

Long-term Maintenance of Reduced Intraocular Pressure by Daily or Twice Daily Topical Application of Prostaglandins to Cat or Rhesus Monkey Eyes

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Substantial evidence indicates that a single topical application of prostaglandins (PGs) can reduce intraocular pressure (IOP) in the eyes of several species. However, earlier literature, dealing with ocular hypertensive and inflammatory responses, shows the development of tachyphylaxis to sub-sequent doses of PGs. If similar tolerance developed to the ocular hypotensive effects of PGs, it would preclude the use of these agents in the treatment of chronic glaucoma. The present study shows, however, that although tachyphylaxis to the ocular hypotensive effects of PGs develops in rabbits, this is not a typical response among mammals. Significant IOP reduction was maintained in cats for up to 9 months by topical application of PGE₂ at 12-, 24-, or 48-hr intervals. The IOP reduction was jeopardized seriously only when the PG was applied every other day for several days or when, on a few occasions, 3 days were allowed to elapse between PGE₂ applications. Ocular hypotension was also maintained during the course of topical treatment of rhesus monkey eyes with PGF_{2α}. Short periods of pupillary constriction followed the application of each dose of PGF_{2α} to cat eyes, but the miotic response of rhesus monkeys to PGF_{2α} and cats to PGE₂ was negligible. Other apparent side effects were noted, but none of these were severe or progressive. These results clearly demonstrate that tachyphylaxis, or tolerance, is not expected to present an obstacle to the development of eicosanoids and/or their derivatives as therapeutic agents for the long-term treatment of ocular hypertension and chronic glaucoma. *Invest Ophthalmol Vis Sci* 24:312-319, 1983

Early studies on the effects of prostaglandins (PGs) on the eye, primarily designed to determine the role of these autacoids in the ocular irritative response, concluded that exogenous PGs can produce increased intraocular pressure (IOP) and breakdown of the blood-aqueous barrier.¹ It has recently been shown, however, that appropriate doses of PGF_{2α} topically applied to the eyes of rabbits,² owl monkeys,³ rhesus monkeys, and cats⁴ can, in fact, reduce rather than increase IOP. In the rabbit there is only a narrow margin between the hypotensive dose of PGF_{2α} and a dose that causes initial hypertension.² Ten- to 100-fold higher PGF_{2α} doses than those that reduce IOP in the rabbit are required to produce the same effect in owl monkeys, rhesus monkeys, and cats, but even

these high doses cause no initial hypertension and little or no flare. These findings suggested that PGs and related autacoids might constitute a new class of ocular hypotensive agents. However, the long-term hypotensive efficacy of PGs had to be determined before their potential value in the control of glaucoma could be assessed.

Earlier studies reported that both rabbits and cats develop tachyphylaxis to the ocular hypertensive effects of intracamerally injected PGs.^{5,6} Recent studies have shown, however, that the rabbit is atypical of vertebrates with regard to its profound PG-mediated, ocular inflammatory, and/or irritative responses.^{7,8} There is also evidence that cannulated eyes may show exaggerated responses to exogenous autacoids or drugs.⁹ Thus, the fact that cannulated rabbit and cat eyes develop tachyphylaxis to PGs does not necessarily imply that tachyphylaxis will occur in the normal, uncannulated eyes of these species or that this response is a general phenomenon among vertebrates.

This investigation was undertaken to study the ocular responses of cats to daily or twice daily topical application of PGs for periods of up to 9 months. Similar but shorter studies were also performed on rhesus monkeys to establish the applicability of our

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findings to primates. For comparison, some of our earlier findings on the development of tachyphylaxis in rabbits to PG-induced ocular hypotension are also reported.

Materials and Methods

Twelve cats of mixed breeds and of either sex (2.5 to 3.5 kg) were trained to accept periodic restraint in animal boxes and tonometry without the use of general anesthesia. All eyes were examined with a slit-lamp. Only animals that showed no signs of ocular inflammation were included in this study.

For 9 months, a 50- μ l aliquot of solution containing 100 μ g of prostaglandin E₂ (PGE₂) was topically applied to one eye of each of six cats, typically at 24-hr intervals, but in some cases at 12-, 48-, or 72-hr intervals. An equal volume of vehicle solution was applied to the contralateral eye of each cat during the first month and for shorter periods thereafter. However, the possibility of accidental confusion between PGE₂ and its vehicle solution was judged to outweigh the benefits of continued routine application of vehicle solution to the control eye. The dose of PGE₂ applied at each treatment was 100 μ g/eye, with the exception of day 100, when 500 μ g was applied. The other six cats received unilateral topical application of PGF_{2 α} tromethamine salt (100 or 500 μ g of PGF_{2 α} free acid equivalent/eye) for shorter periods. At the same times the contralateral eyes of these cats received an equal volume of saline solution.

