1978

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Kim J. Butler
Pacific University

James P. Thompson
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Abstract

This study compares the effects of three sympathomimetic agents used in over-the-counter ocular decongestants, tetrahydrozoline, phenylephrine and naphazoline on intraocular pressure, anterior chamber angle and pupil diameter in normal healthy adult eyes. Both short term effects, monitored at 15 minutes, 30 minutes and 45 minutes following initial drop instillation, and long term effects measured for 96 hours during habitual use were studied. Only one product, Visine, which contains tetrahydrozoline, produced a significant change in the measured parameters. Visine lowered the intraocular pressure an average of 1.9 mmHg thirty minutes after instillation.

Degree Type

Thesis

Degree Name

Master of Science in Vision Science

Committee Chair

Diane Yolton

Subject Categories

Optometry

THE EFFECT OF NON-PRESCRIPTION OCULAR DECONGESTANTS ON INTRAOCULAR PRESSURE, ANTERIOR ANGLE AND PUPIL DIAMETER

KIM J. BUTLER, OD

JAMES P. THOMPSON, OD

DIANE YOLTON, PhD

PACIFIC UNIVERSITY, COLLEGE OF OPTOMETRY

FOREST GROVE, OREGON

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ACKNOWLEDGEMENT

We are grateful to the National Honor Society Beta Sigma Kappa for providing the grant which made this thesis possible.

ABSTRACT

This study compares the effects of three sympathomimetic agents used in over-the-counter ocular decongestants, tetrahydrozoline, phenylephrine and naphazoline on intraocular pressure, anterior chamber angle and pupil diameter in normal healthy adult eyes. Both short term effects, monitored at 15 minutes, 30 minutes and 45 minutes following initial drop instillation, and long term effects measured for 96 hours during habitual use were studied. Only one product, Visine, which contains tetrahydrozoline, produced a significant change in the measured parameters. Visine lowered the intraocular pressure an average of 1.9 mmHg thirty minutes after instillation.

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INTRODUCTION

In today's youth oriented society, the indescriminate use of over-the-counter drugs is common-place in the search for social acceptance. Natural body chemistry is masked and modified with such preparations as deodorants, aspirin, antacids and antihistamines with little regard for the physiological side effects. Presently, the general public's use of ocular decongestants to whiten the eyes is being encouraged by energetic mass-media techniques. The wide use of these preparations could cause undesirable changes in the physiological state of the eye in a significant portion of the population.

Presently available are ouclar decongestants containing one of three sympathomimetics: tetrahydrozoline-HCl, nephazoline-HCl and phenylephrine-HCl.[1] Sympathomimetics mimic sympathic stimulation to the eye and thus could be expected to cause pupil dilation as well as whitening of the eyes due to vasoconstriction. As a consequence of pupil dilation, an individual with a narrow angle could experience elevated intraocular pressure and an acute glaucoma attack due to angle closure.[2] Labels on these drugs warn against use by individuals with suspected or confirmed glaucoma. In contrast, some sympathomimetics have been observed to lower intraocular pressure although the mechanism is not understood.[3]

Several studies on the effects of ocular decongestants on conjunctival vasoconstriction have been reported. Researchers have used tetrahydrozoline-HCl and phenylephrine-HCl in concentrations greater than the 0.05% to 0.125% found in over-the-counter preparations and concluded that in the absence of narrow anterior angle, there was no significant increase in intraocular pressure.[4,5,6] However, there are no studies which looked specifically at the changes in intraocular pressure and anterior angle in normal eyes after instillation of ocular decongestants. Neither are there comparative studies of

these three agents.

Some studies of ocular decongestants have used the contralateral eye as the standard of comparison or there was none cited.[4,5,6] Weiss and Shaffer[4] used a Schoitz tonometer to measure intraocular pressure and Mengel[6] made reference to tonography.

This study compares the effects of three sympathomimetic agents, tetrahydrozoline, phenylephrine and naphazoline, on intraocular pressure, anterior angle and pupil diameter in normal healthy adult eyes. Changes from the base line values measured in the same eyes before drug instillation were compared using standard instrumentation.

MATERIALS AND METHODS

Product Survey

A telephone survey of three large wholesale pharmaceutical outlets was conducted to make a qualitative determination of the most widely used trade-name representative of each sympathomimetic agent used in over-the-counter ocular decongestants. A large retail outlet was also contacted to substantiate the results of the telephone survey. Visine, Prefrin Liquifilm and Clear Eyes were found to be the most popular representatives containing tetrahydrozoline, phenylephrine and naphazoline respectively. Therefore, these products were selected for the study. Lyteers was very similar in basic ingredients and preservatives to these products but without a decongestive agent. It was, therefore, chosen as the control. The characteristics of the agents selected for use are summarized in Table 1.

