Effect of indomethacin in preventing surgically induced miosis

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SUMMARY A double-blind study was performed on 64 patients to assess the effect of preoperative indomethacin in comparison with a placebo in preventing surgically induced miosis during extracapsular cataract extraction. One drop of indomethacin or placebo was instilled at 7.00 p.m. and at 9.00 p.m. the night before surgery and 2 hours, 1 hour, and 15 minutes preoperatively. The pupil diameter was recorded at different stages of the operation. It was found that indomethacin as compared with the placebo significantly reduced the amount of pupil constriction during the operation, making the removal of lens material and the implantation of an intraocular lens easier. The indomethacin is thought to act by inhibiting prostaglandin synthesis caused by iris trauma during surgery.

Miosis induced by surgical trauma is a frequent problem during extracapsular cataract surgery. In spite of vigorous preoperative dilatation with both anticholinergic and sympathicomimetic agents the pupil constricts during the operation. The removal of lens material and the implantation of an intraocular lens in the posterior capsule sac are hampered by this pupil constriction.

There is strong evidence that prostaglandins are at least partially responsible for this miosis. From experimental studies it was found that the miosis could be reduced by treatment with prostaglandin synthetase inhibitors. Indomethacin is one of the nonsteroidal anti-inflammatory agents that has been found to block the synthesis of prostaglandins in various systems.¹⁻⁴

A double-blind study was performed to define clinically the effect of preoperative treatment with indomethacin 0.5% aqueous solution in comparison with a placebo in preventing surgically induced miosis during extracapsular cataract surgery.

Patients and methods

Sixty-four patients underwent extracapsular lens extraction because of senile cataract. They were randomly assigned to the indomethacin or the control

group. Their ages ranged from 43 to 87 years, mean 71 years. There was no statistically significant difference between the 2 groups in sex and age distribution. All the patients were healthy, with no history of ocular disease other than cataract. We excluded one patient from our study who had a rupture of the posterior lens capsule, so that the study finally comprised 63 patients.

Surgical procedure. The operation was carried out under general anaesthesia by 2 of the authors (RdeL; vR), using the same operating technique. After a corneoscleral incision the eye was entered at the 12 o'clock position and the anterior capsule was opened. The wound was enlarged with Troutman's corneoscleral scissors, and the lens nucleus was expressed. The lens cortical remnants were removed by irrigation and aspiration.

Medications. Indomethacin powder was dissolved in a solution of polyvinylpyrrolidone and sodium phosphate H_2O_2 in aqua conservans (0.1% sodium EDTA and 0.01% benzalkonium chloridum) in a concentration of 0.5%. For the control group the vehicle without the indomethacin was used.

Either indomethacin or placebo eyedrops were instilled at 7.00 p.m. and 9.00 p.m. the night preceding surgery and 3 times on the day of surgery—2 hours, 1 hour, and 15 minutes preoperatively. Mydriasis was achieved by instillation of eye drops containing tropicamide 0.5% with phenylephrine 5%

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at 1 hour, 45 minutes, and 30 minutes preoperatively.

Observations. The diameter of the pupil was measured to 0.5 mm under the operation microscope with a calliper. Recordings were made at the beginning of the operation, after capsulotomy, after expression of the lens nucleus, and at the end of the irrigation and aspiration period. The corneal diameter, colour of the iris, and duration of the operation were also recorded.

Results

From the data it was calculated that there was no statistical difference in the pupil diameter between the 2 groups at the beginning of the operation; the mean pupil diameter of the indomethacin group was 8.0 mm and of the control group 7.8 mm. The relevant results are given in Fig. 1.

Fig. 1 Surgically induced miosis in the indomethacin group (mean 2.44 mm) and in the placebo group (mean 3.12 mm). n = Percentage of total number of patients.

The pupillary constriction during the operation from the beginning of the operation up to the end of the irrigation and aspiration was less in the indomethacin pretreated group (mean pupillary constriction 2.4 mm) than in the control group (mean 3.1 mm) ($p < 0.01$). The statistical evaluation of these results was by Student's *t* and the Yates-Cochran test. A comparison of the data obtained at the various stages of the operation showed that the greatest difference in mean pupillary constriction between the 2 groups was after expression of the lens nucleus (Fig. 2).

In this study we had to contend with factors that might possibly influence the results. Sometimes it was not possible to start the operation exactly at the scheduled time because of delay of preceding operations or changes in the operation schedule. These factors could be excluded, as no significant difference (Wilcoxon test) between the indomethacin and con-

trol groups was found in relation to delay or length of the operation. Nor did we find any difference in pupil constriction in relation to different iris colours.

mean pupillary constriction (mm)

Fig. 2 Mean pupillary constriction in the indomethacin group (solid line) and the placebo group (dashed line) at the different stages of the operation: (I) after capsulotomy; (II) after expression of the lens nucleus; (III) after removal of the lens material.