Intraocular pressures and pupil diameters were usually measured every day at approximately 9 am, just before the morning PG treatment, and at 1, 3, 4 and 6 hr thereafter. One drop of 0.5% proparacaine hydrochloride (Alcaine, Alcon Corp., Fort Worth, TX) was applied topically to each eye and IOPs were measured, using a floating-tip pneumatic tonometer (Pneumotonograph; Alcon Corp.). Pupillary diameters (naso-temporal) were measured with a millimeter ruler in normal room light. Because of the unilateral PG-induced pupillary constriction and because frequently, especially on weekends, the same person measured the IOP and administered the PG solution, the observer could not be masked concerning which eye received the PG solution. However, most of the observations and tonometry readings were done by individuals who were not aware of the expected results. When animals were treated twice daily, the second treatment was given between 9 and 10 pm, but tonometer readings and slit-lamp examinations were performed only during the day. Slit-lamp examinations were done 4 to 5 hr after PG applications. Anterior chamber flare was rated as follows: 0 = no Tyndall effect; 0.5+ = barely perceptible Tyndall effect; 1+ = slight to easily visible Tyndall effect; 2+ = mod-

erate to dense Tyndall effect; 3+ = dense Tyndall effect with fibrin clots. Cellular invasion of the anterior chamber was rated as follows: 0 = no cells present; 0.5+ = a very careful search required to find any cells; 1+ = a few cells; 2+ = many cells; 3+ = cell clumps. These are more stringent criteria than those used in our previous study of the ocular inflammatory response of rabbits.¹⁰

Similar experiments were performed on two 5- to 7-year-old female rhesus monkeys. Both of these animals had been used intermittently in ocular drug studies over the previous three years, most recently to establish the single dose of topically applied PGF_{2 α} required to reduce IOP in this species.⁴ However, neither animal had been used in any study for three months prior to these experiments. Both animals were kept in primate chairs throughout most of the present experiments. One animal required tranquilization with ketamine HCl (Ketaset; Bristol Labs., Syracuse, NY; 20–30 mg/kg im) before each IOP reading. The other animal permitted tonometry to be performed under topical (Alcaine) anesthesia. For six days, one eye of each animal was treated twice daily, between 9 and 10 am and between 4:30 and 10 pm, with 50 μ l of a solution containing 100 μ g of PGF_{2 α} equivalent of the tromethamine salt. On day 7, the dose was increased to 500 μ g/eye per treatment. This dose was continued for 11 days, with the exception of day 9, when only the morning treatment was given, and day 10, when no treatment was given. After a seven-day break, 1000 μ g/eye of PGF_{2 α} equivalent was applied two times each day for five days beginning on the 25th day. IOP readings were typically taken immediately before the morning treatment and at 2, 4, and 6 hr thereafter.

In one experiment using nine female New Zealand White rabbits (2.5 to 3.5 kg), 5 μ g of PGF_{2 α} equivalent in 5 μ l of normal saline was applied to one eye of each animal at 8-hr intervals for 5 days, while the control eyes received 5 μ l of normal saline. Eight hours after the 16th treatment the dose of PGF_{2 α} was increased to 10 μ g in 5 μ l of saline. One month later, this group of rabbits was divided into three equal groups. Both eyes of each animal were treated with one of the following solutions at 12-hr intervals for 3 days: Group 1 and Group 2, PGF_{2 α} tromethamine equivalent to 5 and 10 μ g of PGF_{2 α} , respectively, in 5 μ l of saline; Group 3, 5 μ l of saline (controls). In both experiments, IOP was measured using topical anesthesia only and slit-lamp examinations were done, as previously described for cats, just prior to each treatment and occasionally at more frequent intervals.

For all procedures, the free acid of PGE₂ was converted just before each treatment to its more water-