INSERT TABLE 1 ABOUT HERE.

Subjects

Forty subjects were selected from the adult student and staff population at Pacific University. They were screened using the following criteria: 1) presence of light irides, 2) absence of ocular pathology, 3) good general health, 4) non contact lens wearer, 5) anterior angle ratio ½ or wider as determined with biomicroscope using the method outlined by Walker,[7] 6) within the normal range of intraocular pressure (8 to 20 mmHg) as determined with a non contact tonometer.

Procedure

To establish the physiological base lines, intraocular pressure, anterior angle ratio and pupil diameter were measured on each subject on two separate days. These base line measurements on each subject were used as the standards of comparison for subsequent measures of these parameters. The subjects were then randomly placed in four groups, ten subjects per group, and given one of the four products, Visine, Prefrin, Clear Eyes or Lyteers in double blind fashion. After an initial drug instillation of two drops in each eye by self administration, the subjects were monitored for short term drug effects by measuring intraocular pressure, anterior angle ratio and pupil diameter at 15 minutes, at 30 minutes and again at 45 minutes. Subjects were then placed on a three times per day schedule of self instillation and asked to return after 48 hours and again after 96 hours for data collection. This allowed for the study of prolonged accumulative drug effects.

All intraocular pressure measurements were taken with the American Optical Non Contact Tonometer. This instrument was selected for its repeatable measurement capability without the use of any anesthetic. Calibration was easily checked before each use. Pupil diameter was determined using a Mentor biomicroscope with eyepiece reticule modified from a seven power magnifier. Using

this arrangement, pupil diamter could be measured to within 0.05mm. Pupil diameter measurements were done normal to the eye while subjects were asked to fixate on a distant non-detailed target with the opposite eye. Controlled illumination was provided by placing a 25 watt soft-while incandescent lamp in a white diffusing reflector immediately above the instrument and by using no other room or instrument illumination.

Anterior angle ratio was determined using the method described by Walker.[7] An optic section was viewed with the illumination directed normal to the temporal corneolimbal junction and the viewing system 60 degrees from the illumination system. The width of the cornea to iris shadow was compared to the thickness of the cornea. A ratio of 1/1 is considered wide open and 1/4 is considered marginally narrow. Low level instrument illumination was used with no room illumination. Low power objectives were used both in this and the pupil diameter measurement. As some subjectivity was necessary to make these measurements, one experimentor made all observations. All intraocular pressure, anterior angle and pupil diameter measurements were made on the right eye only.

The following was done to reduce the confounding factors in the experiment: 1) all drug samples in each group were from the same lot, 2) each subject's measurements were taken at the same time of day, 3) all measurements were made on the same standardized instruments, 4) all measurements were made by the same observer, 5) subjects were instructed to self administer the drug in the same manner, two drops in the lower fornix of each eye with the lower lid pulled away to form a pocket followed by closed eyes for 15 to 20 seconds, 6) the drug samples were dispensed randomly and in a double blind fashion, and 7) the 48 hour and 96 hour measurements were taken with a minimum of two hours separation between drug instillation and measurement to avoid possible short term drug effect.

The physiological base line data on the four subject groups were compared using single factor analysis of variance to insure population uniformity. The individual subject base line measurements were subtracted from the subsequent intraocular pressure, anterior angle ratio and pupil diameter readings in each time frame. Using single factor analysis of variance, the means of these changes in the three groups given products containing sympathomimetics were statistically compared to the mean of the changes observed in the control group given the artificial tears. Newman Keuls' Multiple Range Test[8] was used for final comparison of data found to be significant with the analysis of variance. The probability level used was 95% in both the analysis of variance and the Newman Keuls' test.

RESULTS

The mean intraocular pressure of the subject population was 13.2 mmHg with a range 8.5 to 19.8 mmHg; the mean anterior angle ratio was 1.0 with a range 0.6 to 1.7; and the mean pupil diameter was 4.9 mm with a range 2.7 to 6.6 mm. The physiological base line measurements of intraocular pressure, anterior angle and pupil diameter for the four study groups were found not statistically different ($P<0.05$).

The means and ranges of the changes produced in intraocular pressure, anterior angle and pupil diameter by the four pharmaceutical agents are shown in Tables 2, 3 and 4.

INSERT TABLES 2, 3 and 4 ABOUT HERE.

As can be seen, all changes in intraocular pressure, anterior angle and pupil diameter are small. None of the sympathomimetics had a significant effect on anterior angle or pupil diameter at the times studied. The only signif-

icant change in intraocular pressure was measured after instillation of tetrahydrozaline. Tetrahydrozoline lowered the intraocular pressure by an average of 1.9 mmHg 30 minutes after instillation ($P<0.05$). This significant differential effect can be seen in Figure 1.

