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RESEARCH ARTICLE

AN EXPERIMENTAL STUDY TO EVALUATE PROTECTIVE EFFECTS OF NAPROXEN AND VALDECOXIB ON NAPHTHALENE INDUCED CATARACT IN ALBINO RATS

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ABSTRACT

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) has conflicting status in cataract formation, previous data has indicated a cataract inducting role as well as a potential protective effect of NSAIDs against cataract formation. Anti-cataract efficacy of NSAIDs has been studied widely in different experimental settings. In view of this naproxen is used as standard and valdecoxib, a COX II (cyclooxygenase II) inhibitor, is used as test drug to evaluate the protective effects on naphthalene induced cataract in albino rats.
Objective: The objective of the present study was to evaluate the protective effects of naproxen and valdecoxib on naphthalene induced cataract in albino rats.
Materials and methods:6 groups were taken, each group consisting 6 rats. Group I (control) received normal saline orally. Group II (control) received normal saline eye drops. Group III received naproxen (4mg/kg) orally. Group IV received naproxen eye drops (2%). Group V received valdecoxib (3mg/kg) orally. Group VI received valdecoxib eye drops (2%). Oral dose and eye drops were given daily for 10 days prior to induction of cataract. Cataract was induced bygiving naphthalene 1gm/kg orally to albino rats. Rats were examined for appearance of lenticular capacity by indirect illumination, direct ophthalmoscopy, slit lamp examination daily, and observed for period of thirty days for any mortality.
Conclusion: Valdecoxib, a COX II selective inhibitor, is not more efficacious than naproxen in retarding progress of naphthalene induced cataract.
Keywords: Naproxen, Valdecoxib, Naphthalene, Cataract

INTRODUCTION

The major cause of blindness in the world is cataract. WHO estimates 47.8% of global blindness is due to cataract. More than 50% of blindness is due to cataract in Southeast Asia. Incidence of cataract increases with age.[1,2] Etiology of cataract formation includes age, nutritional deficiencies, environmental changes, radiation, metabolic diseases like diabetes and oxidative stress.[2] Ageing is a physiological process that leads to gradual decline in antioxidant enzymes. Tissue defense system is modulated by endogenous anti-oxidative enzymes.[3] The enzymes like glutathione reductase and peroxidase, and super oxide dismutase are necessary for removing the free radicals from the organ system including the lens also.[4] Single drug is not effective for arresting cataract. Researches had shown that four group of drugs viz. aldose reductase inhibitors, non-steroidal anti-inflammatory drugs, vitamins &minerals, and antioxidants &drugs acting on glutathione are effective in preventing cataract.[5,6] These drugs block the metabolic pathways of glucose responsible for diabetic vascular dysfunctions which may be due to deposition of sorbitol. Their role in the prevention of diabetic cataract in animals is now well established.

The indication of NSAIDs as prophylactic anti-cataract agent came from studies on aspirin use in patients with rheumatoid arthritis and diabetes.[7-10] The anti-cataract activity is explained by virtue of their effect on different biochemical pathways. NSAIDs with diverse chemical structures were reported to retard the phenomenon of cataract in experimental animals. [11, 12] Test of drugs have been conducted by using oral route. Cataract development is a gradual process, for which drugs will have to be taken for prolong time with unnecessary systemic side effects. Therefore, topical application in the form of eye drops is being evaluated to test their anti-cataract activity of these drugs. NSAIDs after topical application was found to have significant anti cataract activity by delaying both the onset and progression of cataract.[10,13]The mechanism of anti-cataract activity of NSAIDs includes acetylation, inhibition of glycosylation and carbamylation of lens proteins.

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Recently NSAIDs have also been reported to possess anti-oxidant properties. In previous literature it is shown that naproxen is effective both orally and topically in preventing cataract, whereas many other non-selective cyclooxygenase inhibitors like aspirin, sulindac and indomethacin have also being widely studied and shown good results.[14,15] COX2 inhibitor group of NSAIDs had not been well studied for their anti-cataract activity till date.[16,17] COX inhibitors have minimal gastric side effects and is suitable for chronic use for disease like rheumatoid arthritis in elderly who are also likely to develop cataract. Cataract being common in elderly, it will be fruitful if COX inhibitor like valdecoxib retard the development of cataract.

The present study was designed to evaluate the protective effects of naproxen and valdecoxib on naphthalene induced cataract in albino rats.

MATERIALS AND METHODS

Animals: Healthy Wistar albino rats of either sex, weighing between 250-300 g were used in the study. They were housed in clean metallic cages and were maintained on standard laboratory diet and water ad-libitum. After a five day acclimatization period the rats were used for the study. The study was started after getting clearance from Institutional Ethics Committee and conducted as per CPCSEA guidelines.