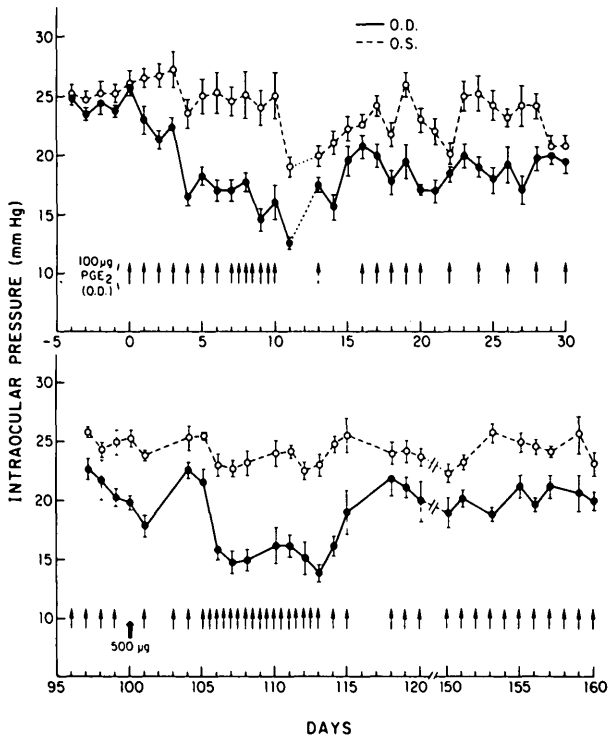


Fig. 1. The maintenance of ocular hypotension for the first 160 days of a 9-month treatment period during which PGE₂ was topically applied once daily or twice daily, and on a few occasions every second or third day, as indicated by the arrows. With the exception of day 100, when 500 µg of PGE₂ was applied, each arrow indicates the application of 100 µg of PGE₂ to the treated eye. Points represent the mean IOPs (±1 SEM) of the treated (—●—) and control (---○---) eyes of six cats, measured at approximately 9 am, just before the morning treatment.

soluble sodium salt by the addition of 0.5 ml of Na₂CO₃ (0.2 mg/ml) in saline. The water-soluble and highly stable tromethamine salt of PGF_{2α} was periodically made up in saline and refrigerated for use over several days. The doses of PGF_{2α} (MW = 356) reported throughout this paper represent the amount of PGF_{2α} tromethamine salt (MW = 476) used divided by 1.3. All PGs were supplied by Dr. J. E. Pike, The Upjohn Co., Kalamazoo, MI.

Results

Intraocular Pressure Effects on Cats

Baseline tonometry, taken thrice daily for up to seven days prior to treatment, indicated no significant difference between the IOPs of the left and right eyes of cats (Fig. 1). The IOP of the treated eyes was significantly lower (*P* < 0.01; paired t-test) than baseline within 1 hr after the unilateral topical application of 100 µg of PGE₂, (Fig. 2, panel A) and remained lowered until the next treatment. Following the second application of 100 µg of PGE₂, immediately after the 24-hr IOP reading, produced a greater maximum