INSERT FIGURE 1 ABOUT HERE.

Although changes in intraocular pressure caused by tetrahydrozoline at other than 30 minutes and by phenylephrine and naphazoline at all times were not significantly different than those of the control group, several trends can be seen. Phenylephrine closely mimics the control over the time observed. Tetrahydrozoline produced a lower average intraocular pressure than the control at all times observed. In contrast, naphazoline produced a higher average intraocular pressure than the control at all times observed.

DISCUSSION

Up to now, no good study has been done comparing over-the-counter ocular decongestants. The use of the Schiotz tonometer or tonography for intraocular pressure measurement or the contralateral eye as standard of comparison is less than ideal. We have used the American Optical Non Contact tonometer to avoid the use of any anesthesia and corneal trauma interent in methods of previous studies which used Schiotz tonometry and tonography. We also feel better control is achieved by the comparison of changes in intraocular pressure, either increased or decreased to the subjects own base line pressure and not that of the contralateral eye because of the possible sympathetic physiological responses.

None of the sympathomimetics found in the over-the-counter ocular decongestants studied produced a significant change in the intraocular pressure,

anterior angle ratio or pupil diameter of the normal healthy eye during the range of 96 hours except tetrahydrozoline. The effect of tetrahydrozoline was to lower the intraocular pressure 30 minutes after instillation by an average of 1.9 mmHg. The range included an individual with as much as 3.8 mmHg reduction. This could have clinical significance if tonometry were performed 30 minutes after an ocular decongestant containing tetrahydrozoline was used by the patient because it would be possible for a borderline high intraocular pressure to be found normal as a direct result of pressure depression due to the drug.

As determined by our study, habitual use of those preparations by subjects with normal healthy eyes does not appear to produce an accumulative effect through 96 hours if the recommended dosage level is not exceeded. However, individuals most prone to use these preparations could well exceed the recommended dosage for a variety of reasons. Contact lens wearers or individuals with eye irritation including abraded corneas may instill more than the recommended dosage in an attempt to relieve the irritation. In addition, these individuals could be predisposed to more rapid drug up-take bacause of discontinuities in the corneal epithelium. Therefore, the trends we observed in the normal subjects in this study could be greatly exaggerated by a combination of drug over-use and tissue exacerbation.

We feel that even with the low concentrations found in these over-the-counter preparations, significant detrimental ocular physiological changes can occur with repeated or excessive use. Further study needs to be undertaken on the effects of ocular decongestants on irritated eyes.

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Table 1. Constituents of Tested Pharmaceuticals.[1]

Preparation	*Sympathomimetic*	*Preservative*	*Buffer*	*Other Ingredients*
Visine	*Tetrahydrozoline-HCl 0.05%*	*Benzalkonium Chloride 0.01% (EDTA) 0.1%*	*1*	*E*
Clear Eyes	*Naphazoline-HCl 0.012%*	*Benzalkonium Chloride 0.01% (EDTA) 0.1%*	*1*	*B*
Prefrin Liquifilm	*Phenylephrine-HCl 0.12%*	*Benzalkonium Chloride 0.004%*	*2*	*C,D*
Lyteers (Control)	-	*Benzalkonium Chloride 0.01% (EDTA) 0.05%*	-	*A,E,F*

[1]
Buffers:

1 = Boric acid + Sodium borate
2 = Sodium phosphate + Sodium biphosphate

[2]
Other ingredients:

A = Hydroxypropylmethylcellulose
B = Methylcellulose
C = Polyvinyl alcohol
D = Antipyrine
E = NaCl
F = KCl

Table 2. Changes in Intraocular Pressure After Instillation of Pharmaceutical Agents.

Time (Minutes)		Control (Lyteers)	Tetrahydroz-oline (Visine)	Phenylephrine (Prefrin)	Naphazoline (Clear Eyes)
15	$\bar{X}$	0.3	-0.8	0.0	0.2
	Range	-2.0 to +1.5	-4.0 to +0.8	-4.2 to +2.5	-2.6 to +2.0
30	$\bar{X}$	-0.1	-1.9	-0.2	0.4
	Range	-2.1 to +1.5	-3.8 to +0.8	-1.8 to +1.2	-2.0 to +2.5
45	$\bar{X}$	-0.4	-1.4	-0.6	-0.2
	Range	-2.5 to +2.5	-3.8 to +0.3	-3.0 to +1.0	-1.6 to +1.8
2900	$\bar{X}$	-0.5	-1.2	-0.3	-0.4
	Range	-3.0 to +1.5	-3.5 to +1.8	-1.8 to +1.0	-2.5 to +2.6
5800	$\bar{X}$	-1.6	-1.4	-1.7	-2.5
	Range	-6.5 to +0.6	-4.4 to +1.5	-3.2 to +0.8	-6.5 to -0.2

Table 3. Changes in Anterior Angle After Instillation of Pharmaceutical Agents.

