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Effect of Sodium Naproxen on Inflammatory Response Induced by Anterior Chamber Paracentesis in the Rabbit

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Abstract

This study evaluated the effect of sodium naproxen (a reversible competitive inhibitor of cyclo-oxygenase) and phenylephrine (a mydriatic α-adrenergic agent) eye drops in maintaining atropine mydriasis in the rabbit after paracentesis. Moreover, to assess the influence of these treatments on vascular and cellular inflammatory responses in the rabbit eye, several biochemical parameters were considered.

Anterior chamber paracentesis significantly reduced atropine-induced mydriasis and a parallel elevation of proteins, polymorphonuclear leucocytes (PMNs), prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4) levels in the secondary aqueous humour (obtained 120 min later) was observed. A significant increase in PMNs in the aqueous humour and a parallel increase in myeloperoxidase activity, a measure of PMN infiltration, in the iris-ciliary body were detected. Atropine-induced mydriasis was maintained in rabbits treated with either sodium naproxen or phenylephrine eye drops. However, only in the former group were the inflammatory parameters significantly reduced, with the exception of aqueous LTB_4 levels.

The inhibition of the protein influx in the aqueous humour and of the miosis produced by sodium naproxen can be related to the high drug levels in the aqueous humour that were effective in inhibiting the cyclo-oxygenase pathway of arachidonic acid metabolism, whereas the effects on PMN infiltration appear to be independent of significant release of the potent chemotactic agent LTB_4, synthesized via the 5-lipoxygenase pathway.

Surgical or mechanical trauma of the anterior segment of the eye induces a vascular inflammatory reaction due to the disruption of the blood-aqueous barrier with a marked rise in protein content of the aqueous humour, a transient ocular hypertension and miosis (Kulkarni & Srinvasan 1987). Aqueous levels of endogenously released prostaglandins (PGs) and leukotrienes (LTs) are elevated in different experimental models of ocular inflammation (Kulkarni & Srinvasan 1987; Latur et al 1989; Csukas et al 1990). Leukotriene B_4 (LTB_4), one of the most potent chemotactic and chemokinetic agents synthesized by the 5-lipoxygenase pathway (Steele et al 1984), causes an influx of polymorphonuclear leucocytes (PMNs) in the aqueous humour (Paterson et al 1984; Bhattacherjee & Paterson 1990). Intraocular or topical administration of prostaglandin E_2 (PGE_2), among the most investigated cyclo-oxygenase products, on the other hand, disrupts the blood-aqueous barrier (Stjernschantz 1984). It has been suggested that miosis induced by paracentesis of the anterior chamber in the rabbit may be, in part, a PGE_2-mediated process (Stjernschantz 1984; Kulkarni & Srinvasan 1987). These considerations are important since miosis is a frequent problem during extracapsular cataract surgery, despite the instillation of topical mydriatic agents (Keates & McGowan 1984; Stark et al 1986; Gimbel 1989). Moreover, the prevention and release of inflammatory mediators in the anterior segment of the eye may prove to be useful in reducing the post operative term after intraocular surgery. Non-steroidal anti-inflammatory drugs (NSAIDs) may prevent pupillary constriction and other signs of ocular inflammation in experimental paracentesis (Kulkarni & Srinvasan 1987; Latur et al 1989), as well as miosis during intraocular surgery (Keates & McGowan 1984; Stark et al 1986; 1989), possibly by inhibiting the enzyme cyclo-oxygenase which converts arachidonic acid into PGs and thromboxanes. Recently, we have observed (Spampinato et al 1991) that topical sodium naproxen, a NSAID widely used in clinical practice (Todd & Clissod 1990), reduces a number of inflammatory responses produced by sodium arachidonate in the rabbit eye.

The aim of this study was to evaluate the effects of eye drops containing sodium naproxen (a reversible competitive inhibitor of cyclo-oxygenase) in maintaining atropine mydriasis in the rabbit after paracentesis. The activity was compared to that of phenylephrine, a mydriatic α-adrenergic agent widely adopted in clinical practice (Keates & McGowan 1984; Stark et al 1986). To evaluate the influence of these treatments on vascular and cellular inflammatory responses in the rabbit eye, several biochemical parameters were considered.