Drugs used for induction of cataract: Naphthalene crystal are crushed in mortar using pestle and dissolved in warm liquid paraffin to make suspension. Cataract was induced by oral administration of naphthalene 1g/kg in albino rats.[11-13]

Drugs used for study: Naproxen is a white, odourless or almost odourless, hygroscopic crystalline powder. It was prepared as suspension in gum acacia of 200mg per ml. A dose of 4mg/kg/day was administered to the rats. A suspension of 2% naproxen powder in normal saline was prepared using 1 g of drug in 100 ml of normal saline to be used as eye drops. Valdecoxib is a white odourless or almost odourless, hygroscopic crystalline powder which was prepared as a suspension in gum acacia of 300mg per ml. A dose of 3 mg/kg/day was administered to the rats.

Control drugs/vehicle: A 5% suspension of gum acacia was prepared for administration to control rats. 0.9% sodium chloride is used as both for eye drops as control.

Oral administration of drugs: The animals were held gently but firmly at the time of feeding. A suitable wooden mouth gag was placed between the teeth of the rat taking care not to cause any injury to the animal. A polythene feeding tube lubricated with liquid paraffin was passed through the hole in the mouth gag into the stomach of the rat. After ensuring that the tube was in the stomach and not in the airway (by looking for air bubbles coming out of the tube into a beaker filled with water), the required amount of the drug was injected into feeding tube using a syringe. About 1 ml of normal saline (dead space of the tube) was injected after each drug so that any drug remaining in the tube was also delivered into the stomach. The tube was gently pulled out after the completion of drug administration.

Administration of eye drops: Rats were restrained manually with the help of assistant, two drops were instilled on cornea of both eyes, and animal was restrained for 10 minutes for drug to have its effect.

Thirty-six adult albino rats were taken and divided into six groups with six animals in each. Group I (control) received normal saline orally. Group II (control) received normal saline eye drops. Group III received naproxen (4mg/kg) orally. Group IV received naproxen eye drops (2%). Group V received valdecoxib (3mg/kg) orally. Group VI received valdecoxib eye drops (2%). Oral dose and eye drops were given daily for 10 days prior to induction of cataract.

Examination was done daily to check for lenticular capacity by indirect illumination, direct ophthalmoscopy, slit lamp examination, and observed for any mortality for period of thirty days. Initiation and measurement of lenticular opacity was graded into four stages.[18]

1. First stage was invasion of lens by vacuoles on periphery.
2. Second stage was presence of linear opacities cataract.
3. Third stage was presence of plaques and clouding of lens.
4. Fourth stage was mature cataract.

Statistical analysis: The data were analyzed by two way ANOVA and followed by post hoc Tukey's test. $P<0.05$ was considered to be statistically significant.

RESULTS

Naproxen significantly delayed appearance and progression of cataract than valdecoxib when given via oral route. Whereas, naproxen were just marginally effective and valdecoxib was not at all effective in preventing cataract when applied topically as eye drops.

Control

All rats from control group subjected to naphthalene challenge developed cataract (100%). (Table 1 and 2). There was no mortality till end of thirty days of observation.

Table 1: Effect of oral gum acacia on naphthalene induced cataract in albino rats

Stage of cataract	Rats no.	Developing cataract %	Days (M&D) of appearance of cataract
I	6	100	6.1+/-1.4
II	6	100	9.2+/-1.1
III	6	100	12.3+/-2.1
IV	6	100	16.6+/-1.8

Table 2: Effect of normal saline eye drops on naphthalene induced cataract in albino rats

Stage of cataract	Rats no.	Developing cataract %	Days (M&D) of appearance of cataract
I	6	100	3.8+/-0.5
II	6	100	7.2+/-1.1
III	6	100	12.1+/-1.4
IV	6	100	14.5+/-1.5

Effect of Oral naproxen on naphthalene induced cataract in albino rats:

Oral naproxen significantly delayed the development of cataract at dose of 4 gm/kg ($p<0.001$). (Table 3) Mature cataract was developed only in two rats at end of 30 days. There was no mortality till end of thirty days of observation.

Table 3: Effect of oral naproxen on naphthalene induced cataract in albino rats

Stage of cataract	Rats no.	Developing cataract %	Days (M&D) of appearance of cataract
I	6	100	18.4+/-2.4
II	6	100	25.5+/-1.4
III	5	83.33	35.7+/-1.9
IV	5	83.33	42+/- 4.8

Effect of naproxen eye drops on naphthalene induced cataract in albino rats:

Naproxen eye drops (2%) did not have significant effect on development of cataract to various stages (Table 4). Mature cataract developed in all rats at end of 30 days. There was no mortality till end of thirty days of observation.