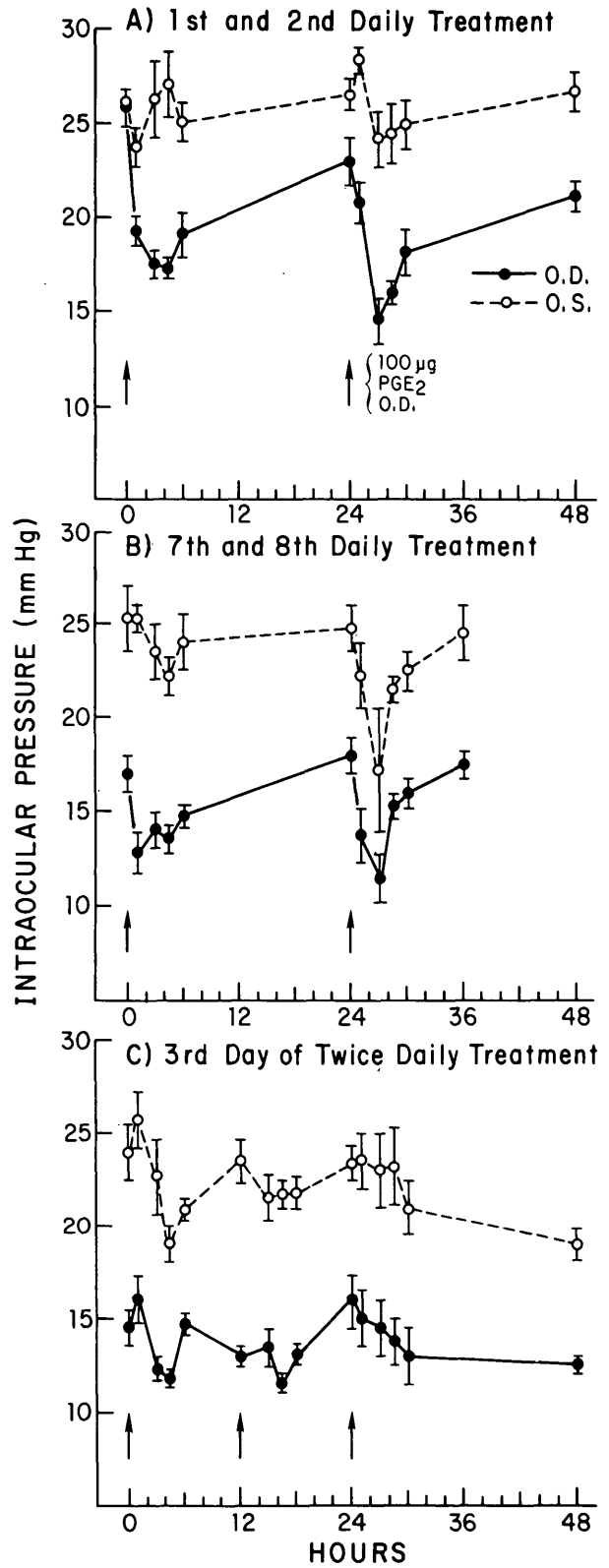


Fig. 2. The effect of topically applied PGE₂ on the IOP of the treated (—●—) and contralateral control (---○---) eyes of cats after the first and second (panel A) and after the seventh and eighth daily treatments (panel B) and after the third day of twice daily treatment (panel C). Arrows indicate each application of 50 µl of a solution containing 100 µg of PGE₂ to the treated eye and an equal volume of vehicle solution to the control eye of each animal. Points represent means ± SEM obtained from six cats.

and a longer maintained decrease in IOP (Fig. 2, panel A).

The lowest 9 am IOP value occurred 24 hr after the fourth treatment and was maintained at approximately the same level for the next three days (Fig. 1), although even greater IOP reductions occurred within the first 2 hr after each daily PG application (Fig. 2, panel B). Between days 7 and 10 and days 105 and 123 after the first PG application, the eyes of these cats were treated with the same dose (100 µg/eye) of PGE₂ twice daily, producing a greater decrease in IOP than that typically observed during the daily treatment (Fig. 1). During twice daily treatment, IOP fluctuations between PG applications were minimal (Fig. 2, panel C). The fluctuations in IOPs of the control eyes were generally much smaller and less consistent than the IOP reductions in the treated eyes. Some of these fluctuations, however, appeared to be temporally associated with the PG-induced IOP reduction in the treated eye, although somewhat delayed in onset (Figs. 1–3).

When PGE₂ treatment of these cats was suspended for 72 hr (days 10 to 13, 14 to 16, and 115 to 118), there was a significant increase in the 9 am IOP readings of the experimental eyes (Fig. 1). When, beginning on the 20th day, these cats received one PGE₂ treatment every other day for 10 days, the IOP of the treated eyes was maintained for several days below pretreatment baseline and, for the most part, significantly below the concurrently measured IOP of the contralateral eyes (Fig. 1). When once daily treatment with 100 µg of PGE₂ per eye was resumed between days 30 and 99, and from day 118 with few exceptions to the end of the ninth month, the IOP of the experimental eyes was maintained below that of the control eyes (Fig. 3). On day 100, a single application of 500 µg/eye of PGE₂ resulted in further IOP reduction (Fig. 1). However, this high dose caused significant flare in the anterior chamber of these eyes and therefore was not applied again.

Qualitatively similar results were obtained during the topical application of 100 µg of PGF_{2α} to one eye of the second group of six cats. Four hours after the first PGF_{2α} application, the IOP of the treated eyes dropped significantly (*P* < 0.05) from the baseline of 23 ± 1.6 to 17 ± 1.1 mmHg, and remained significantly reduced (*P* < 0.05) throughout the seven days of treatment (Fig. 4). The IOP of the contralateral eyes of these animals fluctuated considerably; in fact, 24 hr after the first PGF_{2α} treatment, the IOP of these eyes was reduced almost as much as that of the treated eyes (Fig. 4). When daily treatment of the experimental eyes with 500 µg/eye of PGF_{2α} was initiated 12 days after the last treatment with 100 µg of PGF_{2α}, an even greater decrease in IOP was maintained throughout the ensuing 4-day treatment period (not shown).

