3-20-1982

The effect of three topical agents on posterior subcapsular cataract progression in royal college of surgeon (r.c.s.) rats

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Recommended Citation
Kandel, Judy Smith; Miller, Steven A.; Fong, Dale S.N.; and Ethington, Roger B., "The effect of three topical agents on posterior subcapsular cataract progression in royal college of surgeon (r.c.s.) rats" (1982). College of Optometry. 614.
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The effect of three topical agents on posterior subcapsular cataract progression in royal college of surgeon (r.c.s.) rats

Abstract
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Degree Type
Thesis

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A THESIS PRESENTED TO THE
FACULTY OF PACIFIC UNIVERSITY
COLLEGE OF OPTOMETRY

THE EFFECTS OF THREE TOPICAL AGENTS ON POSTERIOR SUBCAPSULAR CATARACT
PROGRESSION IN ROYAL COLLEGE OF SURGEON (R.C.S.) RATS

IN PARTIAL FULFILLMENT OF
REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF OPTOMETRY

BY:

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MARCH 20, 1982
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March 20, 1982
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Acknowledgements

A special word of thanks to Beta Sigma Kappa for the research grant making this study possible. Additionally, we would like to express our appreciation to the following persons: Dr. Cool for his assistance in the laboratory, Dr. Yolton for her advisory role, and Dr. Meyer-Arendt for his interpretative role, Dr. Kendall and Da Vinci Labs for their information and contribution of NNDMG, and Mr. Glenn Hill and Luyties Pharmacal for their contributions and information regarding Scenicio Maritima. Also, we extend our thanks to Roger's sister for sending us Conjuctivisan A from Germany.
ABSTRACT

Three substances are currently reported to possess cataract retardation properties: Scenecio Maritema, N-N dimethylglycine, and Conjunctivisan A. To test their potential in retarding cataract progression, Royal College of Surgeon (R.C.S.) rats were selected as the experimental model. This strain of rats develops posterior subcapsular cataracts secondarily to an inherited retinal degeneration. At birth, the rats were divided into four groups. The ten rats in each group received twice daily topical instillation of saline, Scenecio Maritema, N-N dimethylglycine, or Conjunctivisan A for eight weeks. Analysis of serial slit lamp evaluations showed a significant delay in cataract progression in the rats receiving any of the three agents compared to the saline control. This suggests that there might be an alternative to surgery in cataract treatment.
Cataract formation is one of the leading causes of blindness in the world today. In the United States, aside from surgical removal of the lens, there is no medically accepted treatment for this condition. Recently, Naturopaths and other related health professionals have been using plant extracts in the form of topical drops to retard the formation of cataracts. Since a cataract can easily be detected early in its development, the topical applications of a substance capable of retarding cataract development would provide an alternate method of treatment. However, these agents when applied topically have not been shown to significantly retard cataract formation in a carefully controlled study.

There are three substances currently being used for cataract retardation: 1) Scenecio Maritema, a plant extract; 2) N-N dimethylglycine (DMG), the active agent in a group of substances called Pangamic Acid; and 3) Conjunctivisan A.

**Scenecio Maritema**

Succus Cineraria Maritema (SCM) or Scenecio Maritema are trade names for an herbal extract from the plant Cinereria Maritima. The sterilized juice of the plant is employed for the treatment of capsular and lenticular cataracts of the eye. Its use is recommended before resorting to an operation.

Cinereria Maritima or Dusty Miller is a plant found most on the shores of the Mediterranean region. Cinereria means "ashy
grey", depicting its mixture of black and white coloring which contrasts against its yellow flowerheads. The juice from leaves are believed to contain a cataract retardant. When applied to the eye, it is thought to act as a lymphagogue, increasing circulation in the intraocular tissue and also stimulating collateral circulation and normal metabolism.

A pilot study has suggested retardation of cataract development in Royal College of Surgeon (R.C.S.) rats treated with Scenecio Maritema as compared to placebo controls. A recent pharmaceutical laboratory study was conducted investigating the use of SCM on the retardation of artificially induced cataracts in albino rats. Significant differences in light transmission values of the lenses between treated and non-treated animals were found. SCM has also been used in a study involving ophthalmologists instilling drops of SCM in human cataracts with favorable results.

**N-N dimethylglycine**

N-N dimethylglycine (DMG) is a substance composed of tertiary amino acids. This substance is referred to as being a non-fuel nutrient. In recent years, this composite has been referred to at times as Pangamic Acid or Vitamin B-15. This confusion has been settled by the extraction of only two common components--DMG and gluconic acid. There have been assertions that the component DMG has cataract retardation effects along with other medicinal cures.

The apparent mechanism of DMG appears to be enhancement of oxygen utilization by tissues, complexing of free radicals.
detoxification phenomenon of gluconic metabolism, and retardation of lactic acid build-up during physical and mental stress. Although this mechanism is not yet fully understood, it appears that these effects create a more efficient metabolic flow.