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Materials and Methods

Animals

Female New Zealand albino rabbits (Charles River, Calco, Italy), 1·8–2·2 kg, free of any signs of ocular inflammation or gross abnormality were used. Animal procedures conformed to the ARVO (Association for Research in Vision and Ophthalmology) resolution on the use of animals in research.

Treatment schedule

Naproxen sodium salt (Secifarma, Milano, Italy) was dissolved in an isotonic, viscosized, buffered solution (vehicle) at a concentration of 0·5% (w/v). Sodium naproxen eye drops or the vehicle alone were instilled (50 μL) into the conjunctival sac 180, 120, 90 and 30 min before the first paracentesis; then immediately after this and 15, 75 and 90 min later. Ninety minutes before the first paracentesis, rabbits were treated with 1% atropine sulphate (Allergan, Pomezia-Roma, Italy) instilled in both eyes (50 μL/eye). One group of rabbits was treated with sodium naproxen and one with the vehicle solution in accordance with the above schedule. Moreover, one other group received 1% atropine plus 2·5% phenylephrine (Allergan, Pomezia-Roma, Italy), 90 min before the first paracentesis. To perform the first paracentesis the rabbits were lightly anaesthetized by intravenous injection of 20 mg kg^{-1} of ketamine HCl (Parke-Davis, Milano, Italy). One drop of a local anaesthetic (0·4% oxybuprocaine) was instilled into the conjunctival sac and 50 μL aqueous humour were collected. In preliminary experiments, sodium naproxen eye drops, administered according to the treatment schedule mentioned, had not altered the pupillary diameter for up to 6 h after the last instillation (data not shown). Moreover, in a separate experiment it was ascertained that atropine produced maximal mydriasis 15–30 min after instillation and no change was observed 6 h after the treatment (data not shown). The pupil diameter was measured with a Castroviejo caliper (Stark et al 1986) 180 min and 5 min before the first paracentesis and 5 min before the animals were killed. The rabbits were killed by intravenous injection of 0·3 mL kg^{-1} Tanax (Hoechst AG, Frankfurt am Main, Germany) 2 h after the first paracentesis and about 50 μL aqueous humour was withdrawn (secondary aqueous humour).

Sample collection and handling

Anterior chamber paracentesis was performed with a 26-gauge needle attached to a tubercolin syringe; the needle was introduced into the anterior chamber through the cornea, taking care not to damage the iris, the lens and the anterior uvea; all eyes were carefully examined using a slit lamp every 60 min thereafter. About 50 μL aqueous humour was removed (primary aqueous humour). PGE_2 and LTB_4 in aqueous humour samples were analysed by radioimmunoassay using two commercial kits (the kit for PGE_2 was purchased from Du Pont, NEN Division, Dreieich, Germany; the kit for LTB_4 was purchased from Amersham, Milano, Italy). In preliminary experiments it was ascertained that the presence of proteins in the aqueous humour could affect accurate RIA determinations of LTB_4. Therefore, samples of aqueous humour used for the assay of LTB_4 were processed as described by Csukas et al (1990) in order to extract the eicosanoid products.

Protein was assayed by the method of Lowry et al (1951) and PMNs were counted using an improved Neubauer chamber. The infiltration of PMNs in the anterior chamber, was also measured by myeloperoxidase activity. After the rabbits were killed, the aqueous humour was collected and the iris-ciliary body and cornea were carefully excised, placed in individual polypropylene tubes and processed for myeloperoxidase activity analysis (Williams et al 1983).