Time (Minutes)		Control (Lyteers)	Tetrahydroz-oline (Visine)	Phenylephrine (Prefrin)	Naphazoline (Clear Eyes)
15	$\bar{X}$	0.0	-0.1	0.0	0.0
	Range	-0.1 to +0.2	-0.3 to +0.2	-0.3 to +0.2	-0.2 to +0.2
30	$\bar{X}$	0.0	0.0	0.0	0.0
	Range	-0.2 to +0.2	-0.2 to +0.2	-0.2 to +0.2	-0.2 to +0.2
45	$\bar{X}$	0.0	0.0	0.0	0.0
	Range	-2.2 to +0.2	-0.2 to +0.2	-0.2 to +0.2	-0.2 to +0.2
2900	$\bar{X}$	0.0	0.0	0.1	-0.1
	Range	-0.3 to +0.2	-0.4 to +0.3	-0.2 to +0.2	-0.4 to +0.2
5800	$\bar{X}$	0.0	0.1	0.3	-0.1
	Range	-0.2 to +0.2	-0.4 to +0.3	-0.2 to +1.4	-0.4 to +0.1

Table 4. Changes in Pupil Size After Instillation of Pharmaceutical Agents.

Time (Minutes)		Control (Lyteers)	Tetrahydroz-oline (Visine)	Phenylephrine (Prefrin)	Naphazoline (Clear Eyes)
15	$\bar{X}$	-0.2	-0.4	-0.6	-0.1
	Range	-0.9 to +0.6	-1.0 to 0.0	-2.0 to +0.5	-0.8 to +0.8
30	$\bar{X}$	-0.3	-0.5	-0.4	-0.6
	Range	-1.1 to +0.6	-1.2 to 0.0	-1.4 to +0.7	-1.1 to +0.2
45	$\bar{X}$	0.1	-0.4	-0.3	-0.5
	Range	-1.2 to +3.5	-1.0 to +0.5	-1.8 to +1.1	-1.1 to +0.4
2900	$\bar{X}$	-0.4	0.0	-0.5	0.0
	Range	-0.9 to +0.2	-0.2 to +0.4	-1.1 to +0.5	-1.5 to +1.4
5800	$\bar{X}$	-0.3	-0.2	-0.3	0.0
	Range	-1.6 to +0.9	-1.0 to +0.4	-1.4 to +0.6	-0.4 to +0.6

