Aqueous Humor Dynamics in Monkeys after Topical 8-Iso PGE₂

B’Ann T. Gabelt, Jennifer L. Seeman, Steven M. Podos, Thom W. Mittag, and Paul L. Kaufman

PURPOSE. To determine in normotensive cynomolgus monkeys, the effects of topical 8-iso prostaglandin (PG)E₂ on intraocular pressure (IOP), aqueous humor formation (AHF), uveoscleral outflow (Fu), and total and trabecular outflow facility.

METHODS. IOP was measured by Goldmann applanation tonometry under ketamine anesthesia after single or twice-daily topical treatments with 8-iso PGF₂. With animals under pentobarbital anesthesia, AHF and flow to blood (equated to trabecular outflow) were determined by anterior chamber perfusion with radioactively labeled albumin solution. Fu and trabecular outflow facility were calculated from these measurements. Total outflow facility was measured by two-level, constant-pressure perfusion.

RESULTS. IOP was not significantly changed after single or multiple 10-μg doses of 8-iso PGF₂. The 25-μg dose significantly decreased IOP by 2 to 3 mm Hg compared to the control vehicle-treated control 4 to 6 hours after a single dose and by 3 to 5 mm Hg within 1.5 hours after twice-daily treatments for 4 to 5 days. Total outflow facility corrected for control eye washout was increased by an apparent 37% (P < 0.02, n = 7) from 2 to 3.5 hours after the ninth dose, largely due to outlier values obtained in one monkey. Isotope studies performed after twice-daily treatments totaling 9 to 29 doses showed no change in AHF, trabecular outflow facility, or total outflow facility. Relative to AHF, trabecular outflow was significantly decreased, and the calculated Fu was significantly increased when all data were analyzed.

CONCLUSIONS. The present findings are consistent with lowering of IOP by 8-iso PGF₂, primarily by increasing Fu. A direct effect on the trabecular meshwork was not indicated by these in vivo studies. (Invest Ophthalmol Vis Sci. 2004;45:892–899) DOI: 10.1167/iovs.03-0911

The isoprostane 8-iso prostaglandin (PG)E₂ (Cayman Chemical, Ann Arbor, MI) is an isoprostane formed by endogenous peroxidation of arachidonic acid, independent of cyclooxygenase. It is structurally different from prostaglandin agonists such as PGF₂α, isopropyl ester (ie)² and its analogues (e.g., latanoprost). PGF₂α-ie, and latanoprost dramatically lower intracocular pressure (IOP) in monkeys and humans, mainly by increasing uveoscleral outflow (Fu).²⁻⁸ It was hypothesized that 8-iso PGF₂ might alter aqueous humor outflow by enhancing trabecular outflow. Several studies support this hypothesis.

Wang et al.⁹ have shown that topical 8-iso PGF₂ reduces IOP in cynomolgus monkeys with normal eyes or those with laser-induced glaucoma. In normal monkeys, there was no effect on aqueous humor formation, but tonographic outflow facility was significantly increased, enough to account for the total reduction in IOP.⁹ This was in contrast with results obtained with latanoprost, which decreased pressure without an increase in tonographic outflow facility in cynomolgus monkeys.¹⁰ Wang et al. also showed that maximum IOP-lowering doses of latanoprost and 8-iso PGF₂ were additive in lowering IOP in glaucomatous monkey eyes.¹¹ This suggests that the two agents may act by different mechanisms—that is, enhancing Fu and trabecular outflow facility, respectively.

Serle et al.¹² found that in glaucomatous monkey eyes, pretreatment with pilocarpine blocked more of the ocular hypotensive effect of latanoprost than of 8-iso PGF₂. This suggests that Fu accounts for less of the response to 8-iso PGF₂ than to latanoprost.

We report studies to investigate further the IOP-lowering mechanism of 8-iso PGF₂. Our initial findings have been reported in abstract form (Seeman JL, et al. IOVS 2000;41:ARVO Abstract 1337; Gabelt BT, et al. IOVS 2002;43:ARVO E-Abstract 1971).