Aqueous levels of sodium naproxen were detected by high-performance liquid chromatography (HPLC) after pretreatment (first paracentesis) and 2 h later (second paracentesis). HPLC was carried out using a solvent delivery pump (Varian Star 9010), a variable UV-vis detector (Varian Star 9050) and an integrator (Varian 4400). Twenty microlitres of aqueous samples was treated with an equivalent volume of 2% $ZnSO_4 \cdot 7H_2O$ solution in methanol:water (50:50) containing an appropriate amount of the internal standard (vale-rophenone, Aldrich Chemical Company, Milwaukee, WI, USA) in order to deproteinize the aqueous. This mixture was vortexed, centrifuged, filtered (0·20 μm Teflon membrane) and 10 μL was analysed by HPLC. The recovery efficiency from blank rabbit aqueous humour to which had been added 30 and 5 $\mu g\ mL^{-1}$ sodium naproxen standard was 96·35 ± 4·50 and 94·50 ± 6·20%, respectively. A reverse-phase column (Hypersil ODS 5 μm; 150 mm × 4·6 mm i.d., obtained from Alltech (Milano, Italy) equipped with a direct-connect guard column was used in conjunction with the HPLC apparatus described above. The HPLC conditions were as follows: mobile phase, CH_3OH:H_3PO_4 0·05 M, 60:40; flow rate 1 mL min^{-1}; detection wave-length 272 nm. The sensitivity of the assay was determined by analysing progressively lower concentrations and was found to be 60 ng mL^{-1} for a signal-to-noise ratio of 3:1. No interfering peaks were observed in the blank aqueous humour chromatograms.

Statistical analysis

Results are expressed as the mean ± s.e. After analysis of variance, Student's *t*-test was used to establish the significance of the differences between mean values. $P < 0.05$ was considered statistically significant.

Results

Rabbits treated with atropine or with atropine and sodium naproxen displayed a superimposable mydriasis 90 min after the instillation of atropine, whereas pupil dilation was significantly greater in rabbits treated with atropine plus phenylephrine ($P < 0.01$ vs the group treated with atropine, Table 1). Mydriasis induced by atropine alone was not maintained in rabbits treated with the vehicle of sodium naproxen eye drops 120 min after anterior chamber paracentesis. In fact, the pupil size was significantly lower than at 5 min before trauma and even lower than the basal value. Mydriasis produced by atropine, however, was maintained in rabbits treated with sodium naproxen eye drops, in spite of paracentesis. However, in the phenylephrine group a small but significant pupil diameter reduction (evaluated 120 min after paracentesis) was observed in comparison with the value taken 5 min before trauma. Protein concentration in secondary aqueous humour taken 120 min after trauma was significantly higher than in the primary sample obtained during the first paracentesis (Table 1). Protein levels were significantly lower in secondary aqueous humour from rabbits treated with atropine plus sodium naproxen eye drops than the other two groups, which had comparable protein increases. A similar profile was observed as regards aqueous PGE_2 levels and the number of PMNs (Table 1). A significant increase in myeloperox-

Table 1. The effect of atropine plus sodium naproxen, atropine and atropine plus phenylephrine on pupil diameter, protein, PGE_2, LTB_4, PMNs aqueous levels and myeloperoxidase activity. All values expressed as mean ± s.e.

	Naproxen plus atropine	Atropine	Atropine plus phenylephrine
Pupil diameter (mm) n = 10			
180 min before paracentesis	6·20 ± 0·35	6·30 ± 0·15	6·20 ± 0·10
5 min before paracentesis	7·50 ± 0·20[a]	7·60 ± 0·20[a]	8·80 ± 0·20[b c]
120 min after paracentesis	7·40 ± 0·15[e]	5·90 ± 0·15[d e]	7·60 ± 0·25[d f]
Aqueous protein levels (mg mL^{-1}) n = 6–8			
Primary paracentesis	0·5 ± 0·01	0·8 ± 0·01	0·5 ± 0·01
Secondary paracentesis	15·0 ± 1·00[g]	35·0 ± 2·20	33·5 ± 4·10
Aqueous PGE_2 levels (ng mL^{-1}) n = 6–8			
Primary paracentesis	0·10 ± 0·01	0·08 ± 0·015	0·12 ± 0·012
Secondary paracentesis	1·80 ± 0·20[g]	3·90 ± 0·100	4·10 ± 0·100
Aqueous LTB_4 levels (ng mL^{-1}) n = 6–8			
Primary paracentesis	0·90 ± 0·10	0·85 ± 0·08	0·95 ± 0·10
Secondary paracentesis	1·50 ± 0·06[h]	1·90 ± 0·07[h]	1·75 ± 0·05[h]
Aqueous PMNs levels (PMNs mm^3) n = 6–8			
Primary paracentesis	5·00 ± 0·36	4·30 ± 0·610	4·80 ± 0·30
Secondary paracentesis	400 ± 130[g]	1800 ± 350	1750 ± 360
Myeloperoxidase activity			
120 min after paracentesis (units MPO mg^{-1} tissue) n = 6–8			
Cornea	0·009 ± 0·001	0·010 ± 0·001	0·013 ± 0·011
Iris-ciliary body	0·041 ± 0·009[g]	0·130 ± 0·012	0·120 ± 0·011