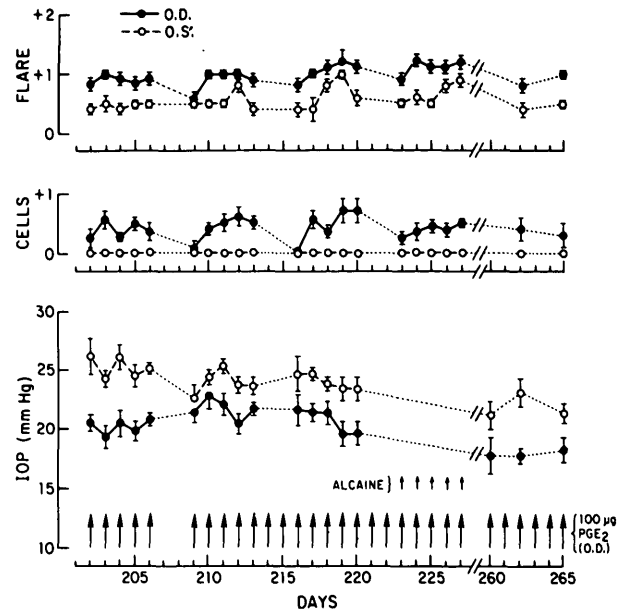


Fig. 3. The effect of topical PGE₂ treatment on the eyes of six cats during the last two months of the 9-month treatment period. All IOP measurements shown were taken just before administration of a dose of 100 µg of PGE₂ (indicated by arrows) to the treated eye (OD) and an equal volume of vehicle solution to the contralateral control eye of each animal. Points represent mean ± SEM obtained from six cats.

Intraocular Pressure Effects on Rhesus Monkeys

Twice daily topical application of 100 µg of PGF_{2α} to one eye of each of two rhesus monkeys produced a decrease in the IOP of those eyes (Fig. 5). The greatest reduction observed within 6 hr after the first application was only slightly greater than that measured after the 3rd, 5th, 9th, and 11th applications of this dose. The lowest IOP measurement obtained within 6 hr after the first application of 500 µg of PGF_{2α} was equal both to that obtained after the first application of 100 µg of PGF_{2α} and to those obtained after subsequent applications of 500 µg of PGF_{2α}. However,

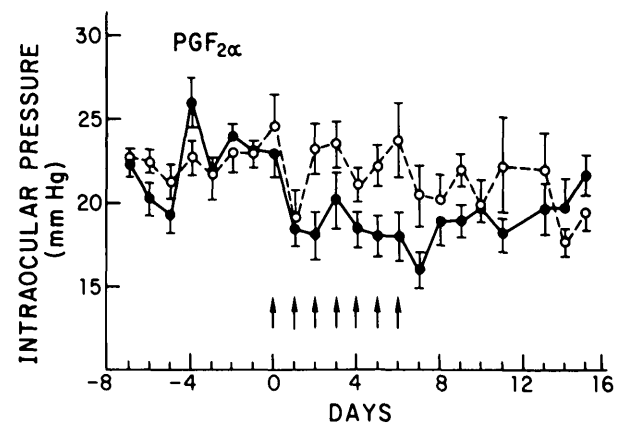


Fig. 4. The effect of seven consecutive daily applications of 100 µg PGF_{2α} on the IOP of the treated (—●—) and contralateral (—○—) eyes of six cats.

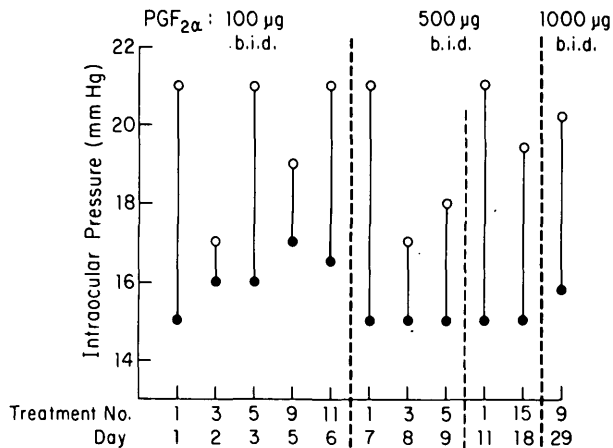


Fig. 5. The effect of twice daily topical application of $\text{PGF}_{2\alpha}$ on the IOP of the experimental eye of one rhesus monkey. Open circles: IOP measured immediately before the morning $\text{PGF}_{2\alpha}$ application. Closed circles: the lowest IOP measured during the following 6 hr. Abscissa: upper row denotes number of consecutive twice daily $\text{PGF}_{2\alpha}$ applications at approximately 9 am and between 4:30 and 10 pm; lower row denotes number of days from the beginning of the treatment period.

when 1000 $\mu\text{g}/\text{eye}$ of $\text{PGF}_{2\alpha}$ was applied twice daily for five days, the IOP of the experimental eye was reduced to a level only slightly higher than that obtained after administration of 500 μg of $\text{PGF}_{2\alpha}$ (Fig. 5). Results similar to those shown in Figure 5 were obtained from the second rhesus monkey, although IOP readings were somewhat complicated by the fact that they had to be obtained under tranquilization.

