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Comparison of anti-mydriatic effects and patient comfort fo the recommended and reduced doses of Rev-Eyes (0.5% dapiprazole HCL)

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Comparison of anti-mydriatic effects and patient comfort fo the recommended and reduced doses of Rev-Eyes (0.5% dapiprazole HCL)

Abstract

The effect on reversal of dilation of two different doses of REV-EYES (dapiprazole HCl), the recently introduced anti-mydriatic, was investigated in this study. The manufacturer's recommended dose, and exactly half that dose were compared in a double masked crossover study design. Subjects were dilated with 2.5% phenylephrine and 1% tropicamide. The pre and post dilation variables examined were near and far visual acuity, accommodative amplitude, pupil diameter, subjective symptoms, conjunctival injection, and corneal epithelial integrity by fluorescein staining. The 60 subjects that participated ranged in age from 21 to 67 years (mean = 28.6 years), in eye color (32 light and 28 dark), and in refractive status (11 emmetropes, 42 myopes, and 7 hyperopes). The results demonstrated that the half dose was functionally equivalent to the full dose in reversing the effects of dilation with fewer subjective symptoms of discomfort. No dependent relationship was found between iris color and the two different doses of REV-EYES.

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Carole Timpone

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AND
PATIENT COMFORT OF THE RECOMMENDED
AND REDUCED DOSES OF REV-EYES
(0.5% DAPIPRAZOLE HCL)**

BY

DAWN A. REINDERS
BRADLEY W. McDOUGALL

A thesis submitted to the faculty of the
College of Optometry
Pacific University
Forest Grove, Oregon
for the degree of
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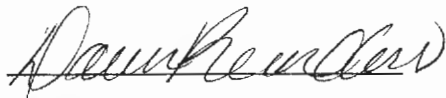
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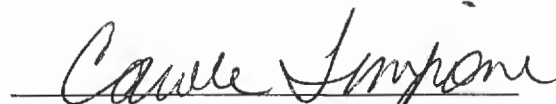
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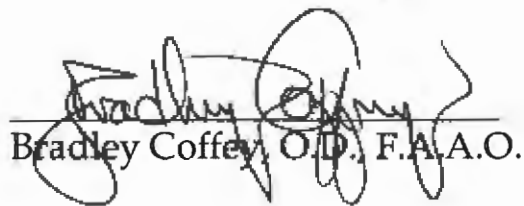

Bradley Coffey, O.D., F.A.A.O.

TABLE OF CONTENTS

ACKNOWLEDGMENTS	i
ABOUT THE AUTHORS	ii
ABSTRACT	iii
INTRODUCTION	1
METHODS	5
RESULTS	15
Tables and Figures	19
DISCUSSION	37
REFERENCES	46

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ABOUT THE AUTHORS

Dawn Reinders is from Peace River, Alberta, Canada. Dawn did her undergraduate work at the University of Alberta in Edmonton, Canada, and received her Bachelor of Science degree from there in 1988 with a major in biological sciences. Dawn entered Pacific University's College of Optometry in the fall of 1989. During the four years Dawn spent in Oregon, she enjoyed the beautiful Oregon scenery, the coast, the skiing, and the Oregon Symphony.

Following graduation in May of 1993, Dawn plans return to Canada to practice in a primary care, family practice setting.

Brad McDougall is from St. Albert, Alberta, Canada. He attended the University of Alberta in Edmonton for two years before entering Pacific's College of Optometry. He completed his Bachelor of Science degree in visual sciences in 1991 at Pacific University. During his education at Pacific, Brad was president of the Student Optometric Association, and developed a keen interest in behavioral and performance vision.

After graduating in May of 1993, Brad plans to complete a one year residency in Family Practice Optometry in Alabama before returning to Western Canada to practice.

ABSTRACT

The effect on reversal of dilation of two different doses of REV-EYES (dapiprazole HCl), the recently introduced anti-mydriatic, was investigated in this study. The manufacturer's recommended dose, and exactly half that dose were compared in a double masked crossover study design. Subjects were dilated with 2.5% phenylephrine and 1% tropicamide. The pre and post dilation variables examined were near and far visual acuity, accommodative amplitude, pupil diameter, subjective symptoms, conjunctival injection, and corneal epithelial integrity by fluorescein staining. The 60 subjects that participated ranged in age from 21 to 67 years (mean = 28.6 years), in eye color (32 light and 28 dark), and in refractive status (11 emmetropes, 42 myopes, and 7 hyperopes). The results demonstrated that the half dose was functionally equivalent to the full dose in reversing the effects of dilation with fewer subjective symptoms of discomfort. No dependent relationship was found between iris color and the two different doses of REV-EYES.

KEY WORDS: REV-EYES, dapiprazole, dose, mydriasis, phenylephrine, tropicamide, alpha-adrenergic blocker

INTRODUCTION

Dilation of the pupil for adequate examination of the fundus is now the standard of care in optometry.¹ Failure to dilate is the most prevalent reason for optometrists being charged with negligence for not diagnosing ocular diseases.² However, the post dilation stage often leaves the patient with blurred vision, decreased accommodative amplitude, photophobia, and concern about performing certain visual tasks such as driving. This can make the patient apprehensive about dilation. Due to these post dilation side effects, safe reversal of mydriasis would be desirable to return the patient to his/her pre-dilated state.³ Safe reversal of dilation may even become part of the standard of care in the eye care profession.²

Pilocarpine, a cholinergic miotic, has been investigated for this use, however, its actions may be more harmful than helpful.⁴ Pilocarpine causes undesirable accommodative spasm, thickening of the crystalline lens, and shallowing of the anterior chamber which can potentiate pupillary block.⁵ Studies involving thymoxamine, an alpha-adrenergic blocker, have shown that it is effective in reversing mydriasis with mild irritation, but is most effective only with blue colored irides.⁶

Dapiprazole HCl, manufactured by Abbott Laboratories and marketed by Storz Ophthalmics as REV-EYES, is an alpha-adrenergic blocker currently approved and available to practitioners for the reversal of mydriasis. Dapiprazole HCl, which is 5,6,7,8-

tetrahydro-3-[2-(4-o.tolyl-1-piperazinyl)ethyl]-s-triazolo[4,3-a]pyridine hydrochloride, exerts its effects by competing for receptor sites on the iris dilator, thus blocking its action and causing relaxation of the radial iris muscle. Reversing mydriasis in this way cannot favor pupil block, and it has been found that dapiprazole decreases IOP, whereas, thymoximine does not.⁷ Dapiprazole does not have any affect on heart rate or blood pressure.⁸ When applied topically, dapiprazole that reaches the endothelium has no toxic affect on the rabbit cornea.⁹ Studies using ultrasonographic techniques show that dapiprazole used topically has no effect on accommodation, as determined by changes in the anterior chamber depth and lens thickness.⁵

The adverse side-effects of dapiprazole include: stinging upon instillation, conjunctival injection, lid edema and redness, corneal staining, tearing, dryness, photophobia, blurred vision, browache, headache, and prolonged miosis.⁸

Studies concerning the effectivity of dapiprazole when used to reverse dilation show that it is most effective when phenylephrine is used alone; complete reversal of mydriasis occurs within an hour.¹⁰ Literature from the company states that 67% of eyes were reversed at one-half hour, and 88% of eyes were reversed at one hour. Dapiprazole is less effective when tropicamide is used for dilation (either alone or in combination with phenylephrine), and it usually takes about two hours for reversal of the pupil diameter.¹⁰

In order to attain quick and wide mydriasis, both an adrenergic agent (which enhances the iris dilator) and an anticholinergic agent (which relaxes the iris sphincter and ciliary muscle) should be used in combination. Phenylephrine and tropicamide have onset and duration times that are similar.¹¹ Using the two in combination offers the most complete dilation. Using each alone will still allow some pupillary constriction when a bright light source, such as a binocular indirect ophthalmoscope, is presented. The two drugs in conjunction also enable the ciliary muscle to be relaxed so that uncomfortable ciliary spasm can be avoided when such a bright light is shone into the eye.¹¹ For dilation purposes it is standard at Pacific University College of Optometry clinics, as is common with many practitioners, to use a combination of 2.5% phenylephrine and 1% tropicamide.