[a] $P < 0·005$, [b] $P < 0·001$ vs the respective values measured 180 min before paracentesis; [c] $P < 0·001$ vs the group treated with atropine; [d] $P < 0·05$ vs the respective value measured 5 min before paracentesis; [e] $P < 0·01$ vs the respective value measured 180 min before paracentesis; [f] $P < 0·01$ vs the group treated with atropine; [g] $P < 0·01$ vs the group treated with atropine or atropine plus phenylephrine; [h] $P < 0·02$ vs the respective value measured in primary aqueous humour samples.

idase activity was found, 120 min after paracentesis, in the iris-ciliary body of the rabbits treated with atropine plus the vehicle of sodium naproxen eye drops or plus phenylephrine in comparison with a control group of rabbits not subjected to trauma (0·13 ± 0·018 and 0·12 ± 0·011 vs 0·034 ± 0·005 units myeloperoxidase (mg tissue)$^{-1}$; n = 8, $P < 0·01$). On the contrary, myeloperoxidase activity was not elevated in the iris-ciliary body of rabbits treated with sodium naproxen (0·041 ± 0·009 vs 0·034 ± 0·005 units myeloperoxidase (mg tissue)$^{-1}$; n = 8, $P < 0·05$). Therefore, this group displayed lower levels than the vehicle- or phenylephrine-treated group 120 min after paracentesis (Table 1). As regards the cornea, no significant changes of myeloperoxidase activity were observed in all groups. LTB_4 in secondary aqueous humour was found significantly increased in all experimental groups and was not modified by sodium naproxen treatment (Table 1). In rabbits treated as previously described and killed 8 h after paracentesis, no significant increase in aqueous levels of PGE_2, LTB_4 and PMNs or of myeloperoxidase activity in the iris-ciliary body nor miosis were observed in comparison with a control group (data not shown). High sodium naproxen levels, 14·9 ± 2·9 and 23·7 ± 8·3 $\mu g\ mL^{-1}$ (mean ± s.e.; n = 4), were detected in the primary and secondary aqueous humour, respectively.

Discussion

The experimental model adopted in this study mimics the miosis, independent of blocking muscarinic cholinergic receptors, and the transient vascular inflammatory response of the eye caused by mechanical trauma (Latur et al 1989). Topical sodium naproxen, a reversible competitive inhibitor of cyclo-oxygenase, and phenylephrine, a mydriatic †-adrenergic agent, both successfully maintained mydriasis induced by atropine following paracentesis in the rabbit eye. However, aqueous levels of proteins and PGE_2 were significantly reduced only in the group treated with sodium naproxen. Aqueous levels of PGE_2, a miotic agent and mediator of the ocular inflammatory response in the rabbit (Stjernschantz 1984; Kulkarni & Srinvasan 1987), were markedly reduced, in agreement with numerous reports that naproxen is a potent cyclo-oxygenase inhibitor (Todd & Clissod 1990). Prostaglandins are synthesized in the iris-ciliary body and may have a constrictor action on the iris sphincter (Stjernschantz 1984). This effect could be the direct action presumably on prostaglandin receptors which have been detected in the iris-ciliary body of several mammals (Bhattacherjee et al 1990). Another possibility is that prostaglandins are released by other mediators, such as substance P, occurring in sensory nerves that innervate the iris sphincter muscles and are directly implicated in their contraction (Yousufzai et al 1986). Infiltration of PMNs in the anterior chamber has been observed in different experimental models of ocular inflammation (Williams et al 1983; Paterson et al 1984). Sodium naproxen significantly reduced PMN accumulation in the aqueous humour, as also shown by the low levels of myeloperoxidase activity in the iris-ciliary body. However, in contrast with our results, Kulkarni (1991) did not detect any PMN response in the aqueous humour and iris-ciliary body in the paracentesis model, despite the breakdown of the blood-aqueous barrier, whereas Hoyng et al (1986), adopting a model of ocular inflammation similar to paracentesis, found a detectable cellular response in the anterior chamber 3 h after puncturing

