

CLINICAL SCIENCE

Effect of non-steroidal anti-inflammatory ophthalmic solution on intraocular pressure reduction by latanoprost

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Br J Ophthalmol 2003;**87**:297–301

Aim: To investigate the effects of a non-steroidal anti-inflammatory drug (NSAID) ophthalmic solution on latanoprost induced intraocular pressure (IOP) reduction using normal volunteers.

Methods: This study was conducted as a prospective and observer masked clinical trial. 13 normal volunteers were enrolled. After measurement of basal IOP and ophthalmic examination, latanoprost ophthalmic solution was initially administered to both eyes once daily. Four weeks later, an NSAID ophthalmic solution, sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate (refer to bromfenac sodium hydrate), was co-administered to one randomly selected eye (NSAID group) twice daily for 2 weeks. The other eye was employed as a control (non-NSAID group). After withdrawal of the NSAID ophthalmic solution, latanoprost ophthalmic solution was continuously administered for another 2 weeks and was then withdrawn. After a 4 week washout, only bromfenac sodium hydrate ophthalmic solution was administered to the eyes of the NSAID group for 2 weeks. During the study period, ophthalmic examination, including IOP measurement was performed in an observer masked fashion.

Results: Before initiation of bromfenac sodium hydrate, baseline IOPs of the non-NSAID group and the NSAID group were 15.73 (SD 1.97) mm Hg and 15.86 (2.06) mm Hg, respectively ($p=0.88$). Although latanoprost ophthalmic solution significantly reduced IOP in both groups, co-administration of bromfenac sodium hydrate significantly inhibited latanoprost induced IOP reduction compared with the non-NSAID group. The IOPs of the non-NSAID and NSAID groups were 10.18 (1.17) mm Hg and 11.63 (1.35) mm Hg with a 2 week co-administration, respectively ($p < 0.01$). Withdrawal of bromfenac sodium hydrate ophthalmic solution diminished the difference between the two groups. Re-administration of bromfenac sodium ophthalmic solution only did not affect IOP.

Conclusion: These results indicate that NSAID ophthalmic solution may interfere with IOP reduction by latanoprost ophthalmic solution in normal volunteers and that we should take this into account when treating patients with glaucoma using latanoprost ophthalmic solution.

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Accepted for publication 17 September 2002

Latanoprost, a prostaglandin (PG) $F_{2\alpha}$ related compound, is now widely used as antiglaucoma ophthalmic solutions because of its efficacy in reducing intraocular pressure (IOP) with few side effects.¹⁻³ The mechanism by which latanoprost reduces IOP is considered to involve an increase in uveoscleral outflow by remodelling extracellular matrix (ECM) and/or the relaxation of ciliary muscle bundles.⁴⁻⁷ Although latanoprost has a high affinity for FP receptors, recent studies have revealed that latanoprost induces endogenous PGs including PGE₂ which could influence the ECM metabolism.⁸⁻⁹ Therefore, it is hypothesised that latanoprost ophthalmic solution may reduce IOP by either direct signal transduction through FP receptor and indirect action through induced endogenous PGs. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the induction of endogenous PGs through suppressing the activity of cyclo-oxygenases. Moreover, recent studies have shown that some NSAIDs also inhibit latanoprost induced endogenous PGs.⁸⁻¹⁰ Taken together, concomitantly used NSAIDs may influence IOP reduction by latanoprost ophthalmic solution. In this study, we applied sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate (referred to as bromfenac sodium hydrate) ophthalmic solution, one of the potent NSAIDs, in combination with latanoprost ophthalmic solution in order to investigate its influence on IOP reduction.

PATIENTS AND METHODS

This study was a prospective, observer masked clinical trial. All experiments were conducted in accordance with the Helsinki

treaty and written informed consent was obtained from all participants.

Subjects

Thirteen healthy adult Japanese volunteers were enrolled. All participants were male (age 34.9 (SD 5.3) years, range 27–44 years). Volunteers with the following conditions were eliminated from this study; those with a history or presence of any ocular and systemic disease, those routinely taking drugs, and those with a history of allergy to experimented ophthalmic solutions. All IOP measurements were performed at the same time by one observer (KK) using applanation tonometer with the same slit lamp. The observer was masked to all information regarding the administration of the tested ophthalmic solutions. The protocol is shown in Figure 1. In brief, visual acuity, routine slit lamp examination, and fundus observation were performed after obtaining the patient's informed consent (at week -2). The mean value from repeated IOP measurement at week -2 and week 0 was considered as a baseline IOP. This study was composed with two parts; in the first part the effects of NSAID ophthalmic solution on latanoprost induced IOP reduction was studied, and in the second part the effect of NSAID ophthalmic solution itself on IOP was studied.