METHODS

Animals and Anesthesia

Twenty-eight normotensive cynomolgus monkeys of either sex were studied. Not all monkeys were used in every experimental protocol. Anesthesia for IOP and slit lamp examinations was intramuscular (IM) ketamine (10 mg/kg). For aqueous humor formation (AHF) and outflow studies, monkeys were anesthetized with IM ketamine followed by intravenous (IV) pentobarbital (10–15 mg/kg; maintenance dose of 5–10 mg/kg as needed, usually every 1–1.5 hours). For Fu and trabecular facility measurements, a femoral artery was cannulated for subsequent blood sampling.

Treatments

8-iso PGF₂ was dissolved in dimethyl sulfoxide (DMSO, Sigma-Aldrich, St. Louis, MO) to make a stock solution of 10%. Immediately before administration, an aliquot was further diluted in DMSO and water added slowly while the solution was vortexed. Vehicle consisted of 20% DMSO. Monkeys were treated topically twice daily under ketamine anesthesia while supine with the eyelids held open. Two 5-μL drops containing either 10 or 25 μg 8-iso PGF₂ were administered to the central cornea of one eye and vehicle to the opposite eye. The 25-μg dose was most efficacious in the aqueous humor dynamics studies of Wang et al.⁷ In experiments designed to determine whether monkey serum albumin (MSA) added to the perfusate during isotope perfusions could itself alter the outflow facility response to 8-iso PGF₂, both eyes were treated with 25 μg 8-iso PGF₂.

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IOP and Slit Lamp Examination

IOP was measured using a "minified" Goldmann applanation tonometer with cream used as a tear film indicator. Two baseline IOP measurements were taken 5 minutes apart. After a single dose of 8-iso PGE$_2$ in one eye and vehicle in the opposite eye, IOP was measured at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours. Slit lamp examination (to determine the presence of biomicroscopic cells or flare) was performed at baseline and at hours 3 and 6. Monkeys were again treated with 8-iso PGE$_2$ vehicle to the opposite eye, after the last IOP measurement and slit lamp examination. Treatment was continued twice daily with the monkeys under ketamine anesthesia for the next 3 days. On day 5, before the ninth dose, the animals were sedated, two baseline IOP measurements were taken, the animals were treated, and then IOP measurements and slit lamp examinations were performed in the same manner as the first day. For the isotope studies and for total outflow facility experiments with MSA, IOP was checked only after the seventh dose on the fourth day and, in some cases, only at 2, 3, and 4 hours after treatment. When a full 6-hour IOP experiment was performed, after the seventh (isotope studies and MSA total outflow facility studies) or ninth (IOP study only) doses, the data from both studies were combined.

Total Outflow Facility

Monkeys were treated with 25 µg 8-iso PGE$_2$ in one eye and vehicle in the opposite eye, for 4 days (eight doses). On the fifth day, with animals under pentobarbital anesthesia, baseline outflow facility was measured with Bärány’s perfusate and two-level, constant-pressure perfusion, alternating pressures between approximately 15 and 25 mm Hg (mean ± SEM: 15.6 ± 0.3 and 25.2 ± 0.4 mm Hg; n = 14). The ninth dose of 8-iso PGE$_2$ or vehicle was administered topically, and flow from the external reservoir was stopped for 1.75 hours. The reservoir was opened, and outflow facility was measured from hours 2 to 5 after treatment. Total outflow facility was also measured in some monkeys during trabecular outflow facility experiments, 2 to 4.5 hours after treatment and/or at the conclusion of the trabecular outflow facility or Fu measurements, usually 3.5 to 5 hours after treatment. In the latter two cases, baseline total outflow facility was not measured.

There was some concern that the albumin present during the isotope studies might bind the 8-iso PGE$_2$ and prevent it from acting. Therefore the effect of MSA on the total outflow facility response to 8-iso PGE$_2$ was determined on day 5 or 6 of twice-daily treatment of both eyes with 8-iso PGE$_2$. Before the morning dose, the anterior chamber fluid of one eye was exchanged with 2 mL of 0.1% MSA, and the other was exchanged with 2 mL of Bärány’s perfusate. The reservoirs were then filled with the corresponding solution. Baseline total outflow facility was determined as described earlier, 8-iso PGE$_2$ was administered to both eyes, and total outflow facility was again measured 2 to 3.5 hours later.