Although REV-EYES is approved only for the reversal of mydriasis by topical ocular instillation, intraocular administration of dapiprazole to induce miosis after extra capsular cataract extraction has been investigated; it was found to be rather comparable to acetylcholine with respect to reducing postoperative pressure rise, but dapiprazole has a slower onset and longer duration.^{12,13} The use of dapiprazole with epinephrine for treating primary angle closure glaucoma has also been studied, and in the opinion of the authors the combination appears to be a good choice.¹⁴

Most published literature to date, including that mentioned above, has been concerned with the reversal rate of pupil diameter.

However, to the dilated patient, an enlarged pupil diameter is not the only significant functional problem. Additional studies have addressed the effect of dapiprazole on other isolated physiological components such as accommodation or anterior chamber depth, but none have examined the clinically relevant functional benefits to the patient. In addition, clinical impressions at Pacific University from the preliminary use of REV-EYES have suggested that a dosage reduced from that recommended by the manufacturer may be functionally adequate and in some cases, more desirable from the patient's perspective.

The purpose of this study is to avail practical information regarding the use of REV-EYES to eye care practitioners to afford maximum benefit with minimal adverse effects to their patients. We examined several variables that may affect a practitioner's decision to use this drug, not use this drug, or use a dose different than that recommended. We compared our subjects' ocular physiological response and visual performance via measurement of pupil diameter, accommodative amplitude, far and near visual acuities, subjective comfort, and observed side effects for the natural, non-pharmacologically induced reversal process, and for two different doses of REV-EYES, the full recommended dose and one half the recommended dose.

METHODS

The subjects in the study were volunteer students and their families at the Pacific University College of Optometry. Of the 60 subjects, 30 were male and 30 were female. The mean age was 28.6, and the age range extended from 21 to 67 years old. Other subject variables considered were: iris color (32 light; 28 dark) and refractive error (11 emmetropes; 42 myopes; 7 hyperopes). Subjects with dark irides were Caucasian, Asian, Hispanic, and Indian.

Potential subjects that were excluded from participation in the study included: those under the age of 18; pregnant women and nursing mothers (as suggested by the manufacturers of REV-EYES); those with a history of anterior uveitis, diabetes, hypertension, or any medical contraindications for dilation; and those with any form of pupil/iris abnormality, pathological or physiological anisocoria, amblyopia or functional inequalities between the two eyes, current use of ocular medication, or ocular or systemic contraindications or allergies to any of the ophthalmic drugs used in this study (proparacaine 1%, phenylephrine 2.5%, tropicamide 1%, or dapiprazole HCl 0.5%).

Full ethical research consent was obtained from the Institutional Review Board Human Research Approval Committee prior to any clinical research. A written informed consent form including a description of the study, exclusion criteria, risks, benefits, and a

freedom to withdraw statement, was read and signed by all subjects prior to their participation.

The design of the study consisted of two phases. The first phase involved a standard dilation of both eyes of each subject without the instillation of REV-EYES. The second phase consisted of a standard dilation of both eyes which was interrupted after 45 minutes with the randomized instillation of either the experimental half dose or the control full dose of REV-EYES into each eye. The first and second phases were separated by at least seven days.

PHASE ONE

The first phase served as a baseline data resource. From these data we were able to determine if each of the subject's eyes responded equally to the mydriatic agents on all variables, as we planned to use a crossover experimental design where one eye serves as a control for the other in phase two. Also from this data we were able to make statements about certain dilating characteristics of the different sub-samples of the subjects. This baseline also allowed us to compare the effectivity and benefits of using REV-EYES as an anti-mydriatic versus a natural reversal process.

In the first phase, for both the left and right eyes of each subject the following variables were measured: pupil size, Donder's accommodative amplitude, and best corrected distance and near visual acuity. Methods of measurement of each of these variables are described later in this section.

After these measurements were recorded, and the subject was deemed safe for standard dilation (a complete optometric examination within the six previous months was required), one drop each of proparacaine 1%, phenylephrine 2.5%, and tropicamide 1% was administered, separately, into the conjunctival sac of each eye. Punctal occlusion to limit systemic absorption was performed by the subject.

Anesthetic was used before the dilation to both decrease the irritation of the medication and also enhance the corneal permeability to the dilating drugs. By eliminating the stinging, both lacrimation and the blink response are decreased, thereby decreasing drug dilution and nasolacrimal drainage.¹⁶ The goal here was to simulate a standard clinical situation, and to achieve maximum dilation.

After the drops had been administered, the subject returned to have each of the variables measured at 45 minutes, 75 minutes, 105 minutes, and 24 hours following drop instillation. This time schedule was adopted so that cross-comparisons could be made to the time schedule used in phase two.

The 45 minute interval was selected as the first time interval for two reasons: 1) this is the approximate time that the subjects would be reaching their maximum pupil dilation with phenylephrine and tropicamide¹¹, and 2) in clinical optometric setting, this is about the

length of time required after instilling the drugs to wait for sufficient dilation, to perform a thorough fundus examination, and to discuss findings with a patient, after which the REV-EYES might be instilled. Thus, in the second phase of the study the introduction of REV-EYES occurred at 45 minutes to simulate clinical practice.

PHASE TWO

The second phase of the study consisted of dilating both of the subjects' eyes, and then randomly introducing either a control dose (manufacturer's recommended) or experimental dose (half of the recommended) of REV-EYES into each of their eyes to iatrogenically reverse the mydriasis.

At the start of the second phase each of the subject's eyes had the following variables measured: pupil diameter, Donder's accommodative amplitude, best far and near visual acuity, conjunctival injection, and corneal staining. Again, the measurement techniques used are described later in this section.

Dilation was once more achieved with proparacaine 1%, phenylephrine 2.5%, and tropicamide 1%. At the 45 minute time interval (45 minutes post dilation/pre REV-EYES) measurements were again taken. At this point, each of the subject's eyes randomly received either the experimental half dose or the control full dose of REV-EYES. In this manner, one of the eyes served as a control for the other. This was valid since in the first phase we had shown that

there were no significant differences between the responses of either the right or left eyes of each subject (see Results).

The control dose used in this study was the manufacturer's suggested dose, as written both on the bottle and in the instruction set enclosed with the drug packaging: two drops in quick succession, a five minute time interval, followed by another two drops in succession into each eye.