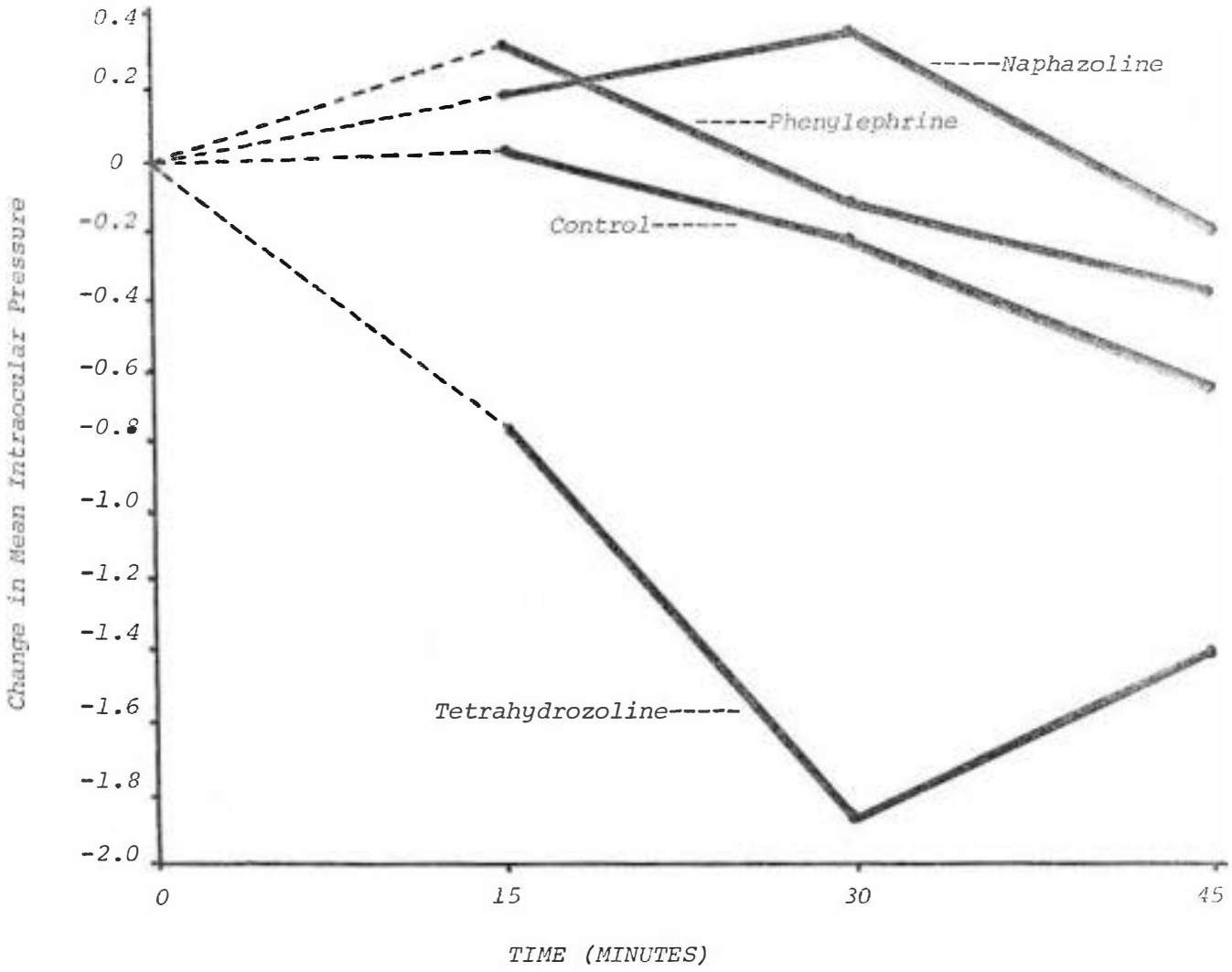
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-2.0
Change in Mean Intraocular Pressure
-----Naphazoline
-----Phenylephrine
Control------
Tetrahydrozoline-----
0
15
30
45
TIME (MINUTES)

FIGURE 1. Short Term Changes in Mean Intraocular Pressure

Appendix A

DATA SUMMARY

CONTROL (LYTEERS)

Time (Minutes)		I.O.P.	A.A.	Pupil Size
15	Mean	0.32	0.023	-0.185
	SS	9.901	0.074	2.895
	Range	-2.0 to +1.5	-.1 to +.22	-0.9 to +.55
	SD	0.995	0.086	0.538
30	Mean	-0.13	-0.002	-0.315
	SS	16.706	0.102	2.225
	Range	-2.1 to +1.5	-0.17 to +.22	-1.1 to +.55
	SD	1.292	0.100	0.471
45	Mean	-0.39	0.025	0.07
	SS	21.354	0.152	15.586
	Range	-2.5 to +2.5	-.15 to +.25	-1.2 to +3.5
	SD	1.461	0.123	1.248
2900	Mean	-0.505	-0.022	-0.361
	SS	16.502	0.280	1.864
	Range	-3.0 to +1.5	-0.3 to +.25	-0.9 to +.2
	SD	1.284	0.167	0.432
5800	Mean	-1.655	0.013	-0.3
	SS	47.317	0.184	8.745
	Range	-6.5 to +.65	-.2 to +.25	-1.6 to +.9
	SD	2.175	0.135	0.935

TETRAHYDROZOLINE-HC1 (VISINE)

Time (Minutes)		I.O.P.	A.A.	Pupil Size
	Mean	-0.765	-0.07	-0.44
	SS	17.745	0.19709	1.084
15	Range	-4.0 to +.75	-.31 to +0.2	-1.0 to +0.05
	SD	1.332	0.140	0.329
	Mean	-1.885	-0.042	-0.5
	SS	12.255	0.14856	1.25
30	Range	-3.75 to +0.75	-.19 to +.2	-1.25 to 0.0
	SD	1.107	0.122	0.353
	Mean	-1.41	-0.009	-0.38
	SS	15.344	0.14229	2.186
45	Range	-3.75 to 0.3	-0.19 to +.12	-1.05 to +0.5
	SD	1.238	0.119	0.467
	Mean	-1.185	-0.047	0.0
	SS	20.005	0.32981	0.31
2900	Range	-3.5 to +1.75	-.41 to +.32	-.2 to +.4
	SD	1.414	0.181	0.176
	Mean	-1.415	-0.077	-0.21
	SS	29.745	0.44481	2.129
5800	Range	-4.45 to +.25	-.41 to +.27	-.95 to +.40
	SD	1.724	0.211	0.461