Isotope Studies: AHF, Fu, Flow to Blood, Trabecular Outflow Facility

For these measurements, monkeys were treated twice daily with topical 8-iso PGE$_2$. Once the IOP lowering response was verified on days 4 or 5, treatments were continued until the time of the experiment. Because only one monkey at a time was tested in these types of experiments, a total of 9 to 29 doses (5–15 days) were administered. AHF, Fu, flow to blood and trabecular facility were determined in various combinations from hours 2 to 4 after the final treatment, using radiolabeled monkey albumin and isotope dilution and accumulation techniques according to modifications of the techniques of Bill and Bärány, Bill and Sperber and Bill, as described in Gabelt and Kaufman and Gabelt et al. Fu was calculated from measurements obtained by circulating 1-125 (one eye) and 1-131 (opposite eye)-labeled albumin solution through the anterior chambers. The difference in the gamma emission spectrum of the isotopes permits determination of how much fluid from each eye entered the general circulation during any particular time interval. The dilution of label by newly formed aqueous was monitored with a well detector and allowed calculation of AHF. Accumulation of isotope in the blood within a 2-hour period after its initial introduction into the eye was assumed to be entirely by outflow through the trabecular meshwork. The difference between the rates of AHF and trabecular outflow was determined as Fu.

To measure trabecular outflow facility, the anterior chamber fluid of each eye was exchanged with iodine-labeled albumin solution. Reservoirs containing the corresponding isotope solution were then opened, and total outflow measured for three 30-minute intervals while the height of the reservoir was changed to produce IOPs of approximately 15, 25, and 15 mm Hg. Blood samples were taken at 5-minute intervals to determine trabecular outflow. Trabecular outflow facility was calculated as the change in the rate of flow to blood divided by the change in pressure.

Analysis

Data are mean ± SEM. Ratios are unitless and were assessed for significant difference from 1.0 by the two-tailed paired t-test. Regression analyses of the 90-minute course of outflow facility measurements were performed using an AR(1) (auto-regression with one lag) error structure to account for the repeated measures (Proc Mixed feature of SAS ver. 8.2; SAS, Cary, NC).

All experiments were conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and the University of Wisconsin Institutional Animal Care and Use Committee.

RESULTS

Slit lamp examination revealed that no corneal toxicity or inflammation resulted from topical doses of either 10 or 25 µg of 8-iso PGE$_2$ or vehicle.

Intraocular Pressure

The 10-µg dose of 8-iso PGE$_2$ had no significant effect on IOP (n = 4), after single or multiple doses (not shown). A single 25-µg dose of 8-iso PGE$_2$ (Fig. 1A–C) significantly decreased IOP in treated compared with control eyes, after correcting for day 1 pretreatment baseline, by 2 to 4 mm Hg from hours 4 to 6 after treatment (P < 0.005; n = 4, Fig. 1C). Figure 1D–F shows the combined IOP results from the same four monkeys and six of those used in isotope studies after the seventh or ninth 25-µg dose. Baseline IOP on day 4 to 5, approximately 17 hours after the prior day’s treatment, was lower in treated eyes (14.2 ± 0.7 mm Hg vs. 16.0 ± 1.0 mm Hg) and higher in control eyes (17.3 ± 1.0 mm Hg vs. 15.7 ± 0.9 mm Hg) compared with the pretreatment baseline IOP on or before day 1, suggesting a sustained effect of the prior treatments. When compared with the pretreatment baseline on or before day 1, posttreatment IOP on day 4 to 5 was decreased by 3 to 4 mm Hg (Fig. 1E) When day-4 to -5 treated and control animals were compared, corrected for pretreatment baseline (i.e., treated minus control in Fig. 1E), IOP was significantly decreased by up to 5 mm Hg from hours 1.5 to 6 after treatment; P < 0.01; n = 10; Fig. 1F).

For the MSA studies, twice-daily treatment of both eyes of 8 monkeys (different from those in any of the other measurements) with 25 µg 8-iso PGE$_2$ significantly decreased IOP from hours 1.5 to 6 after the seventh dose compared with the same-day baseline by 2.3 to 4.3 mm Hg in each eye (Fig. 2B). There was no difference in IOP reduction between the eyes corrected for the same day baseline (Fig. 2C). When compared with the pretreatment IOP on day 1, the reductions in IOP after...
the seventh dose were smaller (1–3 mm Hg reduction during hours 1–6; Fig. 2D).