Effects of NSAID ophthalmic solution on latanoprost induced IOP reduction

After measurement of baseline IOP, patients were given 0.005% latanoprost ophthalmic solution in both eyes just

Weeks	BL										
	-2	0	2	4	5	6	8	10	12	13	14
Informed consent	○										
IOP	○	○	○	○	○	○	○	○	○	○	○
VA	○				○			○	○		
Slitlamp examination	○	○	○	○	○	○	○	○	○	○	○
Fundus examination	○	○	○	○	○	○	○	○	○	○	○
latanoprost		←————→									
NSAID			←————→						←————→		

Figure 1 An experimental schedule. To determine baseline condition, examination was repeated more than twice a month. BL= baseline, VA= visual acuity, IOP = intraocular pressure, NSAID = non-steroidal anti-inflammatory drug.

before going to bed. Ophthalmic examination was performed 2 weeks and 4 weeks later.

Bromfenac sodium hydrate ophthalmic solution (Senju Pharmaceutical Co, Osaka, Japan), was then administered on randomly selected eyes just after breakfast and dinner. Eyes concomitantly given NSAID and latanoprost ophthalmic solutions were categorised as the NSAID group and the other eyes, which were given only latanoprost, were categorised as the non-NSAID group. Ophthalmic examination was performed every week for 2 weeks and only bromfenac sodium hydrate was withdrawn. Only latanoprost ophthalmic solution was continued for another 2 weeks and was withdrawn.

Effect of NSAID ophthalmic solution on IOP

After withdrawing the application of all ophthalmic solutions, all volunteers were followed up every 2 weeks for 4 weeks, and it was confirmed that their IOP had returned to its baseline level. Then, only bromfenac sodium hydrate ophthalmic solution was administered to the eyes of the NSAID group for 2 weeks and ophthalmic examination was repeated every week for 2 weeks.

Statistical analysis

The Wilcoxon signed rank test and Bonferroni's correction were used to compare IOP values, and the Spearman correlation coefficient by rank for correlation analysis was used to investigate the relation between latanoprost induced IOP reduction and NSAID related inhibitory effect. Significant differences were defined by $p < 0.05$. All data are expressed as the mean (SD).

RESULTS

Enrolled subjects

Out of 13 enrolled volunteers, two dropped out because of a latanoprost induced conjunctival hyperaemia. Therefore, 11 volunteers were subject to analysis. Their age was 33.6 (4.6) years (range 27–44 years), and their equivalent sphere refractive errors of the right eyes and left eyes were -2.38 (2.77) dioptres and -2.17 (2.57) dioptres, respectively. The corrected visual acuity of all participants was better than 20/20 and the cup to disc ratios of right eyes and left eyes were 0.31 (0.15) and 0.31 (0.16), respectively. No significant difference in all investigated parameters was observed between eyes in the NSAID group and those in the non-NSAID group.

Slit lamp and fundus examination

Before enrolment, all participants showed no abnormal signs in the anterior, medial, and fundus segments. After the initiation of latanoprost ophthalmic solution, three participants

showed a mild conjunctival hyperaemia and one showed mild corneal erosion. These mild adverse effects did not interfere with this study and had disappeared at the end of the study. Otherwise, slit lamp examination showed no signs of adverse effects including appearance of cells and elevation of flare in the anterior chamber. Throughout this study, all participants maintained good visual acuity and a consistent cup to disc ratio. Pupil diameter showed the same size throughout this study. Only two volunteers forgot to administer latanoprost ophthalmic solution once before initiating an additional application of bromfenac sodium hydrate ophthalmic solution. Otherwise, they complied faithfully with the regimen throughout the study.