The manufacturer of REV-EYES chose to use a gravity-feed dropper as the dispenser of REV-EYES. This type of bottle delivers only approximately half (25 microliters) of a standard dropper's single drop. Clinically, the gravity-feed dropper permits instillation of precise and consistent volumes of drug onto the cornea. Since the conjunctival sac only holds 30 microliters without overflow¹⁶, the purpose of the two drops in quick succession (50 microliters) is to insure that enough drug actually reaches the eye.

The experimental dose selected for this study is simply one half of the recommended dose, that is, two drops from the gravity-feed dropper in quick succession. The benefits of using half of the recommended dose to the eye care practitioner are primarily that of time and cost effectiveness, however, these and other potential benefits to the patient will be discussed at further length in the discussion section of this paper.

To achieve the experimental dose without subjects being aware that they were receiving only half as much drug in one eye, the second set of two drops was replaced with two drops of preservative free artificial tears dispensed from a drug-free and sterilized REV-EYES bottle. These bottles were marked with a small dot so that the researchers were aware of the contents of the bottle. To the subjects, it appeared as though they were receiving all of their drops from a standard REV-EYES bottle. Therefore, the experimental dose consisted of two drops of REV-EYES, followed by a five minute interval, then two drops of artificial tears from the second sterilized REV-EYES bottle.

The study was designed to be double masked. Neither the subject nor the researcher taking the measurements were aware of which eye had received the control or experimental dose. All clinical measurements were taken by the same two researchers throughout the extent of the study. The subjects were arranged so that one researcher would perform all drop administration, including the randomized REV-EYES dosages on one subject, but would do none of the variable measurements on this same subject.

Following the administration of the two different doses, the subject was required to return for measurements at the following intervals: 30 minutes, 60 minutes, and 24 hours post REV-EYES.

In the period between 60 minutes and the 24 hour follow up, all subjects were instructed not to use any lubricant drops or vasoconstrictors on either eye.

The major variables during both the first and second phase which we examined were:

PUPIL SIZE:

Pupil size was measured using a Cogan pupillometer. This consisted of a pair of black opaque goggles, and a strip of black paper with sets of 2 adjacent pinholes, successively separated every half millimeter.¹⁵ Before the study began, each subject was instructed on the use of the pupillometer (measurements are, hence, subjective in nature). The subject was instructed to put on the goggles, cover the left goggle with the palm of the hand, place the black paper strip over the right side of the goggles and look up at the light source (standard fluorescent lighting). The subject was then able to see several sets of two adjacent circles of light as they scrolled the black paper up and down along the goggle. Depending on the subject's pupil size and the various separations in the pinholes, some sets of circles would appear overlapping, while some would appear completely separated. The subject was instructed to find the set of circles such that the two circles of light just touched (where they did not overlap or remain separated). This was to be indicated to the researcher. The subject was informed that the circles may appear to move (this is due to fluctuations in

accommodation), and that if no set of circles just touched, the set of circles that was barely overlapping should be chosen. For ease of subject understanding, examples of what they should expect to see were drawn for them, and each subject was instructed to practice the technique a few times. All subjects quickly became very skilled in measuring their pupils in this manner.

DONDER'S ACCOMMODATIVE AMPLITUDE:

Measurements of an effective nearpoint were made using a standard Donder's card. Subjects were instructed to bring the card as close to their eyes as possible until the 0.62M print was too blurry to read. All measurements were made monocularly in centimeters with a pull out tape measure (one end at the plane of the eye and the other at the plane of the card).

BEST VISUAL ACUITY AT FAR (BVA FAR):

Distance visual acuity was measured through the subject's refractive correction at six meters using a projected Snellen acuity chart under standard room illumination. All measurements were taken monocularly.

BEST VISUAL ACUITY AT NEAR (BVA NEAR):

Near visual acuity was measured through the subject's near correction (which was a bifocal for some subjects) at 40 centimeters using a reduced Snellen acuity card under standard

room illumination with a near point light. All measurements were taken monocularly.

Additionally, in the second phase, each subject was evaluated for signs of injection or corneal staining at the various time intervals.

CONJUNCTIVAL INJECTION:

Injection was rated on a scale of zero to four, where zero indicates no injection and four indicates very severe injection. *See Table 1.*

TABLE 1: Conjunctival Injection

Grade 0: None

1: Minimal conjunctival injection, no chemosis

2: Moderate conjunctival injection, no chemosis

3: Moderate conjunctival injection, moderate chemosis

4: Severe conjunctival injection and chemosis

CORNEAL STAINING:

Staining also was graded on a scale of zero to four, four denoting the most severe superficial punctate erosion. The amount of staining was assessed using fluorescein strips hydrated with sterile saline. *See Table 2.*

TABLE 2: Corneal Staining

Grade 0: Absent

1: Countable dots

2: Increase in number of countable dots, with some clumping

3: Coalescent macropunctate fluorescence

4: Complete coalescence, with epithelial loss

SUBJECTIVE SURVEY:

Symptoms were evaluated by the subjects at two points during the second phase. Immediately following the administration of REV-EYES, each subject was asked by the researcher who did not administer the drops to rate the stinging/discomfort of the drops on a scale of one to seven, where 'one' indicates 'none' and 'seven' ranks 'severe'. At 30 minutes post REV-EYES administration the subjects were given a written questionnaire to fill out. The subjects ranked the following symptoms on a scale of one to seven (none to severe):

Eye itching

Eye dryness

Tearing

Sensitivity to bright lights

Headache or browache

Lids: red, puffy or itchy

Eye redness; "How red do your eyes look?"

To increase awareness of any differences in appearance between eyes, all subjects were instructed to cover the fellow eye with a palm, and to look at each eye separately (each subject was given a mirror to use).

RESULTS

In this crossover study design, since right and left eyes of each subject received a different dose of REV-EYES, it was essential that we establish there was no difference between the subject's eyes for the variables we chose to measure: pupil diameter, Donder's amplitude, near acuity, and far acuity. The phase one dilation data served as a baseline for this purpose. Our analyses showed that there were no significant differences between the left and right eyes of the subjects on any of the variables measured using both a two tailed paired t-test analysis and a two-way ANOVA (analysis of variance) with repeated measures ($p < 0.05$). Therefore, since both eyes of each subject responded the same for the variables measured, one eye could serve as a control for the other.

The results from the phase two dilation, where the two different doses of REV-EYES were used to reverse the mydriasis, were analyzed using a two tailed paired t-test and a two-way ANOVA with repeated measures at a level of significance of $p < 0.05$. The effectivity of the full and half dose on each of the variables was compared. Near visual acuity, pupil diameter, and Donder's accommodative amplitude were the dilation variables found to be significantly different with respect to dosage when two tailed paired t-test analysis was used. *See Table 3; Figures 1, 2, & 3.* However, when comparing the variables using a two-way ANOVA, there were no significant differences found across time between the full dose and the half dose on any of the variables measured. That is, the

mydriatic reversal accomplished using the half dose of REV-EYES was statistically the same as for the full dose of REV-EYES.