Outflow Facility

Total outflow facility measurements in seven monkeys different from those used in the isotope studies showed that baseline facility before the ninth dose was the same in treated and control eyes. After the ninth dose, total outflow facility corrected for baseline and compared with the opposite control eye, appeared to be significantly increased (37%; \( P < 0.02 \)) during the 2- to 3.5-hour interval. However, regression analysis showed that the average of the slopes of the differences in facility between 8-isopG\( \text{E}_2 \) and vehicle-treated eyes for each monkey was not different from zero (Fig. 3). The outflow facility increase was driven mainly by the response of one monkey.

In yet another set of animals, total outflow facility calculated from reservoir outflow during the same 2- to 4.5-hour interval as trabecular outflow facility measurements was the same in treated and control eyes (Table 1, item B), as was total facility measured 3.5 to 5 hours after treatment at the completion of either the uveoscleral outflow or trabecular outflow facility measurements (Table 1, item C).

When both eyes of eight monkeys were treated with 8-isopG\( \text{E}_2 \), outflow facility measured in eyes receiving 0.1% MSA in the perfusate was no different from that in opposite eyes perfused with Bárány’s perfusate only (Table 2). This indicates that 8-isopG\( \text{E}_2 \) was not inactivated by protein binding during the isotope experiments, which was suggested as a possible explanation as to why there was no total outflow facility response measured at the end of those experiments.
Trabecular outflow facility measured by isotope accumulation in the blood was no different in treated and control eyes (Table 1, item D). There was a great deal of variability in the trabecular facility data, as illustrated in Figure 4, also suggesting no clear-cut effect of 8-iso PGE2 on trabecular facility. Two monkeys were considered outliers, as indicated, owing to unphysiologically low values in one eye (treated eye in one monkey, control eye in the other monkey). Deleting these animals from the data set results in mean values of 0.37 ± 0.05 μL/min · mm Hg in treated eyes and 0.48 ± 0.07 μL/min · mm Hg in control eyes (treated control [T/C] ratio = 0.91 ± 0.14, n = 15). Only one monkey of 17 had a T/C ratio higher than 2 SD from the mean.

AHF, Trabecular Outflow, and Fu

Two to 4 hours after the 9th to 29th topical doses of 25 μg 8-iso PGE2, AHF, measured by isotope dilution, was not different between treated and control eyes (Table 3). When all data were analyzed, trabecular outflow, determined by isotope accumulation in the blood, was significantly reduced in the treated eyes by 47% (P < 0.02, n = 10). Fu, calculated as the difference between the two, was variably increased in the treated eyes (Table 3). If the results are expressed relative to AHF, trabecular outflow remains significantly decreased, and Fu is now significantly increased by 183% ± 78% (P < 0.05, n = 10) in 8-iso PGE2-treated eyes (Table 3).
FIGURE 3. Total outflow facility versus time after the 9th 25-μg dose of 8-iso PGE₂ in one eye and vehicle in the opposite eye. (A) Each point represents the mean ± SEM outflow facility at each posttreatment time point beginning 2 hours after the 9th topical dose of 8-iso PGE₂ on day 5 of twice-daily treatments in one eye and vehicle in the opposite eye. These data are from the experiments that generated the data in Table 1, item A. (B) Regression analysis showing the slopes of the differences between 8-iso PGE₂ posttreatment facilities and control posttreatment facilities in each monkey (thin lines) and the mean of all the slopes (thick line). Data for different monkeys are represented by different symbols.

