Prostaglandin D\textsubscript{2} reduces intraocular pressure

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**SUMMARY** When PGD\textsubscript{2} was topically applied to the rabbit eye a reduction of intraocular pressure (IOP) was observed within 30 min. The IOP reduction lasted throughout the observation period of 7 hours. No increase of IOP was observed during the period. The effect of PGD\textsubscript{2} was dose-dependent (0.4 \textmu g to 250 \textmu g), and the minimum effective dose was estimated to be 2.0 \textmu g. The application of PGD\textsubscript{2} did not affect the pupil diameter. No sign of inflammatory response was observed by PGD\textsubscript{2} application, that is, no hyperaemia, no flare, no irritation, and no increase of protein content in the aqueous humour. These results suggest that PGD\textsubscript{2} or its analogues may be useful for treating glaucoma.

Prostaglandins (PGs) are formed in the eye\textsuperscript{12} following various kinds of stimulation and are thought to mediate inflammatory responses.\textsuperscript{3} Among several types of PGs the PGE and F series have been extensively studied in relation to intraocular pressure (IOP).\textsuperscript{4-8} Early studies showed that these compounds are hypertensive.\textsuperscript{4} Recently, however, topical application of them was found to eventually lower the IOP in many animal species.\textsuperscript{5-7} Yet higher doses induce an initial increase of the IOP in rabbits\textsuperscript{5} and monkeys\textsuperscript{5} and also cause aqueous flare in rabbits\textsuperscript{5} and cats.\textsuperscript{7}

More recently the effects of PGF\textsubscript{2a}\textsuperscript{8} and its isopropyl ester\textsuperscript{9} on the human eye have been examined; and these PGs were found, as in animal eyes, to reduce the IOP. However, several side effects such as initial hypertension from higher doses, conjunctival hyperaemia, headache, and ocularsmarting were noted. Thus the clinical usefulness of these PGs as hypotensive agents is limited, as has already been pointed out.\textsuperscript{8}

During the course of biochemical experiments on PG synthesis in ocular tissues we found that PGD\textsubscript{2} is the major PG formed in the rat ocular system.\textsuperscript{10} This PG has been also reported to be synthesised in the rabbit eye.\textsuperscript{12} The effect of PGD\textsubscript{2} on IOP has, however, not been fully studied. We now report that topically applied PGD\textsubscript{2} is effective in reducing the IOP without side effects in rabbit eyes.

**Material and methods**

Albino rabbits (weighing 2.0–2.5 kg at the start of experiment) were used. The animals were restrained in metal rabbit holders, and the IOP was measured with an Alcon planaplanation pneumatonograph after the topical administration of a local anaesthetic (0.4\% oxybuprocaine). PGs were kindly supplied by Ono Central Research Institute (Osaka, Japan). They were dissolved in 50 \textmu l of 100 mM potassium phosphate buffer (pH 7.3) and applied topically to one eye. For the maximum dose of 250 \textmu g the PGD\textsubscript{2}-sodium salt was prepared by addition of an equimolar amount of Na\textsubscript{2}CO\textsubscript{3} dissolved in a minimum volume of water to PGD\textsubscript{2}, and then the pH and concentration were adjusted with a buffer. The other eye received the same amount of the buffer alone. For the long-term experiment (over 7 h) PG was administered between 11 and 12 am. For the measurement of protein content in the aqueous humour one eye was designated as the control and the other was treated with PGs. Aqueous humour was then collected once from each eye with a needle. Protein content was determined according to Lowry et al.\textsuperscript{11} with bovine serum albumin as a standard.
Results

Fig. 1 shows the effect of topical application of 50 μg of PGD₂, PGE₂, or PGF₂α on IOP. The effects of PGE₂ and PGF₂α at this dose were biphasic, as have been reported by several authors, that is, application of either of these PGs resulted in an initial increase followed by a reduction in IOP. PGD₂ on the other hand did not cause any increase but only reduced IOP. The reduction of IOP by PGD₂ was observed within 30 min (but not at 15 min) and lasted throughout the observation period of 7 h. By 24 h, however, the IOP had returned to nearly its original level. The IOP at 24 h was 17.6±2.3 mmHg for the control and 17.7±2.0 mmHg for the treated eyes (n=9) (mean±SEM).

For four to seven hours after administration all three PGs reduced the IOP. As shown in Table 1, the mean IOP reduction during this period was the highest for PGF₂α, followed by PGE₂ and PGD₂. However, since it is generally known that the initial IOP level has a significant influence on the magnitude of IOP reduction, we calculated R values to estimate the relative hypotensive effectiveness (Table 1). Judging from the R values, we considered PGE₂ to be the most effective agent for reducing IOP, followed by PGF₂α and PGD₂ under these conditions. The effect of PGD₂ on IOP was dose-dependent. No hypertensive phase was observed even with the maximum PGD₂ dose of 250 μg. The hypotensive effect reached nearly its maximum with 10 μg of PGD₂ (Fig. 2). The minimum dose effective in inducing a significant IOP reduction was judged to be

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of hypotensive potency among PGD₂, E₂, and F₂α</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>Control IOP (mmHg)</td>
</tr>
<tr>
<td>PGD₂</td>
<td>48</td>
</tr>
<tr>
<td>PGE₂</td>
<td>32</td>
</tr>
<tr>
<td>PGF₂α</td>
<td>16</td>
</tr>
</tbody>
</table>

Data presented in this table were obtained during the hypotensive phase (4-7 h) after topical applications of 50 μg of the PGs. Means±SEM are given.