Table 4: Effect of naproxen eye drops on naphthalene induced cataract in albino rats

Stage of cataract	Rats no.	Developing cataract %	Days (M&D) of appearance of cataract
I	6	100	9.1+/-1.7
II	6	100	14.2+/-2.1
III	6	100	17.3+/-2.6
IV	6	100	19.4+/-2.8

Effect of Oral valdecoxib on naphthalene induced cataract in albino rats:

Oral valdecoxib significantly delayed the development of cataract to various stages with dose of 3gm/kg ($p<0.05$). (Table 5) Mature cataract was developed in all rats at end of 30 days. There was no mortality till end of thirty days of observation.

Table 5: Effect of oral valdecoxib on naphthalene induced cataract in albino rats

Stage of cataract	Rats no.	Developing cataract %	Days (M&D) of appearance of cataract
I	6	100	12.1+/-0.7
II	6	100	17.6+/-1.1
III	6	100	23.3+/-2.4
IV	3	50	28.6+/-3.8

Effect of valdecoxib eye drops on naphthalene induced cataract in albino rats:

Valdecoxib eye drops (2%) showed no significant effect on development of cataract (Table 6). Mature cataract developed in all rats at end of 30 days.

Table 6: Effect of valdecoxib eye drops on naphthalene induced cataract in albino rats

Stage of cataract	Rats no.	Developing cataract %	Days (M&D) of appearance of cataract
I	6	100	5.2+/-0.8
II	6	100	8.3+/-1.6
III	6	100	14.3+/-1.9
IV	6	100	16.2+/-1.4

DISCUSSION

Comparative studies on anti-cataract activity of two NSAIDs revealed that, naproxen is better than valdecoxib in delaying the development of cataract. It may be due to inhibition of lens aldose reductase (AR) by NSAIDs.[19] The mechanism by which naphthalene induced cataract may be by its direct toxic effect reducing glutathione levels.[20,21] In this model only oral naproxen could give some protection. The probable mechanism producing anti cataract effects by naproxen and other NSAIDs can be due to acetylation, inhibition of glycosylation and carbamylation of lens

proteins, and possibly also due to antioxidant and inhibition of aldose reductase.[19,21] The concentration of glutathione, a tripeptide thiol decreases with age in the lens and more markedly in cataracts.[22,24] An approach to glutathione level inside the lens by its increased synthesis or decreased breakdown was tried by some groups using agents acting against glutathione. The potential role of vitamins and anti-oxidants in preventing various diseases is well documented.[4,23,25] Various substances with diverse chemical structures and properties like derivatives of amino acids containing germanium compounds, pantethine, glutathione isopropyl ester etc. have been reported to have protective effect against cataract in different experimental models.

Further studies focusing on the biochemical pathway is needed to reveal the exact mechanism. This study provides the lead for clinical study to reveal the possibilities of prevention of age related cataract by systemic administration as well as topical administration of NSAIDs like naproxen and valdecoxib.

CONCLUSION

Naproxen, a nonselective COX inhibitor, was more effective than valdecoxib, a COX II selective inhibitor, in retarding the development of naphthalene induced cataract. Oral dosage form was found to be more effective than topical form. The results of our previous study on celecoxib and naproxen also support the findings of this study.[26] Despite several known and unknown aspects of the use of COX II selective inhibitors in cataract, these drugs have potential to be developed as a model drug to delay the progression of cataract only after proving its efficacy and safety through clinical studies.