It should be noted that all morning treatments of the two monkeys were done at approximately 9 am,

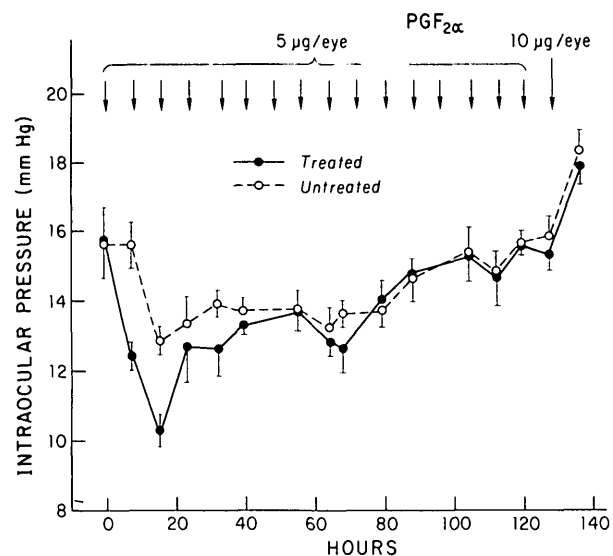


Fig. 6. The effect of thrice daily unilateral $\text{PGF}_{2\alpha}$ treatment on the IOP of eight rabbits. Measurements were taken just before the administration of $\text{PGF}_{2\alpha}$ to the experimental eyes. Control eyes were given an equal dose of vehicle solution. Points represent mean IOP \pm SEM.

while the second daily treatment was given between 4:30 and 10 pm. Thus, the IOP readings taken just prior to the morning treatment (indicated by open circles in Fig. 5) may have been done as much as 17 hr after the previous treatment. This variability in the time of the evening treatment, as well as the breaks in treatment between days 9 and 11 and between days 18 and 25 can, to a large extent, explain the variability of the morning pretreatment IOP.

Intraocular Pressure Effects on Rabbits

A significantly reduced IOP could not be maintained in $\text{PGF}_{2\alpha}$ -treated rabbit eyes, since both the extent and the duration of the ocular hypotensive response to $\text{PGF}_{2\alpha}$ was reduced in this species after the first few treatments (Fig. 6). By 8 hr after the 11th treatment, and thereafter, the IOP of both the treated and control eyes increased to a level comparable to baseline, even though there were 2- to 3-hr episodes of ocular hypotension after each $\text{PGF}_{2\alpha}$ application. Ten micrograms of $\text{PGF}_{2\alpha}$, applied 8 hr after the 16th treatment with 5 μg of $\text{PGF}_{2\alpha}$, also briefly reduced the IOP of both eyes. However, by 8 hr after this larger dose, the IOP of both eyes was elevated significantly above their respective IOPs just prior to this dose (Fig. 6).

In other experiments undertaken to maintain IOP reduction by twice daily application of either 5 μg or 10 μg of $\text{PGF}_{2\alpha}$ to both eyes of two sets of three rabbits, tachyphylaxis to the ocular hypotensive effects of $\text{PGF}_{2\alpha}$ again developed rapidly in both groups. By the third treatment, there were no significant differences ($P > 0.05$, unpaired t-test) between the IOPs of any group.

Other Observations

While PGE_2 caused only slight miosis in cat eyes, there was strong dose-dependent pupillary constriction of relatively short duration (1 to 6 hr) after each application of $\text{PGF}_{2\alpha}$ (Fig. 7, panel A vs panel B). When the dose was increased to 500 $\mu\text{g}/\text{day}$, the extent of miosis within the first 4 hr after treatment was increased. Twenty-four hours after the last treatment with 100 μg of $\text{PGF}_{2\alpha}$, the mean pupil diameter of the experimental eyes was significantly greater than that of the contralateral eyes (7.5 ± 0.6 vs 6.5 ± 0.8 mm; $P < 0.02$). A similar reversal of relative pupil diameters in the experimental vs the control eyes was noted 24 hr after each daily application of 500 $\mu\text{g}/\text{eye}$ of $\text{PGF}_{2\alpha}$, especially during the first few days of this regimen. This was due to a 1-2 mm pupillary constriction, which developed in the control eyes a few hours after the application of $\text{PGF}_{2\alpha}$ to the experimental eyes, and which lasted for over 24 hr. Because absolute pupil size, particularly in cats, can be influenced by several factors not controlled in this study,

further investigation will be required to establish the nature of this phenomenon.