Conjunctivisan A

Conjunctivisan A (C-A) is the trade name for a pharmaceutical agent that is manufactured and utilized in Germany as an alternate treatment of cataracts. It is dispensed as a clear liquid in small disposable plastic vials. Topical administration into the conjunctival sac is intended for home usage two to three times daily, and the product cannot be filled without a prescription. The contents include: proteins, RNA, DNA, phospholipids, and polysaccharides; as well as, lens cell specific nucleic acids and amino acid precursors from the lens, vitreous body, retina, optic nerve, cornea, conjunctiva, and placenta. The macromolecular organic lysins are obtained from various eye tissues. Conjunctivisan A also includes Aesculin derivatives which are used as ultraviolet light filters, and it also contains Lantoside, a digitalis compound.

In the utilization of Conjunctivisan A, anti-cataract therapy assumes that there are required amounts of necessary ingredients which are absent in the cataractous lens. By replenishing this deficient agent with an external vehicle such as Conjunctivisan A, the expected result would be a retardation in cataract formation. This requires that the topical drops be absorbed through the mucous membranes of the conjunctiva and transmitted to the lens.
Conjunctivisan A has been described as an organotropism of cytoplasmic substances.7

In 1979, Dr. J. Fuchs, a German ophthalmologist reported on his treatment in 192 cases of senile cataractous eyes with Conjunctivisan A over a five year period. He concluded that 45% of the eyes treated demonstrated improved vision due to a decrease in lenticular opacification. Of the remaining patients, 36% showed no changes, and 19% followed the typical course of increased opacification and decreased vision.8

In order to determine the potential of the three agents to retard cataract progression, a suitable animal model was needed. R.C.S. rats which developed posterior subcapsular cataracts secondarily to an inherited retinal degeneration were used in this study because there has been extensive research on the inherited retinal dystrophy in the strain of R.C.S. rats.9,10,11,12,13 The physical appearance is very similar to the tapetoretinal degeneration found in humans.14

In humans, the tapetoretinal degeneration in retinitis pigmentosa is characterized by rod outer segments not meeting with retinal pigment epithelium. This is due either to excessive phagocytosis of the outer segments or to incomplete development. In the R.C.S. rats, the rod outer segments are not phagocytized and they accumulate between the retinal receptor layer and the pigment epithelium of the retina. In both cases there is a gap between retinal receptors and pigment epithelium. This lack of development leads to the degeneration of the retina.15
As a result of this retinal degeneration, a secondary posterior subcapsular cataract develops. The exact mechanism is yet unknown. The cataracts are grossly observable with a direct ophthalmoscope as fine dust-like opacities approximately eight weeks after birth. The period of active cataractogenesis occurs just prior to and during the active period of destruction of the photoreceptors.\textsuperscript{9,10}

According to an unpublished document on cataracts in R.C.S. rats, the major histological feature observed with the slit lamp is abnormal elongations of lens fibers toward the posterior pole.\textsuperscript{16} As the animal matures, normal tissue separates the initial dis-oriented lens fibers from the lens capsule at the posterior pole.\textsuperscript{16} The influence of the retina on the differentiation of embryonic lens fibers is well documented.\textsuperscript{17} The fully developed cataract can be observed approximately twenty weeks after birth.\textsuperscript{16}
Animals

The animal subjects were forty outbred R.C.S. rats, which have been outbred and maintained over the past two years from a previous study involving the R.C.S. strain. The original rats were obtained from Dr. Matthew LaVail and consisted of three brother-sister pairs. By crossbreeding the original R.C.S. rats with a Sprague-Dowley breed, a strain was developed that possessed a slower evolution of the retinal degeneration with less penetrance. This creates a much slower cataract progression than that observed in a purer R.C.S. breed when monitored by serial slit lamp evaluations.

In an unpublished study by Dr. Steve Wells, it was estimated that full cataract development occurred after approximately five months of age without outbreeding. Due to the outbreeding of our R.C.S. breed, achievement of full cataract development took longer. This difference was not measured, since the achievement of a full-blown cataract was not expected to occur during the eight week experimental period.
The S-C group received an isotonic .9% NaCl saline solution prepared daily from Baush and Lomb sof lenses tablets and distilled water.

The other group of experimenters monitored cataract progression at weekly intervals during the same eight week period with the biomicroscope. Lens opacities were graded according to apparent size, location, and density. (See figure 1). Data was not computed or compared until the final data set had been collected at the end of the eighth week.

The methods were consistent for all test groups with the exception of C-A. The group of ten rats was split into two groups of five. One group of the five rats received topical applications for a four week period which started at the beginning of the usual eight week experimental period. The second group of five rats received topical applications starting at the eighth week and continuing for four additional weeks.