PHENYLEPHRINE-HCl (PREFRIN)

Time (Minutes)		I.O.P.	A.A.	Pupil Size
15	Mean	0.03	-.005	-0.55
	SS	41.281	0.231	4.45
	Range	-4.25 to +2.5	-0.3 to +.2	-1.95 to +0.5
	SD	2.031	0.152	0.667
30	Mean	-0.22	0.049	-0.42
	SS	12.686	0.202	4.911
	Range	-1.8 to +1.25	-.23 to +.25	-1.45 to +0.7
	SD	1.126	0.142	0.700
45	Mean	-0.65	0.013	-0.34
	SS	14.305	0.244	6.089
	Range	-3.0 to +1	-0.23 to +0.19	-1.75 to +1.1
	SD	1.196	0.156	0.780
2900	Mean	-0.32	0.052	-0.457
	SS	11.616	0.156	2.328
	Range	-1.75 to +1	-0.2 to +0.19	-1.12 to +.5
	SD	1.077	0.124	0.482
5800	Mean	-1.73	0.295	-0.32
	SS	15.091	2.786	3.401
	Range	-3.25 to +.75	-.17 to +1.35	-1.4 to +0.55
	SD	1.228	0.527	0.583

NAPHAZOLINE-HCl (CLEAR EYES)

Time (Minutes)		I.O.P.	A.A.	Pupil Size
	Mean	-0.1966	-0.036	-0.060
	SS	18.571	0.294	1.576
15	Range	-2.6 to +2	-.25 to +.22	-.85 to +.75
	SD	1.362	0.171	0.396
	Mean	+0.3744	-0.026	-0.566
	SS	15.737	0.246	1.505
30	Range	-2 to +2.5	-.25 to +.22	-1.1 to +.35
	SD	1.254	0.157	0.388
	Mean	-0.203	-0.0218	-0.455
	SS	11.667	0.248	1.937
45	Range	-1.6 to +1.8	-0.25 to +.22	-1.1 to +0.35
	SD	1.080	0.157	0.440
	Mean	-0.386	-0.117	0.005
	SS	16.128	0.236	5.677
2900	Range	-2.5 to +2.6	-.35 to +.22	-1.5 to +1.35
	SD	1.269	0.153	0.753
	Mean	-2.47	-0.108	0.033
	SS	34.711	0.152	1.075
5800	Range	-6.5 to -0.2	-0.35 to +.07	-.45 to +0.6
	SD	1.863	0.123	0.327

Appendix B

STATISTICAL DATA TOTAL POPULATION

Analysis of Variance on Group Population Base Line Data:

Parameter		Control Group	Tetrahydrozoline Group	Phenylephrine Group	Naphazoline Group
I.O.P.	$\bar{X}$	12.51	13.71	12.72	13.78
	SS	65.58	80.13	29.56	70.86
A.A.	$\bar{X}$	1.05	1.14	0.95	1.02
	SS	0.80	0.70	0.41	0.35
P.D.	$\bar{X}$	5.22	5.06	5.18	4.58
	SS	7.77	8.19	4.99	8.04

Parameter		Sum Sq.	d.f.	Mean Sq.	F. ratio
I.O.P.	Among	13.07	3	4.36	0.66
	Within	246.13	36	6.6	
A.A.	Among	0.19	3	0.063	1
	Within	2.26	36	0.063	
P.D.	Among	2.58	3	0.86	1.06
	Within	29.01	36	0.81	

$F_{.95}(3,36) = 2.86$ There is no significance indicated in this data at the $p=0.05$ level.

Appendix C

STATISTICAL ANALYSIS OF PHYSIOLOGICAL EFFECTS

Analysis of Variance on Intraocular Pressure Data:

Time (Minutes)		Control Lyteers)	Tetrahydroz- oline (Visine)	Phenylephrine (Prefrin)	Naphazoline (Clear Eyes)	Grand Mean
15	$\bar{X}$	.32	-.765	.03	.1966	-.0546
	SS	9.901	17.745	41.281	18.571	
30	$\bar{X}$	-.13	-1.885	-.22	.3744	-.4652
	SS	16.706	12.255	12.686	15.737	
45	$\bar{X}$	-.39	-1.41	-.65	-.203	-.6632
	SS	21.354	15.344	14.305	11.667	
2900	$\bar{X}$	-.505	-1.185	-.32	-.386	-.599
	SS	16.502	20.005	11.616	16.128	
5800	$\bar{X}$	-1.655	-1.415	-1.73	-2.47	-1.818
	SS	47.317	29.745	15.091	34.711	

Time (Minutes)		Sum Sq.	d.f.	Mean Sq.	F ratio
15	Among	7.1525	3	2.3842	0.9809
	Within	87.498	36	2.4305	
30	Among	28.932	3	9.6441	6.050
	Within	57.384	36	1.5940	
45	Among	8.4431	3	2.8144	1.6167
	Within	62.670	36	1.7408	
2900	Among	4.7544	3	1.5848	0.8880
	Within	64.251	36	1.7848	
5800	Among	6.2182	3	2.0727	0.5882
	Within	126.86	36	3.5240	

$F_{.95}(3,36) = 2.86$ 30 minute data is significant. Post hoc analysis of this time frame was done to isolate the effective agent.