The effects of a drug induced mydriatic reversal were also compared to a natural, without administration of REV-EYES, reversal. These were analyzed using a two tailed paired t -test. Differences ($p < 0.05$) in pupil size, accommodative amplitude, and NVA were found when using no drug compared to using either dose of REV-EYES. *See Table 3.*

We also examined the data to see if there were any differences in the extent to which subjects with light or dark irides were affected by the two different doses of REV-EYES. With the t-test analysis, there was no difference ($p > 0.05$) between the effectivity of the full or half dose when used on subjects with light or dark irides with respect to any of the variables across time. Both the full and half dose affected each group equally. However, the unpaired t-test showed that subjects with light irides returned to their baseline near acuity and pupil diameter faster than subjects with dark irides. *See Table 4; Figures 5a, & 5b.* This difference is independent of whether the full or half dose was used.

Two-way ANOVA statistics also showed no significant difference between iris color and either dosage. However, there was a significant relationship over time with respect to iris color and pupil size with both doses of REV-EYES. The light iris group showed larger pupil sizes initially, 5.14 mm versus 4.76mm, (before

administration of any mydriatic agents), but at and after administration of either dose of REV-EYES, they had smaller pupils than the dark iris group (at time zero minutes, 30 minutes, and 60 minutes). This suggests that subjects with light iris color reacted more quickly to REV-EYES than those with darker iris color.

Each of the subjects completed the subjective survey, and their responses were analyzed using descriptive statistics, a percentage distribution, and the Wilcoxon signed-rank test ($Z > 1.65$, $p < 0.05$). See *Table 5; Figures 6,7,8,9,&10*.

Each subject was objectively examined under double masked conditions to determine the level of conjunctival injection and corneal staining due to the instillation of REV-EYES. These measurements were taken before REV-EYES instillation, and at 30 minutes, 60 minutes, and 24 hours after instillation of REV-EYES. The results were also analyzed using the Wilcoxon signed-rank test ($Z > 1.65$, $p < 0.05$). See *Table 6*.

The two-way ANOVA test also showed that there was a significant difference in objectively measured conjunctival injection between the full and half dose of REV-EYES: the full dose causing significantly more conjunctival injection than the half dose ($p = 0.0008$). There was no significant difference in corneal staining with the ANOVA.

Our statistical analysis included one-way ANOVA comparisons of emmetropic, myopic, and hyperopic subjects in the first baseline

phase of the study. There were no significant differences between these three groups with respect to far or near acuity, or pupil size. However, comparisons of these samples revealed that the hyperopic subjects have a significantly worse Donder's accommodative amplitude than the myopes or the emmetropes at all times of measurement including the initial measurement ($p < 0.05$). See *Figure 11*. The manner in which the different refractive status groups were affected by the two doses of REV-EYES, with respect to the variables measured, was analyzed using two-way ANOVA statistics. The only significant difference found was that the myopes' accommodative amplitude returned faster than the other two groups, but only with the full dose ($p=0.0136$). See *Figures 12&13*.

Table 3: Full Dose, Half Dose, and No Dose of REV-EYES

FULL DOSE, HALF DOSE, & NO DOSE OF REV-EYES TWO TAILED PAIRED T-TEST		(Significant Differences Highlighted p<0.05)		
TIME	DILATION VARIABLE	NODOSE (MEAN)	FULL DOSE (MEAN)	HALF DOSE (MEAN)
BASELINE	PUPIL SIZE (mm)	5.292	4.87	4.958
	ACCOM. AMP. (cm)	9.758	10.508	10.367
	NEAR ACUITY	20/20	20/20	20/20
0 MINUTES	PUPIL SIZE (mm)	8.075	8.058	8.058
	ACCOM AMP. (cm)	53.58	56.233	56.4
	NEAR ACUITY	20/92	20/104	20/104
30 MINUTES	PUPIL SIZE (mm)	8.1	7.375	7.575
	ACCOM. AMP. (cm)	44.5	30.35*	32.98*
	NEAR ACUITY	20/67	20/42	20/47
60 MINUTES	PUPIL SIZE (mm)	8.033	6.725	7.05
	ACCOM. AMP. (cm)	33.85	18.117	23.317
	NEAR ACUITY	20/45	20/26	20/28
24 HOURS	PUPIL SIZE (mm)	5.275**	4.55	5.692**
	ACCOM. AMP. (cm)	11.05	10.608	10.95
	NEAR ACUITY	20/20	20/20	20/20
* NO SIGNIFICANT DIFFERENCE BETWEEN FULL DOSE AND HALF DOSE AT 30 MINUTES				
** NO SIGNIFICANT DIFFERENCE BETWEEN NO DOSE AND HALF DOSE AT 24 HRS POST				
THERE WERE NO DIFFERENCES WITH ANOVA FOR FULL DOSE VS. HALF DOSE (p<0.05)				

Table 4: Reversal Rates of Light and Dark Irides

REVERSAL RATES: LIGHT vs DARK IRIDES UNPAIRED T-TEST			(Significant Differences Highlighted Text: $p < 0.05$)	
TIME	DILATION VARIABLE	DOSE	LIGHT IRIDES (MEAN)	DARK IRIDES (MEAN)
BASELINE	PUPIL SIZE (mm)	FULL	5.14	4.77
		HALF	5.14	4.75
	NEAR ACUITY	FULL	20/20	20/20
		HALF	20/20	20/20
0 MINUTES	PUPIL SIZE (mm)	FULL	8.046	8.071
		HALF	8.046	8.071
	NEAR ACUITY	FULL	20/97.81	20/110.35
		HALF	20/98.44	20/110.35
30 MINUTES	PUPIL SIZE (mm)	FULL	7.094	7.696
		HALF	7.359	7.821
	NEAR ACUITY	FULL	20/32.2	20/53.2
		HALF	20/34.8	20/60.9
60 MINUTES	PUPIL SIZE (mm)	FULL	6.438	7.054
		HALF	6.75	7.393
	NEAR ACUITY	FULL	20/22.2	20/30.4
		HALF	20/22.8	20/35.4
THERE WERE NO SIGNIFICANT DIFFERENCES FOUND BETWEEN DARK AND LIGHT IRIDES WITH ANOVA STATISTICS ACROSS TIME ($p < 0.05$).				