Effects of bromfenac sodium hydrate ophthalmic solution on IOP reduction (Fig 2)

Latanoprost ophthalmic solution significantly reduced IOP beyond a 2 week administration. All latanoprost treated eyes regardless of the concomitant use of bromfenac sodium hydrate ophthalmic solution had significantly reduce IOP in comparison with the baseline IOP. Latanoprost treated eyes maintained a significantly sub-baseline IOP 2 weeks after withdrawal of latanoprost ophthalmic solution (week 10). It took 4 weeks to return to the baseline IOP after withdraw of latanoprost ophthalmic solution. Although both groups showed a very similar IOP profile until the initial application

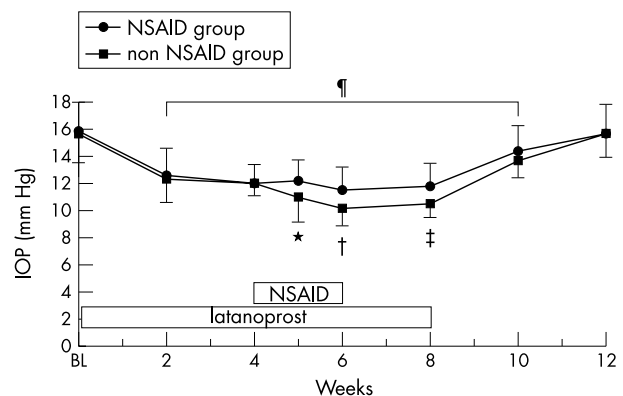


Figure 2 IOP profile during the current study. BL= baseline, NSAID = non-steroidal anti-inflammatory drug, IOP = intraocular pressure, bar = standard deviation, * $p = 0.0$, † $p < 0.01$, and ‡ $p = 0.04$ between NSAID group and non-NSAID group, ¶ $p < 0.01$ v BL. The Bonferroni's correction, Wilcoxon signed rank test, and Mann-Whitney U test were employed.

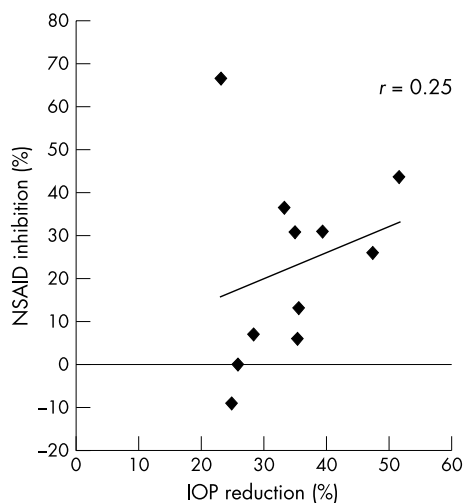


Figure 3 Relation between latanoprost induced IOP reduction and the inhibitory effect of bromfenac sodium hydrate. The Spearman correlation coefficient by rank was employed for statistical analysis. NSAID = non-steroidal anti-inflammatory drug, IOP = intraocular pressure.

of the NSAID ophthalmic solution, their IOP profile differed following the initial administration of the solution (week 4). At week 5, the IOPs of the non-NSAID and NSAID groups were 11.09 (1.70) mm Hg and 12.27 (1.34), respectively ($p=0.06$), and at week 6, the IOPs of the non-NSAID and NSAID groups were 10.18 (1.17) mm Hg and 11.63 (1.35) mm Hg, respectively ($p < 0.01$). The difference in IOP between two groups was still observable even after bromfenac sodium hydrate ophthalmic solution had been withdrawn for 2 weeks ($p=0.04$). The maximum difference between two groups was 1.45 mm Hg (14.3%) at week 6. The NSAID group and the non-NSAID group showed constantly reduced IOPs that reached their lowest level at week 6, although no significant difference was observed between IOPs at week 6 and week 8 in both groups. Withdrawal of bromfenac sodium hydrate did not result in further IOP reduction in the NSAID group. The degree of IOP reduction by latanoprost varied widely depending on the subject. The IOP reduction range of the non-NSAID group was 51.5% to 23.1%, while that of the NSAID group was 35.0% to 7.3% at week 6.

Relation between IOP reduction and inhibitory effect of bromfenac sodium hydrate (Fig 3)

The inhibitory effect of bromfenac sodium hydrate on latanoprost induced IOP reduction somewhat correlated with the reduction's magnitude, although their correlation coefficient was low at week 6 ($r=0.25$, $p=0.45$). The maximum inhibitory effect was 66.7%, while four subjects showed inhibitions of less than 10% at week 6.