The randomization test for two independent samples was incorporated statistically to determine differences between the results in the rats each receiving the topical agent as compared to the rats receiving the saline. This was performed in order to isolate the different chemical agents and to see if there was a significant difference in the effect of each individual agent. A one tailed test was used to examine the research hypothesis that topical agents will retard cataract progression as compared to the saline control group.
**Results**

Between the ages of four and seven weeks, posterior subcapsular cataracts were typically noted as the remnant hyaloid artery atrophied. There was no qualitative difference in cataract progression in animals of either sex or skin coloration. A difference in the rate of cataract progression was found between the S-C group for DMG and the other S-C groups. The rate of cataract progression in the DMG, S-C group was faster than those of the other two-SM, S-C, and C-A, S-C. The animals used in the DMG group were obtained from an earlier generation of R.C.S. rats. Therefore, the rats in DMG and its S-C are a purer breed than the other rats used in the experiment. It has been mentioned earlier that as the strain is outbred, the period of time for cataract progression is extended. 18

The cataract progression was noted to have been retarded in rats receiving DMG, SM, or C-A. The results are shown in Figures 2a-2e.

Statistical comparison showed that in the rats receiving DMG, SM, or C-A, cataract development was found to be significantly slower than in those rats receiving saline at all times. (Figure 2e). DMG showed a slightly larger amount of mean cataract retardation than did the other substances. SM showed just a little less mean cataract retardation effect than DMG (Figure 2a and 2b). The two C-A groups did not show any significant mean retardation of cataract progression until the end of the fourth week of use.
The results gathered show that the mean cataract development in all the S-C animals followed a similar linear progression. The test animals receiving drops of the substances showed a similar mean retarding effect on cataract progression. Each substance delayed the development of the cataract to some degree.
Discussion and Conclusions

The physiological mechanism causing the development of secondary posterior subcapsular cataracts in R.C.S. rats may still be speculative, but the three topical agents employed in this study have demonstrated perhaps an alteration in that mechanism. There appears to be differences in the mean results obtained on each of the substances used. But in each case, the evidence of the results shows that cataract retardation has occurred to some degree (Figure 2a-2e).

When comparing the mean graphs on Figures 2a-2d, they all seem to be different; however, they take a similar time course and pattern. The molecular differences between the actual substances and their effect on cataract progression could possibly be the reason for varied results. One of these differences is the supposed mechanism. Both DMG and SCM are assumed to help facilitate normal metabolic flow, while C-A is assumed to replenish lost nutrients. Although DMG and SCM are said to have the same mechanism, their origins differ. DMG is a non-fuel nutrient composed of tertiary amino acids. SCM is a plant extract. the other substance C-A is also different, being composed from an array of proteins and cytoplasmic substances found in the body. This difference may well explain the dissimilarities in the results between each substance.

Another dissimilarity is noted when looking at Figure 2e. It is noted that the initial stage of cataractogenesis differs between test groups. The initial recorded stage of cataract
progression differs between DMG subjects and the other test
groups probably because the DMG subjects were taken from an
earlier generation, thus making it a purer R.C.S. breed. This
would account for a more rapid cataract onset and development
than those observed in following generations of R.C.S.\textsuperscript{18}

The figures indicate that all three agents tested do retard
cataract progression to some degree in this experimental model.
However, because these animals also have retinal degeneration
and no vision, the visual parameters associated with the retardation
of cataract progression could not be assessed. Thus, this study
suggests a potential for these agents to aid in the treatment of
cataracts. The next step would have to be a follow-up clinical
study which involves visual assessment in cataractous humans
using these substances. If these substances truly retarded
cataract formation sufficiently to provide useful vision, they
would allow the cataract patient an alternative to surgery.
REFERENCES


STAGE ZERO: HYALOID REMNANTS

Posterior Y-suture and hyaloid remnants only are observable shortly after birth when eyes open until the 4th week.

STAGE ONE: INITIAL GRANULES

A few minute granules bordering the Y-suture between the 4th and 5th week.

STAGE TWO: DIFFUSE GRANULES

Smaller and denser granules with early clouding of the posterior region at 5 weeks of age.

STAGE THREE: CIRCULAR

Definite round-shaped border and increased clouding giving a translucent appearance at 6 and 7 weeks of age.

STAGE FOUR: ANGULAR

A more quadrilateral shape with denser and compacted form of translucency occurring at about 8 to 12 weeks of age.

STAGE FIVE: FULL BLOWN

Dense, white cataract (and opaque) develops in animals between 19 and 26 weeks of age.

Figure 1. The cataract grading system used for assessing posterior subcapsular cataracts found in R.C.S. rats.
Legend. Cataract progression is shown over an eight week experimental period for the three topical agents. Solid lines denote experimental rats and broken lines denote littermate controls.
Stage Five: Full Blown

Stage Four: Angular

Stage Three: Circular

Stage Two: Diffuse Granular

Stage One: Initial Granulants

Stage Zero: Hyaloid Remnants

Figure 2c. Cataract progression over an eight week experimental period. Solid lines denote the experimental rats (-----), and the broken lines denote littermate controls (----). The topical agents are denoted by circles—NNDMG (O—O); triangles—SM (A—A); square one—younger rats with C-A(1—1); and square two—older rats with C-A(2—2).