseline (day 1)</td>
<td>31.8 ± 1.3</td>
<td>34.5 ± 2.4</td>
<td>34.3 ± 2.1</td>
<td>35.0 ± 1.5</td>
<td>33.8 ± 1.0</td>
</tr>
<tr>
<td>First drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>26.5 ± 1.0 (16%)†</td>
<td>29.3 ± 2.1 (15%)†</td>
<td>28.5 ± 1.0 (16%)†</td>
<td>29.0 ± 1.1 (17%)†</td>
<td>26.3 ± 1.3 (22%)†</td>
</tr>
<tr>
<td>Day 7</td>
<td>26.3 ± 1.2 (17%)†</td>
<td>27.5 ± 2.0 (20%)†</td>
<td>28.0 ± 0.7 (18%)‡</td>
<td>28.5 ± 1.7 (18%)†</td>
<td>26.8 ± 1.9 (20%)†</td>
</tr>
<tr>
<td>Both drugs</td>
<td></td>
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</tr>
<tr>
<td>Day 13</td>
<td>25.8 ± 0.9 (18%)†</td>
<td>28.0 ± 1.6 (18%)†</td>
<td>25.0 ± 1.1 (27%)‡</td>
<td>25.0 ± 0.8 (28%)‡</td>
<td>26.0 ± 1.7 (22%)‡</td>
</tr>
<tr>
<td>Day 14</td>
<td>24.5 ± 1.3 (22%)‡</td>
<td>26.3 ± 2.2 (23%)‡</td>
<td>24.0 ± 1.7 (29%)‡</td>
<td>24.8 ± 1.5 (29%)‡</td>
<td>26.5 ± 1.3 (21%)‡</td>
</tr>
</tbody>
</table>

Abbreviation: IOP, intraocular pressure.
*Comparison is by groups. Second drug indicates additive therapy. Each group consisted of 4 monkeys with laser-induced glaucoma. Numbers in parentheses indicate percentage of reduction of IOP compared with baseline.
†Indicates significant IOP reduction compared with baseline (2-tailed paired t test, P < .05).
‡Indicates significant IOP reduction for combination compared with single-agent therapy (days 13 vs 6 and days 14 vs 7) (2-tailed paired t test, P < .05).

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Figure 2. Mean ± SEM reduction of intraocular pressure (IOP) compared with baseline in 4 glaucomatous monkey eyes for 1 week of latanoprost or travoprost monotherapy followed by 1 week of combined therapy. Values are the average of days 6 plus 7 and days 13 plus 14. For significant changes in reduction of IOP between days 13 plus 14 and days 6 plus 7 (2-tailed paired t test), asterisk indicates P < .05; dagger, P < .005.
Tanoprost belies this hypothesis. In addition, tonography appears to measure more than just trabecular resistance. These conflicting findings on latanoprost and aqueous dynamics by various investigators need to be explained. Nevertheless, it is conceivable that relative differences among latanoprost, bimatoprost, and travoprost in their effects on trabecular and uveoscleral outflow may contribute to their combined ocular hypotensive effect when used together.

Although latanoprost, bimatoprost, and travoprost lower IOP primarily by increasing uveoscleral outflow, the precise mechanisms by which this occurs are not yet known. Various theories to explain the observed increase in uveoscleral outflow have been investigated and include ciliary muscle relaxation, vasodilation of the ciliary body, and alterations in the extracellular matrix of the ciliary muscle by several different mechanisms. Thus, prostaglandins may lower IOP primarily through an increase in uveoscleral outflow, but it is possible that they accomplish this through different pathways. It is therefore conceivable that the prostaglandins we studied increase uveoscleral outflow via parallel but distinct mechanisms and thereby demonstrate additivity when used together.

For these drugs to act by different or parallel mechanisms, there may be differences in their receptor profiles. The respective free acids of all 3 parent compounds have been shown to have potent agonist activity at the FP receptor, which has been identified in human cell cultures of trabecular meshwork, ciliary epithelium, and ciliary muscle. Bimatoprost itself is an FP receptor agonist. It is possible that differences in FP receptor subtypes may exist that would account for distinct actions among these 3 prostaglandin analogues. It is also possible that bimatoprost binds to an unidentified receptor, in addition to its known activity as an FP receptor agonist. A unique receptor profile for bimatoprost would be consistent with our finding that the combination of bimatoprost and latanoprost results in a greater lowering of IOP than that of travoprost and latanoprost.

It should be emphasized that our findings of additivity were demonstrated in nonhuman primates. There may be species differences in the onset, duration, and extent of the reduction in IOP produced by these 3 prostaglandins. Although it is unclear what the maximum effective doses of latanoprost, bimatoprost, or travoprost are in nonhuman primates, the lack of any additional reduction in IOP when we doubled the dose of latanoprost implies that the single application of the commercially available preparation of the drug is at or close to the maximum effective dose in glaucomatous monkeys.
The differences in the second baseline IOP, the results in days 6 plus 7 after monotherapy, among the 5 groups could account for apparent differences in additivity. Ocular hypotensive drugs are well known to be more effective in eyes with higher baseline IOPs. The variability in our untreated baseline IOPs and in our treated baselines at days 6 plus 7 after monotherapy (Table 1) may be due in part to the small number of monkeys in each treatment group, as well as to the wide fluctuations that are known to occur in the laser-induced glaucomatous monkey eye. However, the untreated mean baseline IOPs in the 5 treatment groups are statistically similar, as are the mean IOPs after monotherapy.

The mechanisms responsible for the apparent pharmacologic additivity of bimatoprost or travoprost to latanoprost that we have shown in this study are not known. Further investigations into the methods by which these drugs lower IOP, their effects on aqueous humor dynamics, and differences in their receptor profiles may be helpful in elucidating our results.

CONCLUSIONS

Latanoprost, bimatoprost, and travoprost demonstrated equivalent effectiveness in lowering IOP when used as single agents in glaucomatous monkey eyes, consistent with the results of the only reported 3-way clinical trial in humans.1 In monkeys, bimatoprost and travoprost showed an additional ocular hypotensive response when used with latanoprost, regardless of which drug was used first, suggesting pharmacologic additivity. These results suggest that bimatoprost, travoprost, and latanoprost may have relatively different receptor profiles and mechanisms of IOP reduction, which require further study. These results also suggest that combination therapy with these drugs may prove to be beneficial in some patients with glaucoma and that controlled additivity studies in patients with ocular hypertension or glaucoma may be worth pursuing for these clinically available prostaglandins.

Submitted for publication August 12, 2003; final revision received January 22, 2004; accepted January 29, 2004.

This study was supported in part by grant EY01867 from the National Institutes of Health, Bethesda, Md, and an unrestricted grant from Research to Prevent Blindness, Inc, New York, NY.

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