Effects of bromfenac sodium hydrate on IOP

The 2 week administration of bromfenac sodium hydrate ophthalmic solution itself did not change the IOP level. Before administration of bromfenac sodium hydrate ophthalmic solution at week 12, the IOPs of treated eyes and the paired control eyes were 15.71 (1.60) mm Hg and 15.71 (2.06) mm Hg, respectively. The IOP difference in eyes treated by bromfenac sodium hydrate ophthalmic solution was 0.5 (1.26) mm Hg compared with the baseline IOP ($p=0.82$), and that between treated eyes and the paired control eyes was 0.18 (0.84) mm Hg ($p=0.72$).

DISCUSSION

In the current study, latanoprost significantly reduced IOP even in normal volunteers as has been reported earlier.^{11 12}

Although in the present study two volunteers stopped the administration of latanoprost ophthalmic solution, their conjunctival hyperaemia and corneal erosion were not severe and disappeared immediately after withdrawal of the solution. We did not detect any side effects except for these throughout this study. Visual acuity, pupil diameter, and fundus appearance showed no change as has been similarly reported in many previous studies.^{3 13-16}

Although the IOP reducing mechanism of latanoprost is not fully understood, several studies indicated that latanoprost increases outflow facility through the uveoscleral outflow by either the remodelling of ECM in ciliary muscle and/or the relaxation of ciliary muscle bundles.⁴⁻⁷ We have already reported that latanoprost increases matrix metalloproteinase (MMP) activities in ciliary smooth muscle cells^{7 17} and we hypothesised that the activation of MMPs enhances the remodelling ECM in ciliary muscle bundles. It has been reported that several types of PGs as well as latanoprost increase MMP activity.^{7 18-20} Although PGE₂ transiently elevated IOP,²¹ several reports have shown that PGs including endogenous PGs induced by latanoprost reduce IOP.²²⁻²⁵ NSAID suppresses production of endogenous PGs through the inhibition of cyclo-oxygenase activity. We have reported that endogenous PGE₂ induced by latanoprost was inhibited by indomethacin, one of the more potent NSAIDs.¹⁰ The current study showed that bromfenac sodium hydrate inhibits latanoprost induced IOP reduction in normal volunteers. Taken together, we hypothesise that latanoprost reduces IOP at least in part by endogenously induced PGs in addition to the direct stimulation of FP receptor, and that this indirect IOP reducing action may be inhibited by NSAID. Since, however, latanoprost does not reach the maximum IOP reduction with a 4 week administration, the current results simply mean that bromfenac sodium hydrate inhibits further IOP reduction by latanoprost.

The inhibitory effect of bromfenac sodium hydrate on latanoprost induced IOP reduction continued after the withdrawal of bromfenac sodium hydrate administration. Based on an experiment involving albino rabbits' eyes, Isaka *et al* reported that metabolic intraocular bromfenac sodium hydrate could not be detected in any portions of the eye except for the lens later than 72 hours after administration. It is not clear why inhibition of latanoprost induced IOP reduction remained for more than 2 weeks after withdrawal. Further investigation is necessary to answer this question.

Recently, Sponcel *et al* have reported that indomethacin suppressed brimonidine induced IOP reduction, and they hypothesised that endogenous PGs induced by brimonidine may be partly involved in brimonidine's reduction of IOP.²⁶ They did not show the direct effect of indomethacin on latanoprost induced IOP reduction. There are several points of difference between Sponcel's study and the current study. First of all, their main purpose was to assess the effect of an oral nonsteroidal anti-inflammatory drug on the hypotensive actions of latanoprost and brimonidine. Therefore, their results failed to show the effect of indomethacin on only latanoprost induced IOP reduction. They administered indomethacin systemically, and the duration of latanoprost treatment before the initiation of indomethacin treatment was only 1 week. Moreover, the inhibiting potentials of endogenous PGs are different between indomethacin and bromfenac sodium hydrate. Therefore, we cannot simply apply their results to ours, though their study does indicate that NSAID could influence IOP reduction through the biosynthesis process of endogenous PGs. Bromfenac sodium hydrate is a potent inhibitor of cyclo-oxygenase activity and has a better penetration inside the eye. Bromfenac sodium hydrate inhibited the production of prostaglandins from rabbit iris-ciliary body 3.8 and 10.9 times more potently than did indomethacin and pranoprofen, respectively²⁷ and showed no effect on IOP.²⁸