During the first weeks of treatment, slit-lamp examination of cats 4–5 hr after daily treatment with 100 μg of PGE₂ and PGF_{2 α} showed no flare in the anterior chamber of the experimental eyes beyond that usually seen in untreated eyes or that seen in the contralateral eyes. Cells were not observed in the anterior chamber of either eye of these cats until day 100 when a single dose of 500 μg of PGE₂ rather than the usual 100 μg was applied resulting in extensive anterior chamber flare. From this point on, low-level flare in excess of that in the contralateral eyes was frequently seen, as were occasional cells in the anterior chamber.

It should be noted, however, that in addition to PGE₂ treatment, up to four tonometer readings, each preceded by the application of one drop of Alcaine, were taken on most days during the 9 months of treatment. While the contralateral control eyes were exposed to the same number of Alcaine doses and tonometry readings, the possibility cannot be ruled out that the development of flare, which was also observed occasionally in control eyes, was a result of a combination of factors, including the overdose of PGE₂ on day 100, the possible systemic effects of PGE₂ and the trauma caused by the tonometry. The main focus of this paper was the demonstration that PGs can maintain lowered IOP over a prolonged period without the development of tachyphylaxis or tolerance. Thus, in this particular set of experiments, tonometry took precedence, even though it clearly affected some other observations.

Systematic observation of flare and cells in the PGE₂-treated cats was not begun until day 160. From then to day 205, barely visible flare (+0.5) was noted in most of the control eyes, while most treated eyes showed a more readily noticeable flare (Fig. 3). Only occasionally was the cellular response in any of these eyes extensive enough to have been noticeable on routine examination (+1). At the same time, the IOP of these treated eyes was maintained at an average of 5 mmHg below that of the contralateral eyes (Fig. 3). When PGE₂ treatment, tonometer readings, and slit-lamp examinations were suspended for 72 hr (day 206 to 209), the flare in the experimental eyes was reduced to a level not statistically different from that of the control eyes; the mean cellular response was also reduced. However, by the end of the 72-hr suspension of treatment, the significant difference between the IOPs of the treated and control eyes was also abolished (Fig. 3). When daily treatments were continued but tonometry readings were suspended for 72 hr after day 213, the flare declined slightly and cells cleared from the anterior chamber of the treated eyes (Fig. 3). Tonometry was again suspended on day 220, resulting in a slight decrease in the flare and cell

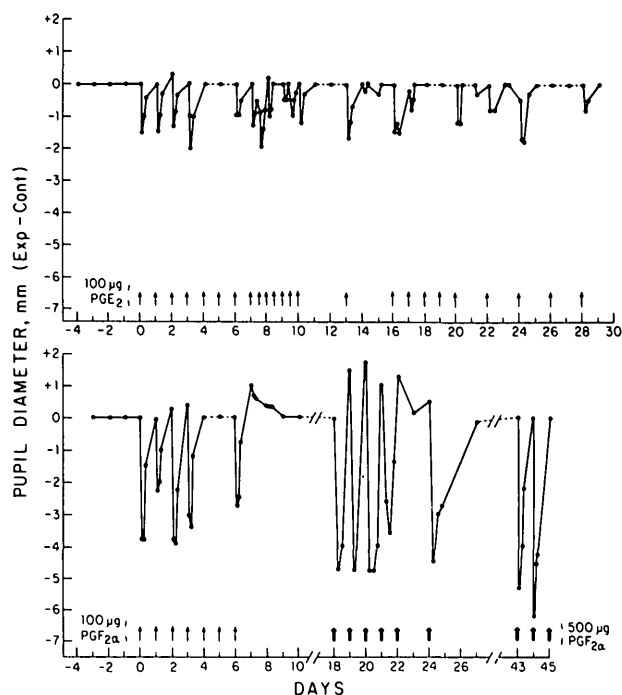


Fig. 7. The effect of topical application of PGE₂ (top panel) or PGF_{2 α} (bottom panel) on the mean pupillary diameter (naso-temporal) of cat eyes relative to that of the contralateral untreated eyes. (Points represent means; $n = 6$).

response. However, when the topical anesthetic used with the tonometry was instilled daily into both eyes of these cats, starting on day 223, there was a statistically significant increase in flare ($P < 0.05$) and in the cellular response ($P < 0.01$; Fig. 3). After each PGE₂ or PGF_{2 α} application, the cats tended to hold the lids of their treated eyes closed for variable periods. Because the vehicle solution for the PG was not adjusted to minimize discomfort, no attempt was made to quantify the lid-closure response.