Table 5: Subjective Symptoms

SUBJECTIVE SURVEY OF SYMPTOMS		(Significant Diff. $p < 0.05$)
Wilcoxon Signed Rank		MEAN SCORE
<i>SYMPTOMS</i>	<i>DOSE</i>	<i>(out of 7)</i>
TEARING	FULL	1.633
	HALF	1.45
HEAD/BROWACHE	FULL	1.783
	HALF	1.583
LID REACTION	FULL	2.233
	HALF	2.033
PERCEIVED REDNESS	FULL	4.55
	HALF	3.917
INITIAL DISCOMFORT OF DROPS	FULL	4.075
	HALF	3.925

Table 6: Conjunctival Injection and Corneal Staining

CONJUNCTIVAL INJECTION & STAINING POST REV-EYES			
WILCOXON SIGNED RANK (Significant Differences Highlighted p<0.05)			
			<i>MEAN</i>
<i>TIME</i>	<i>OBJECTIVE MEASURE</i>	<i>DOSE</i>	<i>RANKING</i>
<i>BASE LINE</i>	<i>INJECTION</i>	<i>FULL&HALF</i>	<i>0.267</i>
	<i>STAINING</i>	<i>FULL&HALF</i>	<i>0.008</i>
<i>0 MINUTES</i>	<i>INJECTION</i>	<i>FULL&HALF</i>	<i>0.592</i>
	<i>STAINING</i>	<i>FULL&HALF</i>	<i>0.2</i>
<i>30 MINUTES</i>	<i>INJECTION</i>	<i>FULL*</i>	<i>2.183</i>
		<i>HALF*</i>	<i>1.933</i>
	<i>STAINING</i>	<i>FULL</i>	<i>0.308</i>
		<i>HALF</i>	<i>0.275</i>
<i>60 MINUTES</i>	<i>INJECTION</i>	<i>FULL*</i>	<i>2.058</i>
		<i>HALF*</i>	<i>1.617</i>
	<i>STAINING</i>	<i>FULL</i>	<i>0.308</i>
		<i>HALF</i>	<i>0.275</i>
<i>24 HOURS</i>	<i>INJECTION</i>	<i>FULL*</i>	<i>0.667</i>
		<i>HALF*</i>	<i>0.517</i>
	<i>STAINING</i>	<i>FULL</i>	<i>0.008</i>
		<i>HALF</i>	<i>0</i>
*SIGNIFICANT DIFFERENCES BETWEEN FULL AND HALF DOSE WITH ANOVA (p<0.05) FOR CONJUNCTIVAL INJECTION.			