To minimise intentional and unintentional interposition on the results, we employed a prospective, randomised, and

observer masked trial. Therefore, we consider that the current results are highly reliable. We administered NSAID ophthalmic solution to randomly selected eyes, while the other eyes did not receive the vehicle ophthalmic solutions. Benzalkonium chloride has been reported to induce endogenous PGs,^{29,30} which could influence the results. Since, however, the vehicle of bromfenac sodium hydrate ophthalmic solution contains 0.005% benzalkonium chloride like most other ophthalmic solutions, the effect of benzalkonium chloride in bromfenac sodium hydrate ophthalmic solution may be minor. No report shows that bromfenac sodium hydrate influences IOP, and the current study confirmed that bromfenac sodium hydrate itself did not influence IOP.

The IOP level of normal volunteers is relatively low, and insufficient duration of administration could result in insufficient IOP reduction. Since it has been reported that latanoprost needs more than 1 month to stabilise the IOP level^{14,15} we administered latanoprost for 4 weeks before the application of bromfenac sodium hydrate ophthalmic solution in the current study.

Although latanoprost is the most potent ophthalmic solution among antiglaucoma ophthalmic solutions for reducing IOP, it has been reported that the incidence of non-response cases against latanoprost treatment is higher than that of other antiglaucoma ophthalmic solutions.³¹ The variation of IOP reduction in the current cases was relatively large. Maximum and minimum latanoprost induced IOP reductions in the current subjects were 51.6% and 23.1%, respectively. The current study indicated that the magnitude of latanoprost induced IOP reduction showed a positive correlation with the inhibitory effect of bromfenac sodium hydrate, although this relation was not significant. These results indicate that latanoprost induced endogenous PG may be involved in IOP reduction and may have a role, at least in part, in the mechanism of individual difference in response to latanoprost. Further investigation for clarifying the mechanism of individual difference and correlation in response to latanoprost and NSAID is necessary.

The inhibitory effect of bromfenac sodium hydrate ophthalmic solution was 1.45 mm Hg (14.3%) by 2 week administration. It is unclear whether or not this inhibition is clinically important. Although we determined the inhibitory effect of bromfenac sodium hydrate on latanoprost induced IOP reduction, latanoprost is still an effective antiglaucoma ophthalmic solution, because latanoprost administered with bromfenac sodium hydrate still reduced IOP by 26.6% at week 6 from the baseline. Since we employed normal volunteers in the current study, further study using glaucoma patients should be necessary to confirm the inhibitory effect of NSAID on IOP reduction.

The current results suggest many important points. When we administer NSAID to patients with glaucoma treated with latanoprost, we should take into consideration the NSAID related inhibition of IOP reduction. Recent studies have reported that latanoprost induced several specific adverse effects, including iridial pigmentation,³²⁻³⁴ recurrence of uveitis,^{35,36} and onset of cystoid macular oedema (CMO).³⁶⁻³⁹ The mechanisms of these adverse effects are not clear. It is possible that endogenous PGs induced by latanoprost may be partially involved in these adverse effects. Therefore, the administration of NSAID may alleviate these side effects. Indeed, we had a patient who developed CMO after the initiation of treatment with latanoprost ophthalmic solution, and the administration of indomethacin seemed to be effective to improve CMO.⁴⁰ Miyake *et al* have reported that coadministration of topical NSAID, diclofenac sodium ophthalmic solution, effectively suppressed the occurrence of postoperative CMO.⁴¹ Taken together, the systematic or topical application of NSAID may be effective for improving or preventing adverse effects caused by latanoprost ophthalmic solution.

Isopropyl unoprostone is another PG related antiglaucoma compound, and we have reported that this compound also

induces endogenous PGE₂.¹⁰ Since isopropyl unoprostone did not sufficiently reduce IOP of normal volunteers, it is necessary to determine whether NSAID inhibits isopropyl unoprostone induced IOP reduction in an investigation using glaucoma patients with high IOP.

ACKNOWLEDGEMENTS

This study was supported in part by grant No 11307036 from the Japanese Ministry of Education, Culture, Sports, Science and Technology to Dr K Kashiwagi.

Proprietary interest: none.

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Br J Ophthalmol 2003 87: 297-301

doi: 10.1136/bjo.87.3.297

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