REFERENCES

1. World Health Organization. Global initiative for the elimination of avoidable blindness: An informal consultation. Geneva: WHO; 1997.
2. Gupta VB, Rajagopala M, Ravishankar B. Etiopathogenesis of cataract: An appraisal. Indian J Ophthalmol 2013 Nov 11.
3. Radhakrishnan M, Venkatesh R, Valaguru V, Frick KD. Ophthalmic Epidemiol. Household Preferences for Cataract Surgery in Rural India: A Population-based Stated Preference Survey. 2013 Sep 25.
4. Thiagarajan R, Manikandan R. Antioxidants and cataract. Free Radic Res. 2013 May; 47(5):337-45.
5. Gupta SK, Joshi S. Dev. Naproxen: an aldose reductase inhibitor and potential anti-cataract agent. Ophthalmol. 1991; 21:170-8.
6. Gupta SK, Joshi S Dev. Relationship between aldose reductase inhibiting activity and anti-cataract action of various non-steroidal anti-inflammatory drugs. Ophthalmol. 1991;21:151-6
7. Schoenberger SD, Kim SJ. Nonsteroidal anti-inflammatory drugs for retinal disease. Int J Inflam. 2013; 2013:281981. doi: 10.1155/2013/281981. Epub 2013 Jan 14.
8. Weber M, Kodjikian L, Kruse FE, Zagorski Z, Allaire CM. Efficacy and safety of indomethacin 0.1% eye drops compared with ketorolac 0.5% eye drops in the management of ocular inflammation after cataract surgery. Acta Ophthalmol. 2013 Feb; 91(1):e15-21.
9. Moschos MM, Chatziralli IP, Pantazis P, Rouvas AA, Sergentanis TN. Is topical diclofenac essential before and after uneventful phacoemulsification cataract surgery? J Ocul Pharmacol Ther. 2012 Aug;28(4):335-9
10. Russo P, Papa V, Russo S, Di Bella A, Pabst G, Milazzo G, Balestrazzi A, Caporossi. A Topical nonsteroidal anti-inflammatory drugs in uncomplicated cataract surgery: effect of sodium naproxen. Naproxen Study Group. Eur J Ophthalmol. 2005 Sep-Oct;15(5):598-606.
11. Holmen JB, Ekesten B, Lundgren B. Naphthalene-induced cataract model in rats: A comparative study between slit and retroillumination images, biochemical changes and naphthalene dose and duration. Curr Eye Res. 1999 Nov;19(5):418-25
12. Lou MF, Xu GT, Zigler S Jr, York B Jr. Inhibition of naphthalene cataract in rats by aldose reductase inhibitors. Curr Eye Res. 1996 Apr;15(4):423-3
13. Rathbun WB, Holleschau AM, Cohen JF, Nagasawa HT. Prevention of acetaminophen- and naphthalene-induced cataract and glutathione loss by CySSME. Invest Ophthalmol Vis Sci. 1996 Apr; 37(5):923-9.
14. Vincento Papa, Giovanni Milazzo, Marcello Santocono, Valerie Servolle, et al. Naproxen ophthalmic solution to manage inflammation after phacoemulsification. Journal of Cataract & Refractive Surgery. February 2002;Vol. 28(2): Pages 321-327
15. Papa V, Russo S, Russo P, Di Bella A, Santocono M, Milazzo G. Topical naproxen sodium for inhibition of miosis during cataract surgery. Prospective, randomized clinical trials; Naproxen Study Group. Eye (Lond). 2002 May;16(3):292-6
16. Alexander Reis, Florian Birnbaum, Lutz L. Hansen, Thomas Reinhard. Cyclooxygenase-2 inhibitors: A new therapeutic option in the treatment of macular edema after cataract surgery. . Journal of Cataract & Refractive Surgery. July 2005; Vol. 31(7): Pages 1437-1440
17. Joshi RS. Pre-operative use of the topical steroidal and non-steroidal anti-inflammatory agents to maintain intra-operative mydriasis during cataract surgery. Indian J Ophthalmol. 2013 May;61(5):246-7
18. Hugh R Taylor, Sheila K West. The clinical grading of lens opacities. Australian and NewZealand Journal of Ophthalmology.1989; 17(1).
19. Gupta SK, Joshi S. Role of naproxen as anti-oxidant in selenite cataract. Ophthalmic Res. 1994;26(4):226-31
20. Xu GT, Zigler JS Jr, Lou MF. The possible mechanism of naphthalene cataract in rat and its prevention by an aldose reductase inhibitor (ALO1576). Exp Eye Res. 1992 Jan; 54(1):63-72.
21. Korte I, Hockwin O, Bours J, Wegener A. Alterations of lens metabolism with experimentally induced cataract in rats. Ophthalmic Res. 1988; 20(3):174-8.
22. Petersen A, Zetterberg M, Sjostrand J, Palsson AZ, Karlsson JO. Potential protective effects of NSAIDs/ASA in oxidatively stressed human lens epithelial cells and intact mouse lenses in culture. Ophthalmic Res. 2005 Nov-Dec; 37(6):318-27. Epub 2005 Aug 28.
23. Suresha BS, Srinivasan K. Antioxidant potential of fungal metabolite nigerloxin during eye lens abnormalities in galactose-fed rats. Curr Eye Res. 2013 Oct; 38(10):1064-71.
24. Chan VC, Liu DT, Lee VY, Lam PT. Successful treatment of cystoid macular edema with valdecoxib. J Cataract Refract Surg. 2007 Nov; 33(11):1837-8.
25. Reis A, Birnbaum F, Hansen LL, Reinhard T.Cyclooxygenase-2 inhibitors: a new therapeutic option in the treatment of macular edema after cataract surgery. J Cataract Refract Surg. 2005 Jul; 31(7):1437-40.
26. Brashier DB, Khadka A, Mishra P, SharmaAK, Dahiya N, Gupta AK. Evaluation of the protective eff ects ofnaproxen and celecoxib on naphthalene-induced cataract in albinorats. Niger J Exp Clin Biosci. 2014; 2:28-32.