Figure 1

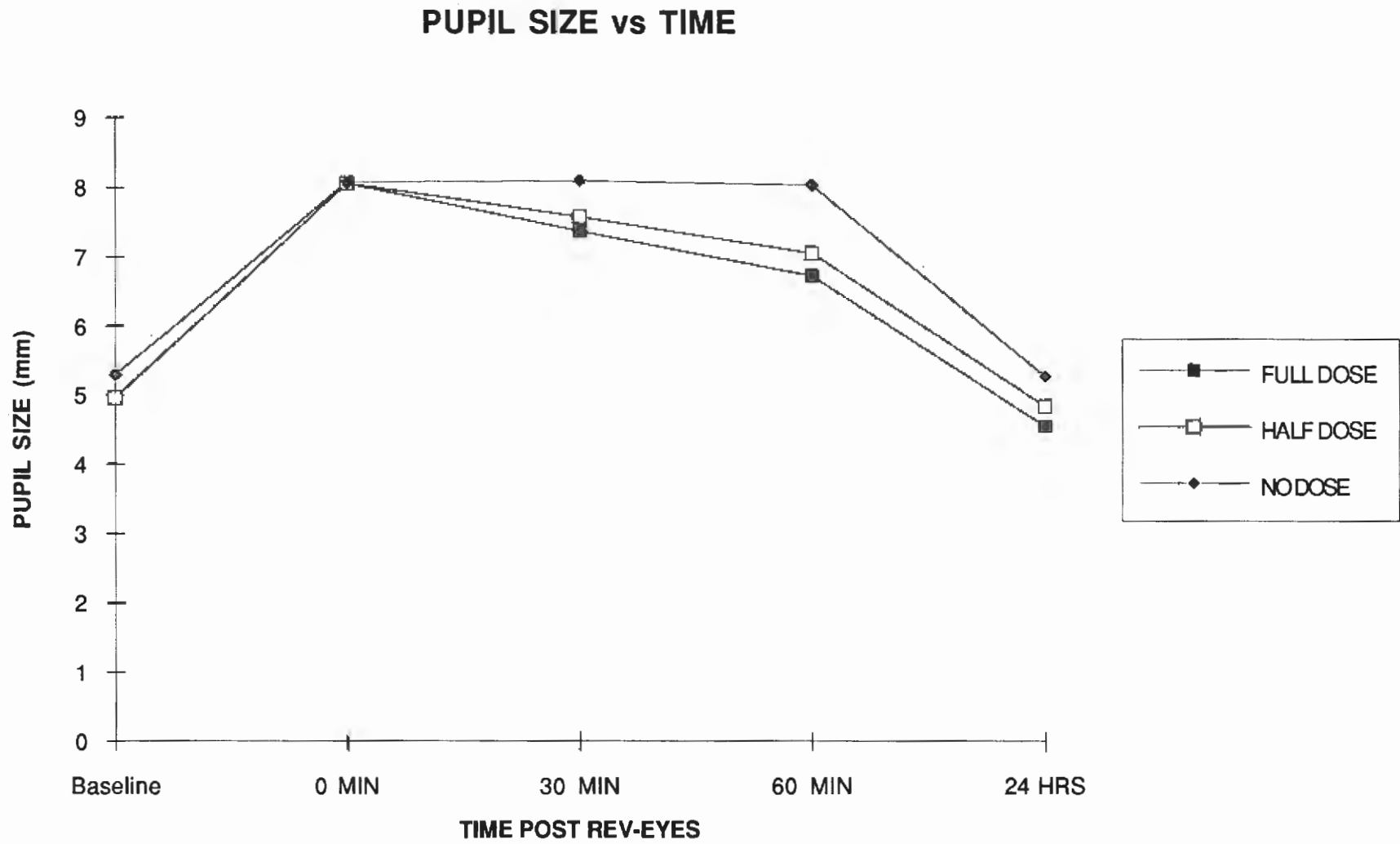


Figure 2

NVA vs TIME

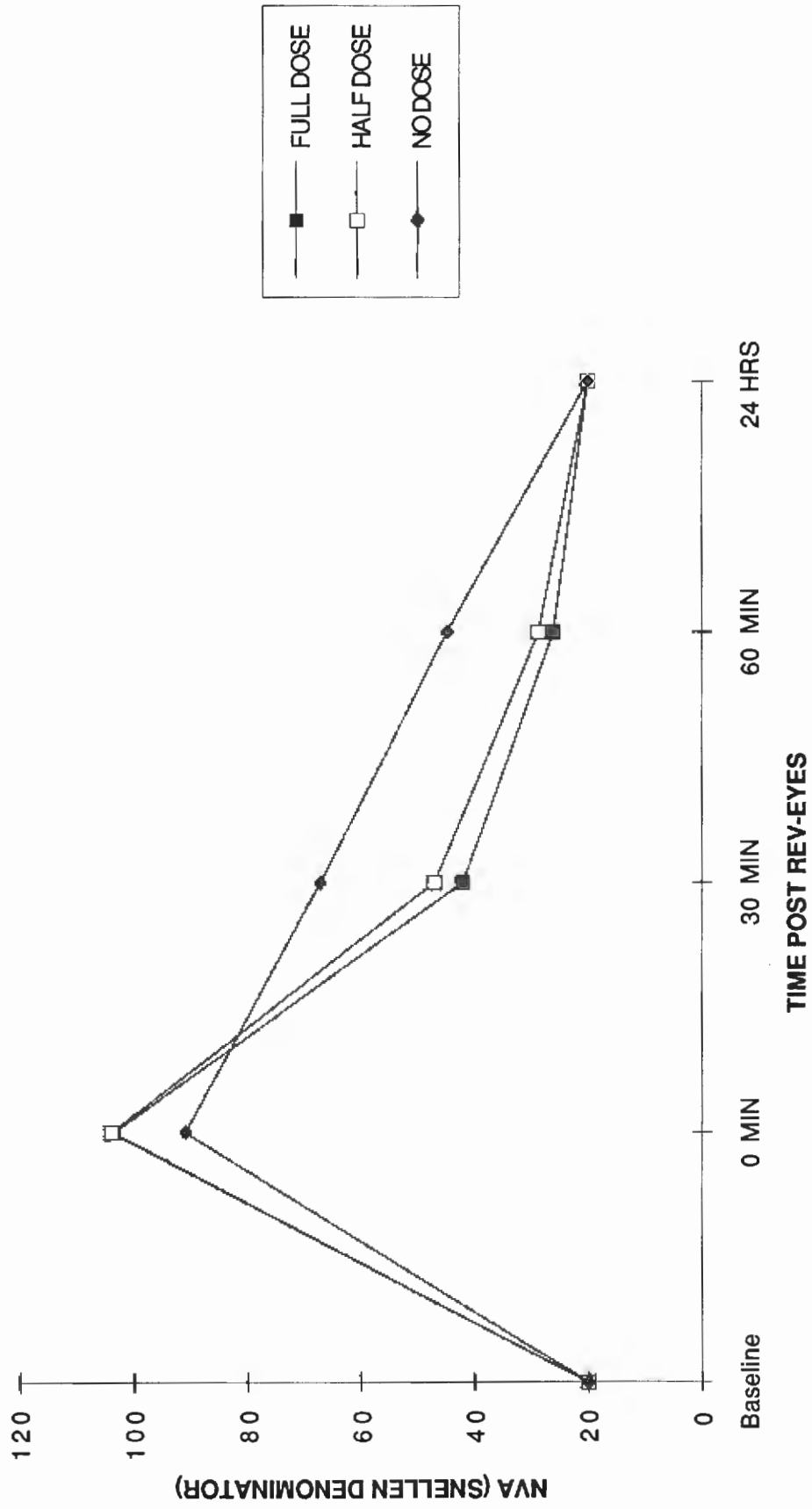


Figure 3

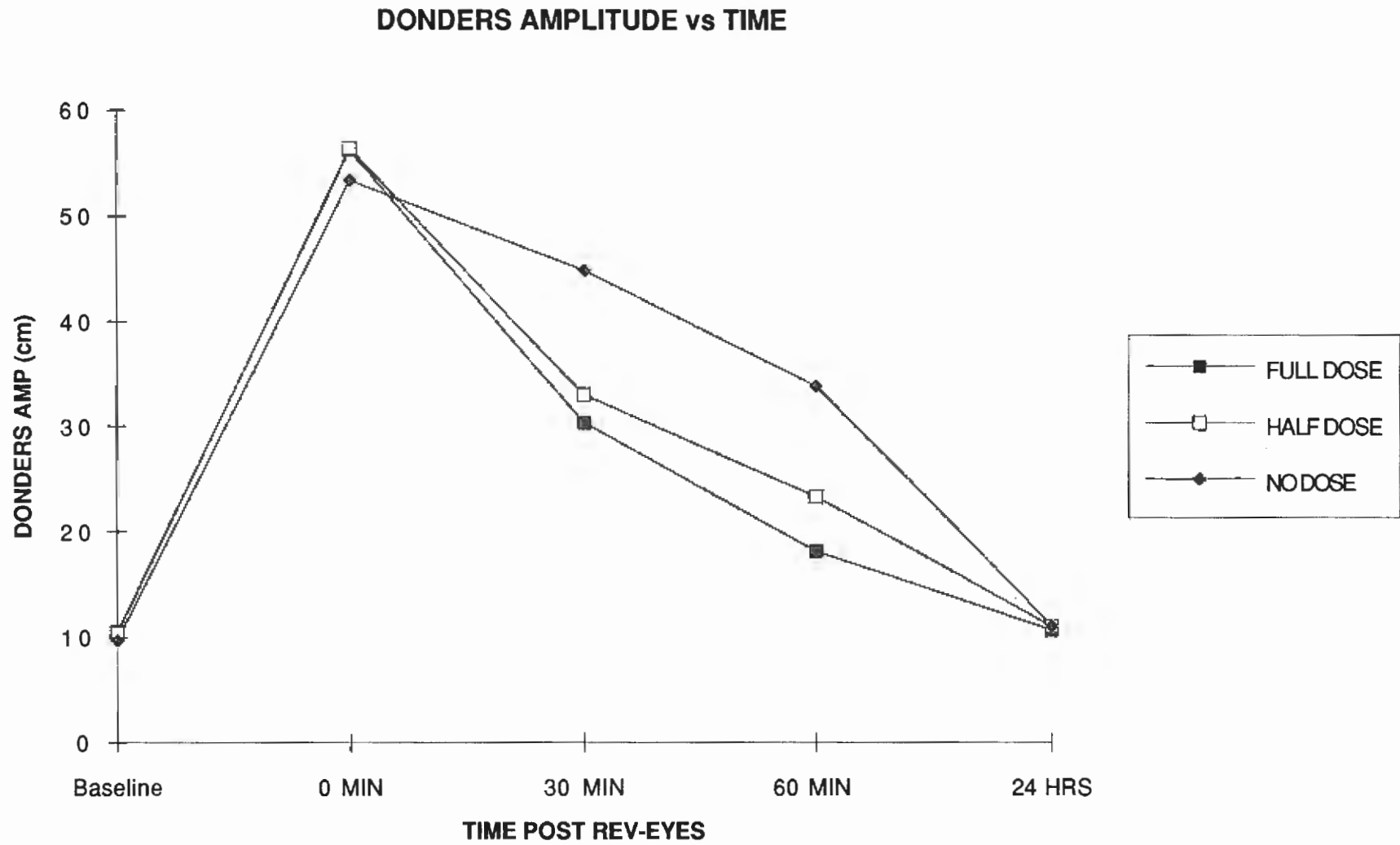