the cornea of the rabbit eye. Interestingly, following the breakdown of the blood-aqueous barrier, we observed a significant increase of LTB_4, which was not affected by sodium naproxen treatment. This eicosanoid is synthesized from arachidonic acid through the 5-lipoxygenase pathway and is a potent chemoattractant, causing a sustained leukocyte influx into the aqueous humour when injected intraocularly (Bhattacherjee & Paterson 1990). LTB_4 levels in aqueous humour are elevated after blunt trauma and their increase precedes the appearance of PMNs (Latanza et al 1988). However, paracentesis may elicit a vascular and cellular inflammatory response through the production and release of different endogenous mediators. Therefore, the significant influx of PMNs into the aqueous humour and the increase of myeloperoxidase activity in the iris-ciliary body, found in this study, could be due to a chemoattractant other than LTB_4 (Hoekzema et al 1990; Tilden et al 1990). It has been previously reported that prostaglandins may inhibit aqueous infiltration of PMNs induced by LTB_4 (Kulkarni 1991), thus suggesting that the secondary release of cyclo-oxygenase products may contribute to the chemotactic effect of leukotrienes as observed in other tissues (Piper & Samhoun 1981). However, our data do not support this hypothesis. In fact, the aqueous humour levels of LTB_4 were not significantly different in rabbits treated with sodium naproxen or with the vehicle. Nevertheless, this drug significantly blocked the cyclo-oxygenase pathway and reduced PMNs infiltration in the aqueous humour through a mechanism that did not involve leukotrienes. Some authors have already described that the modification of cellular migration by some NSAIDs (Parente et al 1979; Smith & Iden 1980) does not seem to be directly correlated with the inhibition of arachidonic acid metabolism. The fact that topical sodium naproxen reduced PMN infiltration into the aqueous humour and myeloperoxidase activity in the iris-ciliary body is of clinical interest since leucocytes participate in the events associated with the initiation and continuation of ocular inflammation (Baiton 1980; Csukas et al 1990) and in the process that leads to corneal damage (Kenyon et al 1987). Nielsen (1982) and Nørrelykke Nissen & Ehlers (1986) reported that oral naproxen significantly reduced immediate postoperative corneal oedema after intraocular surgery. Pritchett et al (1985) found that naproxen administered by gavage at the loading dose of 6·7 mg kg^{-1} followed by maintenance doses of 3·3 mg kg^{-1} did not modify the ocular inflammatory response following extracapsular lens extraction in rabbits. However, as these authors point out, plasma drug levels were probably not sufficient. In this study, we detected high levels of naproxen in the primary and secondary aqueous humour, suggesting that a treatment by eye drops may be effectively used in routine pre- and postoperative cataract surgery. Present data are in agreement with our previous findings (Spampinato et al 1991) that sodium naproxen eye drops significantly reduce the primary signs of ocular inflammation and the levels of PGE_2, PMNs and proteins in aqueous humour from the eye of rabbits treated with 0.5% sodium arachidonate. Taken together these findings suggest that sodium naproxen eye drops may not only be useful in maintaining mydriasis during surgery but may significantly reduce the release of inflammatory agents during eye trauma that may damage ocular tissues. However, it might be of interest to provide a more detailed evaluation of sodium naproxen interaction with other activities of elicited phagocytes in order to determine whether this drug alters defence mechanisms in inflammatory response.

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