R was calculated from the following equation: $R = \frac{(IOP_c - IOP)}{IOP_c - ESVP}$, where $IOP_c$ and $IOP_t$ are IOP in the control and in the treated eye, respectively.

The episcleral venous pressure (ESVP) has been reported to be 10 mmHg.12
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Table 2  Effects of PGs on protein content of the aqueous humour

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Protein content (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control eye</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>0.62±0.04</td>
</tr>
<tr>
<td>PGD$_2$</td>
<td>3</td>
<td>0.67±0.09</td>
</tr>
<tr>
<td>PGE$_2$</td>
<td>3</td>
<td>0.58±0.04</td>
</tr>
<tr>
<td>PGF$_{2a}$</td>
<td>4</td>
<td>0.63±0.08</td>
</tr>
</tbody>
</table>

The aqueous humour was collected 1 h after topical application of 50 μg of PG (buffer alone for the control group). Means±SEM are given.

2.0 μg. Interestingly, even after the maximum dose of PGD$_2$ (250 μg) was given, the IOP was reduced only to about 13 mmHg. On the other hand 50 μg of PGE$_2$ or PGF$_{2a}$ reduced the IOP to 9–10 mmHg. The pupillary diameter was not affected even by 250 μg of PGD$_2$ for at least four hours after application.

No hyperaemia or flare was noted by slit-lamp examination during four hours after the application of up to 250 μg of PGD$_2$. However, PGE$_2$ and PGF$_{2a}$ (50 μg) caused strong conjunctival and iridal hyperaemia and irritation (eyes tightly closed) within 30 min after the application. These inflammatory responses lasted for at least four hours. Flare was also noted during one to two hours after the application of PGE$_2$.

The effect of PGD$_2$ on the protein content in the aqueous humour was also different from that of PGE$_2$ or PGF$_{2a}$. At one hour after application PGD$_2$ (50 μg) did not induce any increase of the aqueous protein, while PGE$_2$ and PGF$_{2a}$ caused a 40- and 4-fold elevation respectively (Table 2). PGD$_2$ failed to increase the aqueous protein not only at 1 h but also at later times after its application. Protein contents at 2, 4, and 6 h were 0.72±0.08 mg/ml (mean±SEM, n=4), 0.65±0.08 (n=4), and 0.59±0.03 (n=4), respectively, and did not differ from the control level.

Discussion

The effect of PGD$_2$ on IOP is distinct from that of PGE$_2$ or PGF$_{2a}$. While 50 μg of PGE$_2$ or PGF$_{2a}$ caused an initial elevation of IOP, PGD$_2$ (up to 250 μg) reduced IOP without any elevation phase. The effect of PGD$_2$ is also totally different from that of the other PGs in terms of inflammatory response. PGD$_2$ (up to 250 μg) caused no sign of inflammation, that is, no hyperaemia, no flare, and no irritation. At the dose of 50 μg PGD$_2$ did not cause an increase in the protein content of the aqueous humour, while the other two PGs induced a marked increase. Thus the action of PGD$_2$ on the eye appears to differ from that of the other two.

The hypertensive and inflammatory responses to PGE$_2$ or PGF$_{2a}$ have been shown to be dose-dependent,$^{12,13}$ and lower doses of these two PGs have been reported to cause less inflammation and no hypertension. The present experiment has shown that the relative hypotensive potency of the three PGs is PGE$_2$>PGF$_{2a}$>PGD$_2$. Therefore it is conceivable that PGD$_2$, being a weak agent, did not cause the initial IOP elevation or any inflammatory response. However, as our data show, the hypotensive effect of PGD$_2$ was saturated at about 10 μg, and a 25-fold increase in the PGD$_2$ dose did not induce any hypertensive or inflammatory response.

Our observations on the effects of PGD$_2$ on IOP and inflammatory responses differ from those reported by Kulkarni and Srinivasan,$^13$ who also used rabbits. They reported that either topical or intravitreal application of PGD$_2$ (10 μg) slightly raised the IOP of both eyes. In their experiment a five- to six-fold increase in the aqueous protein at three hours after application was also observed, but we did not find any such increase six hours after PGD$_2$ application. Although only a single dose experiment, PGD$_2$ (100 μg) topically applied to cats eyes is reported to decrease IOP.$^{14}$ A reduction in IOP by 10 to 50 μg of PGD$_3$ (an equivalent product from eicosapentaenoic acid to PGD$_2$ from arachidonic acid) has also been reported in rabbits.$^{15}$

Species differences in PG-mediated responses are well documented. Therefore the results obtained in this study cannot necessarily be extended to the human eye. However, since PGD$_2$ was found to be effective in reducing the IOP without causing any sign of inflammatory response, it is worth examining PGD$_2$ or its analogues as therapeutic agents for the treatment of glaucoma in man.

We are grateful to Drs Y Watanabe, Y Urade, N Uyimoto, M Hatanaka, and K Matsuda for useful discussions. Thanks are also due to Y Ueha and M Harada for secretarial assistance.

References

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Accepted for publication 23 April 1987.
Prostaglandin D2 reduces intraocular pressure.

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doi: 10.1136/bjo.72.6.461

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