Figure 4

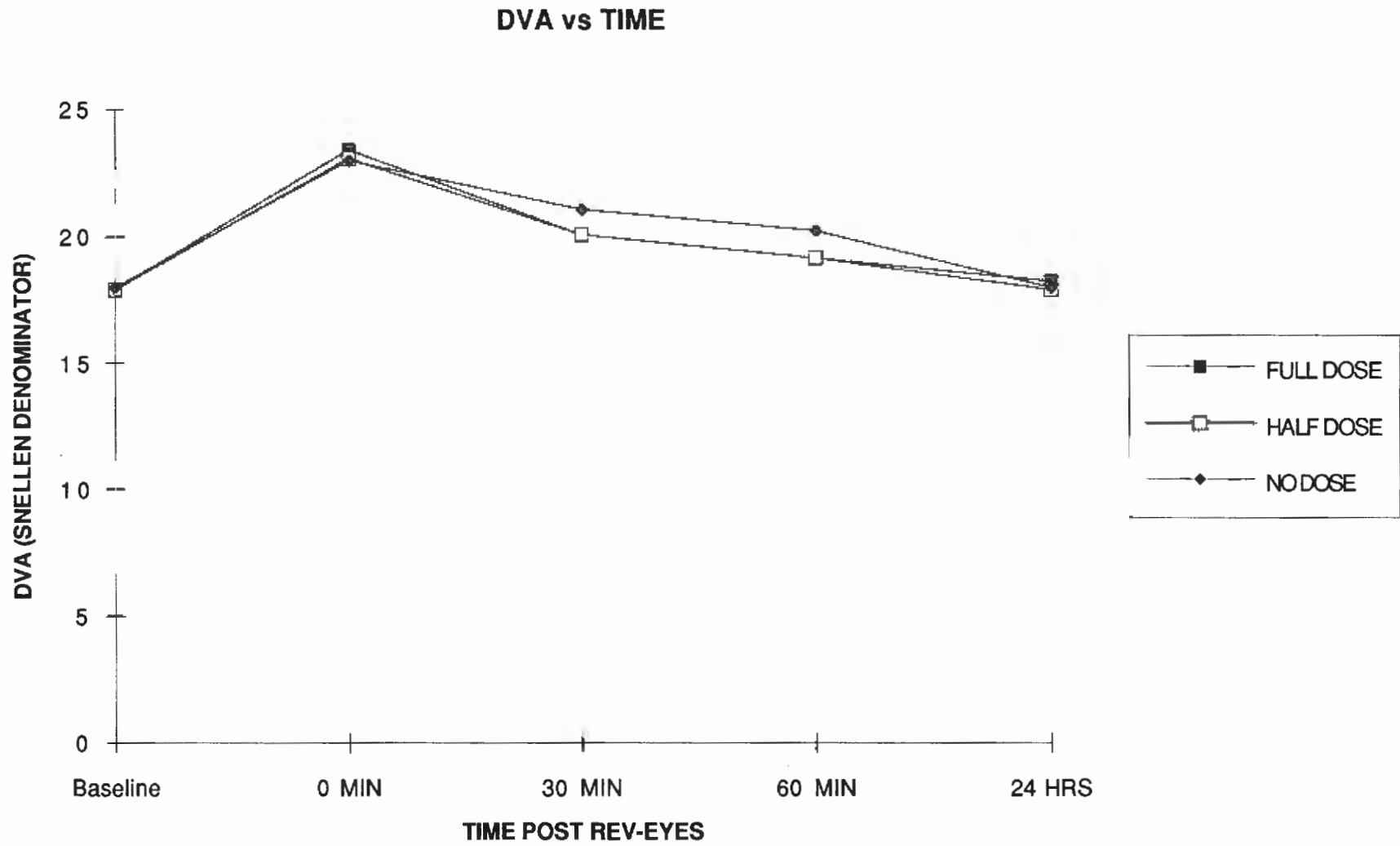


Figure 5a

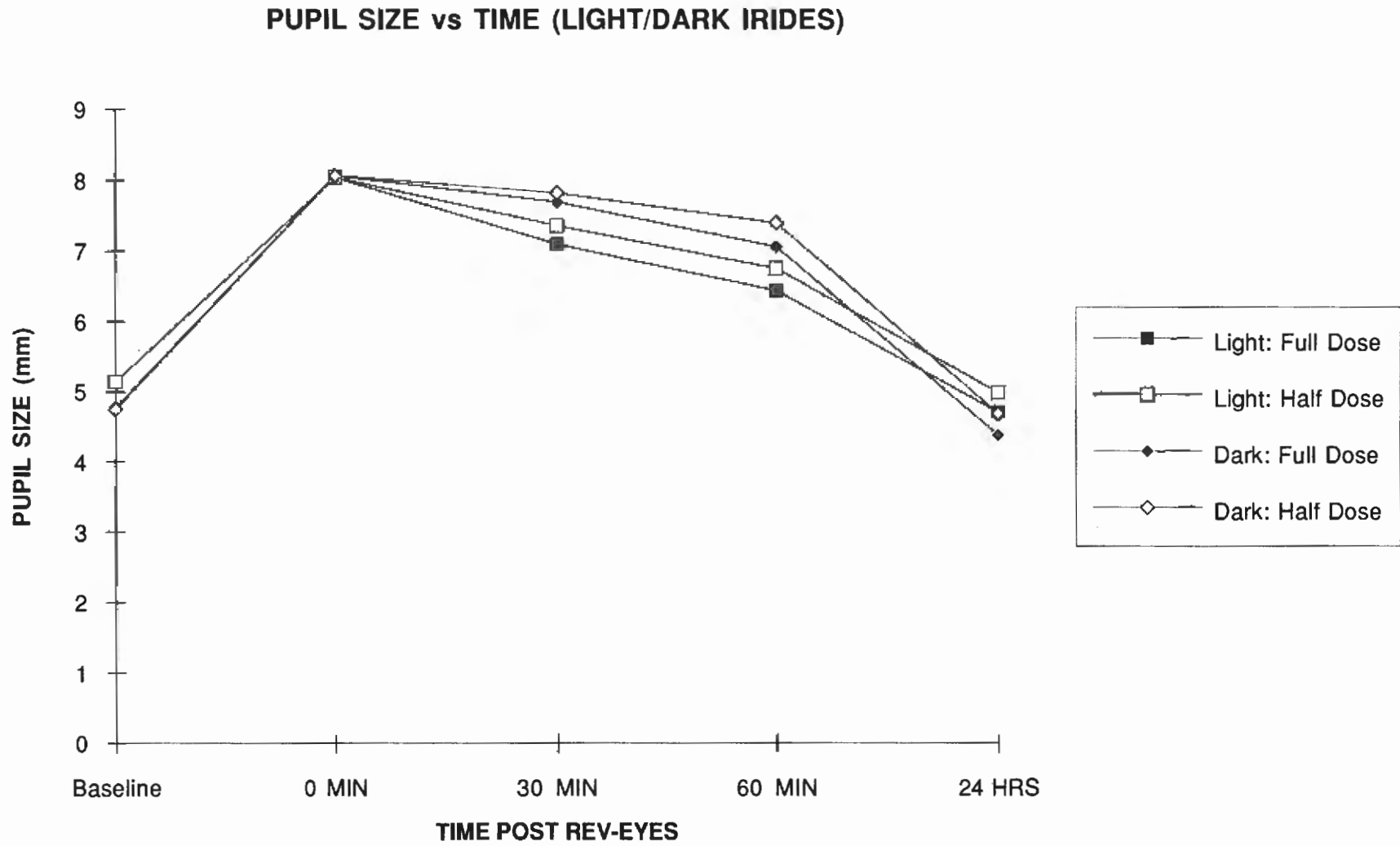


Figure 5b