TABLE 1. Outflow Facility after 25 μg Topical 8-iso PGE₂

<table>
<thead>
<tr>
<th>Time Post Rx</th>
<th>Outflow Facility</th>
<th>Outflow Facility</th>
<th>Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8-Iso</td>
<td>8-Iso/BL</td>
<td>Vehicle</td>
</tr>
<tr>
<td>A. Ctot1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.27 ± 0.04</td>
<td>0.26 ± 0.02</td>
<td>1.05 ± 0.09</td>
</tr>
<tr>
<td>2-3.5 h</td>
<td>0.54 ± 0.16</td>
<td>1.85 ± 0.28*</td>
<td>1.42 ± 0.20</td>
</tr>
<tr>
<td>B. Ctot2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4.5 h</td>
<td>0.33 ± 0.04</td>
<td>0.34 ± 0.05</td>
<td>1.01 ± 0.11</td>
</tr>
<tr>
<td>C. Ctot3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5-5 h</td>
<td>0.39 ± 0.07</td>
<td>0.38 ± 0.06</td>
<td>1.04 ± 0.11</td>
</tr>
<tr>
<td>D. Ctrab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4.5 h</td>
<td>0.35 ± 0.05</td>
<td>0.45 ± 0.07</td>
<td>1.09 ± 0.26</td>
</tr>
</tbody>
</table>

A. Ctot1, total outflow facility measured prior to and 2-3.5 hours after the 9th dose, n = 7. B. Ctot2, total outflow facility measured during the same interval as trabecular outflow facility, 2-4.5 hours after the 9th to 23rd dose, n = 15. C. Ctot3, total outflow facility measured after trabecular outflow facility or uveoscleral outflow measurements, 3.5-5 hours after the 9th to 29th dose, n = 11. D. Ctrab, trabecular outflow facility measured 2-4.5 hours after the 9th to 25rd dose, n = 17. Data are mean ± SEM. Units, μL/min · mmHg. Ratio significantly different from 1.0 by the two-tailed paired t-test: * P < 0.05; † P < 0.02.
In another unrelated study, it was determined that IOP in monkeys during the isotope measurements had to remain above 6.5 mm Hg for trabecular outflow to occur. Otherwise, most of the outflow was calculated to be through Fu. Therefore, we reanalyzed the current data with results obtained when the IOP remained above 6.5 mm Hg throughout the experiment (Table 3, n = 5). Trends similar to those described earlier were found, although variability and the small number of animals did not allow the changes to reach significance.

**DISCUSSION**

The IOP-lowering response of 2 to 3 mm Hg after a single 25-μg dose of 8-iso PGE2 is comparable to that found by Wang et al.9 Repeated administration resulted in approximately a 4- to 5-mm Hg reduction in IOP compared with control versus pretreatment IOP, which was comparable to the response reported by Wang et al.9 in glaucomatous monkey eyes.

When total outflow facility was measured as an isolated experiment (Table 1, item A) after the ninth topical dose of 8-iso PGE2, we found an apparent 37% increase during the overall 2- to 3.5-hour postdrug period. If 8-iso PGE2 is capable of enhancing both trabecular and Fu pathways, it is possible that repeated doses may lead to Fu’s being the preferred pathway. Our results in the experiments in which only total outflow facility was measured (Table 1, item A) are different from those in which total outflow facility was measured at the same time as trabecular outflow facility (Table 1, item B) or at

In the conclusion of trabecular outflow facility and Fu experiments (Table 1, item C). However, when the data from Table 1, item A, were analyzed as the slope of the differences between treated and control eyes with time, there was no outflow facility effect of 8-iso PGE2. This variability in outflow facility response is typically seen between groups of humans22 or monkeys5,23,24 when measuring the total outflow facility responses to PGF2α, latanoprost, or other PGF2α analogues. We reported in 199019 that total outflow facility was increased by PGF2α, but trabecular facility was not, suggesting nontrabecular contributions to the increased total outflow facility. 8-iso PGE2 also seemed to give variable total outflow facility results. In any case, the effect on total facility was rather small and not sufficient to explain the IOP decrease.

Trabecular outflow facility appears to be unchanged after multiple topical doses of 8-iso PGE2. MSA in the perfusate does not alter the total outflow facility response or lack thereof after 8-iso PGE2, making it unlikely that inactivation of 8-iso PGE2 by binding to albumin circulating through the eye during the isotope studies accounted for the absence of an effect. In addition, we have not encountered this theoretical problem with other classes of drugs, including other prostaglandins. If 8-iso PGE2 must be constantly present to exert an effect on the trabecular outflow pathway, then the dilution with the fluid in the circuit during the Fu measurements or the exchange of the anterior chamber contents during the trabecular facility experiments would have washed it out of the system. Also, no baseline facility values are collected during trabecular outflow

**Figure 4.** Trabecular outflow facility (Ctrab) data for each monkey. Plots of values in 8-iso PGE2 versus vehicle-treated eye show the scatter of the data. Line indicates equivalence. Two monkeys, were considered to be outliers due to nonphysiologic values in one eye (n = 17).