Post Hoc Analysis (Newman Keuls') of the 30 Minute Intraocular Pressure Data:

$$\text{Crit. Diffs} = q_r \sqrt{\frac{\text{Mean Sq. Within groups}}{n \text{ per cell}}} = q_r \sqrt{\frac{1.594}{10}} = q_r \ 0.399$$

r	$q_{r\ .95}(3,36)$	Standard Error	Crit. Diff.
2	2.87	0.399	1.145
3	3.46	"	1.380
4	3.82	"	1.524

Tetrahydrozoline vs. Control:

Difference of means = 1.755
Crit. Diff.$_3$ = 1.380 (Significant)

Phenylephrine vs. Control:

Difference of means = 0.090
Crit. Diff.$_2$ = 1.145

Naphazoline vs. Control:

Difference of means = 0.504
Crit. Diff.$_2$ = 1.145

Tetrahydrozoline vs. Phenylephrine:

Difference of means = 1.665
Crit. Diff.$_2$ = 1.145 (Significant)

Phenylephrine vs. Naphazoline:

Difference of means = 0.594
Cit. Diff.$_3$ = 1.380

Naphazoline vs. Tetrahydrozoline:

Difference of means = 2.259
Crit. Diff.$_4$ = 1.524 (Significant)

Indicated significance is at the $p = 0.05$ level.

Analysis of Variance on Anterior Angle Date:

Time (Minutes)		Control (Lyteers)	Tetrahydroz-oline (Visine)	Phenylephrine (Prefrin)	Naphazoline (Clear Eyes)	Grand Mean
15	$\bar{X}$	.023	-.071	-.005	-.0366	-.0224
	SS	.07441	.19709	.23105	.294	
30	$\bar{X}$	-.002	-.042	.049	-.0266	-.0054
	SS	.10216	.14856	.20189	.246	
45	$\bar{X}$	.025	-.009	.013	-.0218	.0018
	SS	.15205	.14229	.24421	.24813	
2900	$\bar{X}$	-.022	-.047	.052	-.117	-.0335
	SS	.28036	.32981	.15596	.23621	
5800	$\bar{X}$	.0133	-.077	.295	-.1088	.0306
	SS	.1838	.44481	2.7866	.15189	

Time (Minutes)		Sum Sq.	d.f.	Mean Sq.	F ratio
15	Among	.04928	3	.01642	.74233
	Within	.79655	36	.02213	
30	Among	.04760	3	.01587	.81762
	Within	.69861	36	.09406	
45	Among	.01340	3	.00447	.20440
	Within	.78668	36	.02185	
2900	Among	.14597	3	.04866	1.7475
	Within	1.0023	36	.02784	
5800	Among	1.0122	3	.33739	3.4049
	Within	3.5672	36	.09909	

$F_{.95}(3,36) = 2.86$ 5800 minute (96 hour) data is significant at the $p = 0.05$ level. Post hoc analysis of this time frame was done to isolate the effective agent.

Post Hoc Analysis (Newman Keuls') of the 5800 Minute Anterior Angle Data:

$$\text{Crit. diffs} = q_r \sqrt{\frac{\text{Mean Sq. within groups}}{n \text{ per cell}}} = q_r \sqrt{\frac{.09909}{10}} = q_r \cdot 0.0995$$

r	$q_{r.95}(3,36)$	Standard Error	Crit. Diff.
2	2.87	.0995	0.285
3	3.46	"	0.344
4	3.82	"	0.380

Tetrahydrozoline vs. Control:

Difference of means = 0.090
Crit. Diff.$_2$ = 0.285

Phenylephrine vs. Control:

Difference of means = 0.282
Crit. Diff.$_2$ = 0.285

Naphazoline vs. Control:

Difference of means = 0.122
Crit. Diff.$_3$ = 0.344

Tetrahydrozoline vs. Phenylephrine:

Difference of Means = 0.372
Crit. Diff.$_3$ = 0.344 (Significant)

Phenylephrine vs. Naphazoline:

Difference of means = 0.404
Crit. Diff.$_4$ = 0.380 (Significant)

Naphazoline vs. Tetrahydrozoline:

Difference of means = 0.032
Crit. Diff.$_2$ = 0.285

Indicated significance is at the p = 0.05 level.