The doses of PGF_{2 α} used produced only very slight miosis in rhesus monkeys. Neither the degree nor the duration of pupillary constriction after twice daily PGF_{2 α} application differed significantly from that obtained after a single dose of PGF_{2 α} .⁴ Only negligible flare occurred in the anterior chamber of experimental eyes. We cannot determine whether this slight, occasional flare was a direct effect of PGF_{2 α} or of self-inflicted trauma, since these animals almost invariably rub their eyes, even after the topical application of commercial ophthalmic drugs, as soon as the arm holes on their primate chairs are opened.¹¹

Discussion

The present results demonstrate that unlike rabbits, neither cats nor rhesus monkeys develop resistance to the ocular hypotensive effect of PGs during prolonged topical PG treatment. Although small fluctuations in the degree of ocular hypotension occurred during the 9-month PGE₂ treatment of cat eyes, it is

not clear whether these fluctuations reflect true variations in sensitivity of the eye to the hypotensive effects of this PG or simply fluctuations in the physiologic state of the animals. Clearly, in a study of such length, comparison of the IOP of a treated eye to its pretreatment baseline IOP value may be complicated by behavioral adaptation to the procedures, seasonal variations, or even aging. Comparison between the IOPs of the treated and control eyes may, on the other hand, be complicated by accidental contamination of the control eye, a problem especially difficult to avoid in primates, or by possible systemic effects of the topically applied agent.

The facts that our cats showed no ill effects at any time during the nine months of treatment and that all three of the female cats in the PGE₂ group conceived, gave birth to, and nursed healthy litters during this treatment clearly demonstrates that the doses of PGE₂ used did not have overtly toxic systemic effects. However, because ocular tissues have little or no capacity to inactivate or metabolize PGs^{1,12} and because some ocular tissues can, in fact, actively transport PGs from intraocular fluids to the circulation,^{13,14} much, and possibly all, of a topically applied PG must eventually enter the systemic circulation and may account for the decreased IOP and delayed miotic effects frequently observed in the contralateral eyes. It should be noted, however, that both of the PGs used here are actively removed from the circulation and are effectively metabolized by the lungs¹⁵; hence, their systemic distribution must be greatly limited.

Thus, while we cannot rule out the possibility that fluctuations in the ocular hypotensive efficacy of PGE₂ or PGF_{2α} may have occurred during long-term treatment, our data clearly show that neither tachyphylaxis nor progressive tolerance to the ocular hypotensive effects of PGE₂ or PGF_{2α} develops in cat eyes. Our more limited experiments on rhesus monkeys suggest that this conclusion is also applicable to the primate eye.

These conclusions, however, appear to conflict with previous reports on the development of tachyphylaxis to the ocular hypertensive effect of PGs in cats.⁶ These studies were, however, based on the intracameral injection into cannulated cat eyes of doses of PGs sufficient to cause a sharp rise in IOP and breakdown of the blood-ocular barrier and a second dose of PG was administered into these eyes before normal barrier function could recover. It should be noted that in our studies with rabbits, tolerance to the hypotensive effects of PGF_{2α} could not be overcome by doubling the PGF_{2α} dose from 5 μg to 10 μg/eye. Further increase in the dose would not have been feasible, since, in rabbits, a PG dose of 50 μg/eye causes a pronounced initial increase in IOP,

which is associated with a breakdown of the blood-ocular barrier.²

This extreme sensitivity of the rabbit eye to PG-induced breakdown of the blood-ocular barrier is not surprising, since the rabbit, compared to other vertebrates, is atypically prone to the development of an ocular irritative response that, at least in part, is mediated by PGs.^{7,8} Indeed, an inverse relationship appears to exist between the evolutionary development of the eyes of various vertebrate species and the severity of their acute ocular (PG-mediated) responses to irritation or trauma.⁸ Thus, information obtained from rabbits on the ocular effects of PGs and on other aspects of the irritative or inflammatory responses of the eye does not appear to be applicable to other species, particularly not to primates.

The present demonstration that tachyphylaxis to the hypotensive effect of PGs does not develop in cat or rhesus monkey eyes suggests that eicosanoids may constitute a potential new class of long-term hypotensive agents for the control of chronic glaucoma in humans. The task remains, however, to identify the stable PG or PG derivative that is best suited for topical delivery and that has the least local or systemic side-effects. Although some differences clearly exist even between the responses of carnivore and primate eyes to PGs, the cat can be regarded as a better animal model than the rabbit for the initial screening of PGs and PG analogues for their long-term ocular hypotensive efficacy in primates, presumably including humans.

Key words: cat, rhesus monkey, *Macaca mulatta*, rabbit, eye, prostaglandin, prostaglandin E₂, prostaglandin F_{2α}, ocular hypotension, intraocular pressure, glaucoma, pupillary constriction

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