**Table 2.** Total Outflow Facility after 25 μg Topical 8-iso PGE2 to Both Eyes, Twice Daily for 5 to 6 Days

<table>
<thead>
<tr>
<th>Time Post Rx</th>
<th>MSA</th>
<th>MSA/BL</th>
<th>Bárány's</th>
<th>Bárány's/BL</th>
<th>MSA/Bárány's</th>
<th>MSA/BL/Bárány's/BL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.47 ± 0.06</td>
<td>1.46 ± 0.30</td>
<td>0.47 ± 0.06</td>
<td>1.75 ± 0.36</td>
<td>1.06 ± 0.09</td>
<td>0.97 ± 0.25</td>
</tr>
<tr>
<td>2–3.5 h</td>
<td>0.75 ± 0.14</td>
<td>1.46 ± 0.30</td>
<td>0.75 ± 0.10</td>
<td>1.75 ± 0.36</td>
<td>1.02 ± 0.12</td>
<td></td>
</tr>
</tbody>
</table>

Perfusate is either Bárány’s alone or Bárány’s containing 0.1% MSA. Total outflow facility measured prior to and 2–3.5 hours after the 9th or 11th dose; n = 8. Data are mean ± SEM. Units, μL/min · mmHg. Ratio significantly different from 1.0 by the two-tailed paired t test: * P < 0.02; † P < 0.005.
facility and Fu experiments; hence, small differences between treated and control eye baseline facility could have masked postdrug effects. However, the relatively large number of animals used in those measurements (17 for trabecular outflow facility and simultaneous total outflow facility; 11 for postisoptope total outflow facility) should have allowed any significant drug-induced changes to be revealed.

Direct effects of 8-iso PGE₂ on the trabecular meshwork must be studied further, perhaps using human and monkey anterior ocular segment organ culture systems.²⁵,²⁶ Evidence for trabecular effects of PGE compounds was shown by EP₂ receptor stimulation by PGE₁, which enhanced trabecular flow in perfused human anterior segments.²⁷ FP receptors can also be stimulated by PGD₂ and PGE₂.²⁸ Receptor pro-

<table>
<thead>
<tr>
<th>8-Iso PGE₂</th>
<th>Vehicle</th>
<th>8-Iso/Veh</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHF All data</td>
<td>1.22 ± 0.09</td>
<td>1.23 ± 0.09</td>
</tr>
<tr>
<td>F trab</td>
<td>IOP&gt;6.5 mm Hg</td>
<td>1.20 ± 0.30</td>
</tr>
<tr>
<td>Fu All data</td>
<td>0.33 ± 0.12</td>
<td>0.77 ± 0.12</td>
</tr>
<tr>
<td>F trab/FH All data</td>
<td>IOP&gt;6.5 mm Hg</td>
<td>0.52 ± 0.43</td>
</tr>
<tr>
<td>Fu AHF All data</td>
<td>0.29 ± 0.10</td>
<td>0.64 ± 0.09</td>
</tr>
<tr>
<td>8-ISO PGE2</td>
<td>IOP&gt;6.5 mm Hg</td>
<td>0.44 ± 0.40</td>
</tr>
<tr>
<td>8-ISO PGE2</td>
<td>IOP&gt;6.5 mm Hg</td>
<td>0.71 ± 0.10</td>
</tr>
<tr>
<td>8-ISO PGE2</td>
<td>IOP&gt;6.5 mm Hg</td>
<td>0.56 ± 0.40</td>
</tr>
</tbody>
</table>

Measurements taken at 2–4 hour after the 9th to 29th dose. Data are mean ± SEM. Units = μL/min. n = 10 (all data) or n = 5 (IOP>6.5 mm Hg). Ratio significantly different from 1.0 by the two-tailed paired t-test: * P < 0.02; † P < 0.05.

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