Analysis of Variance on Pupil Diameter Data:

Time (Minutes)		Control (Lyteers)	Tetrahydroz-oline (Visine)	Phenylephrine (Prefrin)	Naphazoline (Clear Eyes)	Grand Mean
15	$\bar{X}$	-.185	-.440	-.550	-.0604	-.3088
	SS	2.8952	1.084	4.45	1.5766	
30	$\bar{X}$	-.315	-.500	-.420	-.566	-.4502
	SS	2.2252	1.25	4.911	1.5050	
45	$\bar{X}$	.070	-.380	-.340	-.455	-.2762
	SS	15.586	2.186	6.089	1.9372	
2900	$\bar{X}$	-.361	0	-.457	.005	-.2032
	SS	1.8639	0.310	2.3284	5.6772	
5800	$\bar{X}$	-.300	-.210	-.320	.033	-.1992
	SS	8.745	2.129	3.401	1.0750	

Time (Minutes)		Sum Sq.	d.f.	Mean Sq.	F ratio
15	Among	1.5242	3	.50807	1.8280
	Within	10.006	36	.27794	
30	Among	.35081	3	.11694	.42559
	Within	9.8913	36	.27476	
45	Among	1.6667	3	.55556	.77530
	Within	25.798	36	.71662	
2900	Among	1.7395	3	.57983	2.0506
	Within	10.180	36	.28276	
5800	Among	.78786	3	.26262	.61590
	Within	15.350	36	.42638	

$F_{.95}$ (3,36) = 2.86 There is no significance indicated in this data at the $p = 0.05$ level. No post hoc analysis performed.

Appendix D

STUDY RECORD FORMS

SCREENING RECORD

Name		Phone	Age	Sex	Allergies ?	History of Glaucoma	I.O.P.	Pupil Diameter	Anterior Angle

MASTER RECORDING SHEET

FOR

COMPARATIVE STUDY OF O-T-C TOPICAL OPHTHALMIC DECONGESTANTS

SUBJECT: _____

	DATE	TIME	I.O.P.(mmHg)	ANTERIOR ANGLE	PUPIL SIZE(mm)	OTHER
BASE LINE						
SHORT TERM CONDITION						
LONG TERM CONDITION						

A COMPARATIVE STUDY

OF

O-T-C TOPICAL OPHTHALMIC DECONGESTANTS

NAME:_____ AGE:_____ SEX:_____

Drug instillation schedule: Two drops are to be placed in the lower conjunctival sack as instructed three times a day. The first upon rising, the second following measurements on measurement days and the third prior to retiring in the evening. To allow for data collection and analysis, be sure to record the exact time of each instillation.

	DATE	MORNING	AFTERNOON	EVENING	COMMENTS

HUMAN SUBJECT RELEASE FORM

1. Institution
   A. Title of Project: "Getting the RED out or Hey! - White Eyes --- A Study of Non-Perscription Ocular Decongestants"
   B. Principle Investigators: Kim J. Butler
      James P. Thompson
   C. Advisor: Dr. Diane Yolton
   D. Location: Pacific University College of Optometry
   E. Date: 1977

2. Description of Project
   This project is an investigation into the changes in the physiological state of the eye induced by commonly available over-the-counter topical ophthalmic decongestants. The measured changes in the eye I.O.P., state of mydriasis and anterior angle will be used as the indeces of change. All eye drops will be self induced in a perscribed manner. All changes in eye state will be statistically compaired drug to drug to determine if a significant difference exists.

3. Decription of Risks
   The only problems reported with these drugs as cited in the literature were slight stinging sensation upon instillation in a small percentage of people and extreamly rare instances of acute angle closure glaucoma attacks in narrow angle glaucoma patients. The initial subject screening will select out all people with narrow angles and known glaucoma thus minimizing to the extream any possibility of an attack of angle closure glaucoma.

4. Description of Benefits
   This study will serve to determine which of the commonly used O-T-C decongestants, if any, produce the least changes in eye physiology. It will also serve as a well controlled experiment to either document and support commonly made claims of no significant changes in eye state with use of these drugs or find otherwise.

5. Alternatives Advantageous to Subjects
   They will now know the best method of eye drop instillation. They will be given free of charge three types of ocular decongestants and an artificial tear preparation.

6. Offer to Answer any Inquiries
   The experimenter will be happy to answer any questions that you may have at any time during the course of this study.

7. Freedom to Withdraw
   You are free to withdraw your consent and to discontinue participation in this project or activity at any time without prejudice to you.

I have read and understand the above. I am 18 years of age or over.

Signed_____ Date_____