Discussion

In this double-blind study the preoperative treatment with topical indomethacin, compared with a placebo, significantly inhibited miosis during extracapsular surgery. It is well established that prostaglandins are synthesised in the iris and ciliary body in response to trauma to the anterior segment of the eye, particularly to the iris.⁵⁻⁸ Prostaglandins thus released give rise to so-called irritative ocular responses, which embrace miosis, rise of intraocular pressure, and disruption of the blood-aqueous barrier with a rise in aqueous protein concentration.⁹⁻¹³ From experimental studies it was found that these effects could be suppressed by treatment with prostaglandin synthetase inhibitors.^{1,3,8,9,12,14,15}

In the human eye it has also been reported that prostaglandins are synthesised during cataract surgery.¹⁶ Prostaglandin synthetase inhibitors were

found to be effective in suppressing the ocular irritative responses during soft-cataract aspiration¹⁷ and the postoperative inflammatory reactions.¹⁶⁻²¹ The present results support the hypothesis that prostaglandins are indeed partly responsible for the surgically induced miosis during cataract surgery. It was possible to inhibit the miosis by pretreatment with indomethacin 0.5% aqueous solution.

Indomethacin inhibits prostaglandin synthesis but cannot antagonise its effects. It is therefore necessary to achieve an effective intraocular concentration at the time of surgery. Compared with the effect of placebo in the control group the effect of indomethacin pretreatment became most obvious after the expression of the lens nucleus. This observation can be explained by the irritation of the iris during this procedure, which gives rise to the synthesis of prostaglandins. The mean difference (0.8 mm) in pupillary constriction between the 2 groups of patients constitutes a widening of the operation field, making removal of lens materials and implantation of an intraocular lens easier, thereby also reducing per- and postoperative complications.

References

- Bhattacharjee P, Eakins KE. A comparison of the inhibitory activity of compounds on ocular prostaglandin biosynthesis. *Invest Ophthalmol Visual Sci* 1974; **13**: 967-72.
- Katz IM. Pharmacology of ocular drugs: indomethacin. *Ophthalmology* 1981; **88**: 455-8.
- Podos SM, Becker B. Comparison of ocular prostaglandin synthesis inhibitors. *Invest Ophthalmol Visual Sci* 1976; **15**: 841-44.
- Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature* 1971; **231**: 232.
- Ambache N, Kavanagh L, Whiting J. Effect of mechanical stimulation on rabbits' eyes, release of active substances in anterior chamber perfusates. *J Physiol* 1964; **176**: 378.
- Ambache N, Brummer HC. A simple chemical procedure for distinguishing E from F prostaglandins with application to tissue extracts. *Br J Pharmacol Chemother* 1968; **33**: 162.
- Angaard E, Samuelsson B. Smooth muscle stimulating lipid in sheep iris. *Biochem Pharmacol* 1964; **13**: 281.
- Bhattacharjee P, Eakins KE. Inhibition of the prostaglandin synthetase systems in ocular tissues by indomethacin. *Br J Pharmacol* 1974; **50**: 227-30.
- Cole DF, Unger WG. Prostaglandins as mediators for the responses of the eye to trauma. *Exp Eye Res* 1973; **17**: 357-68.
- Eakins KE. Prostaglandin and non-prostaglandin mediated breakdown of the blood-aqueous barrier. *Exp Eye Res* 1977; suppl: 483-98.
- Neufeld AH, Sears ML. Prostaglandin and eye. *Prostaglandin* 1973; **4**: 157-75.
- Podos SM, Becker B, Kass MA. Prostaglandin synthesis, inhibition and intraocular pressure. *Invest Ophthalmol Visual Sci* 1973; **12**: 426-33.
- Waitzman MB, King CD. Prostaglandin influences on intraocular pressure and pupil size. *Am J Physiol* 1967; **212**: 329-34.
- Klug RD, Krohn DL, Breitfeller MJ, Dieterich D. Inhibition of trauma-induced miosis by indoxole. *Ophthalmic Res* 1981; **13**: 122-8.
- Neufeld AH, Jampol LM, Sears ML. Aspirin prevents the disruption of the blood-aqueous barrier in the rabbit eye. *Nature* 1972; **238**: 158.
- Miyake K, Sugiyama S, Norimatsu I, Ozawa T. Prevention of cystoid macular edema after lens extraction by topical indomethacin (III) Radioimmunoassay measurement of prostaglandins in the aqueous during and after lens extraction procedure. *Albrecht von Graefes Arch Klin Ophthalmol* 1978; **209**: 83-8.
- Sawa M, Masura K. Topical indomethacin in soft cataract aspiration. *Jpn J Ophthalmol* 1976; **20**: 514-9.
- Araie M, Sawa M, Takase M. Effect of topical indomethacin on the blood-aqueous barrier after intracapsular extraction of senile cataract—a fluorophotometric study. *Jpn J Ophthalmol* 1981; **25**: 237-47.
- Miyake K, Sakumura S, Miura H. Long-term follow-up study on prevention of aphakic cystoid macular edema by topical indomethacin. *Br J Ophthalmol* 1980; **64**: 324-8.
- Mochizuki M, Sawa M, Maruda K. Topical indomethacin in intracapsular extraction of senile cataract. *Jpn J Ophthalmol* 1977; **21**: 215-26.
- Zimmermann TJ, Gravenstein N, Sugar A, Kaufman HE. Aspirin stabilization of the blood-aqueous barrier in the human eye. *Am J Ophthalmol* 1975; **79**: 817-9.