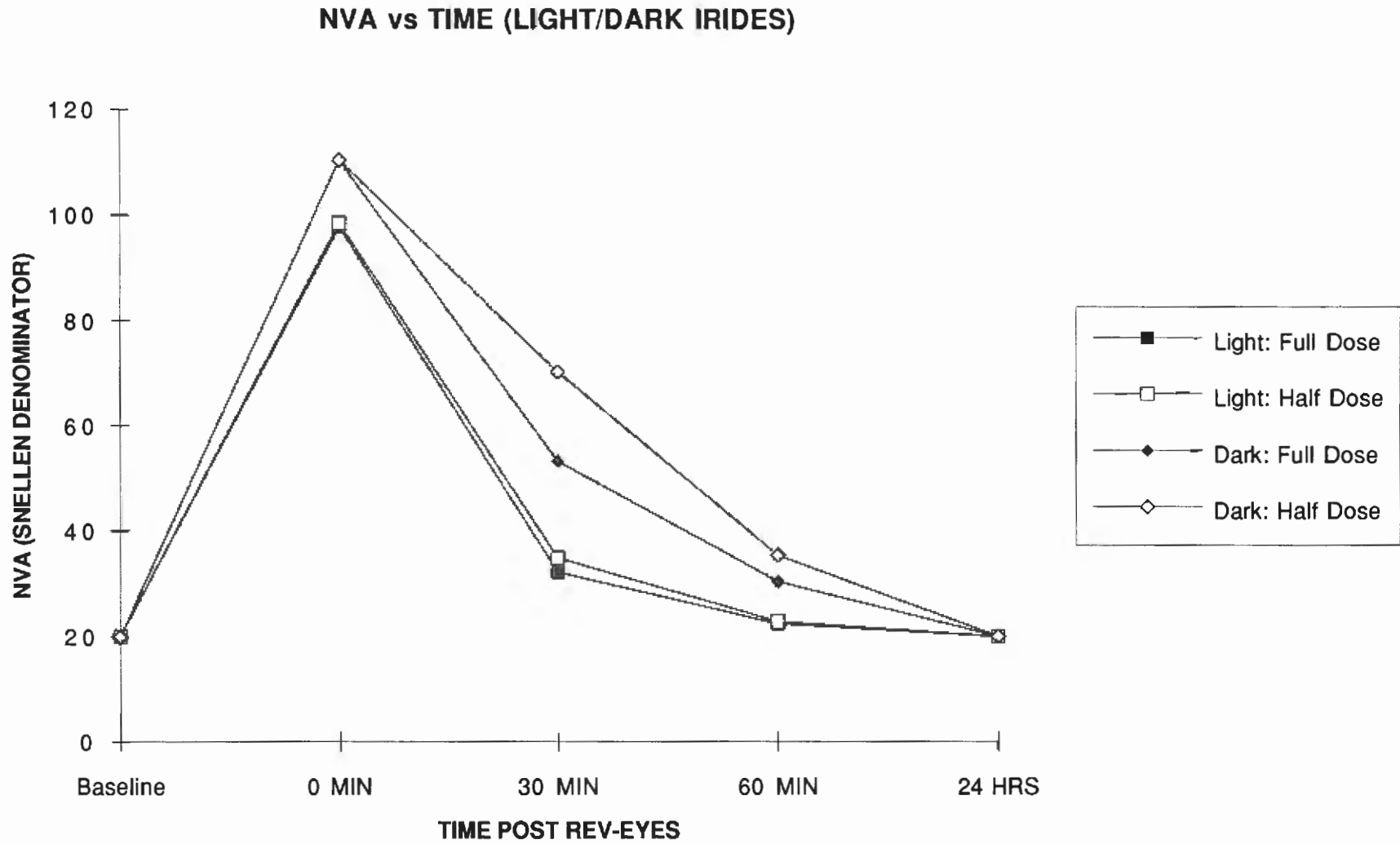


Figure 6

SUBJECTIVE RATING OF TEARING

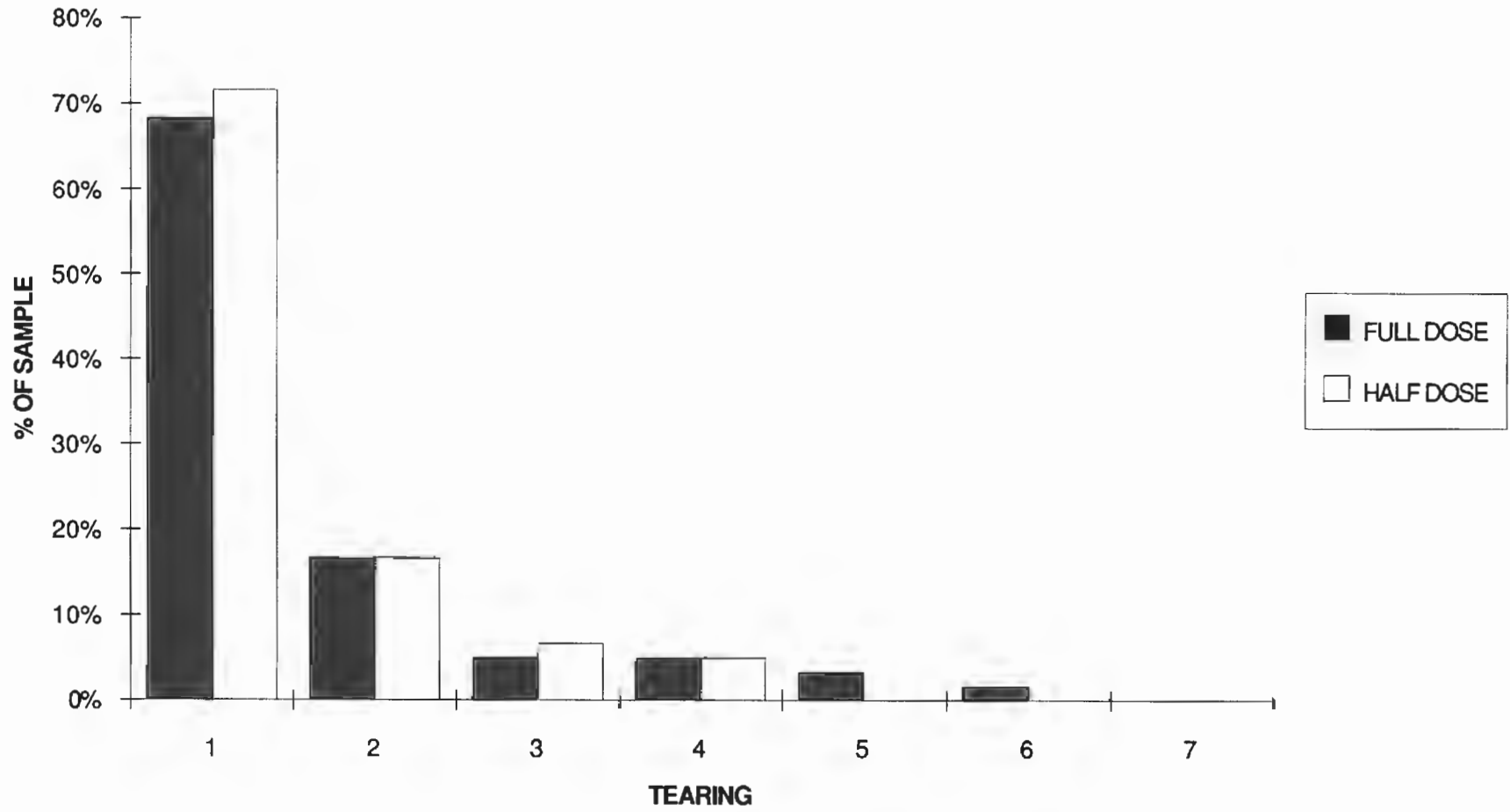


Figure 7

SUBJECTIVE RATING OF HEAD/BROWACHE

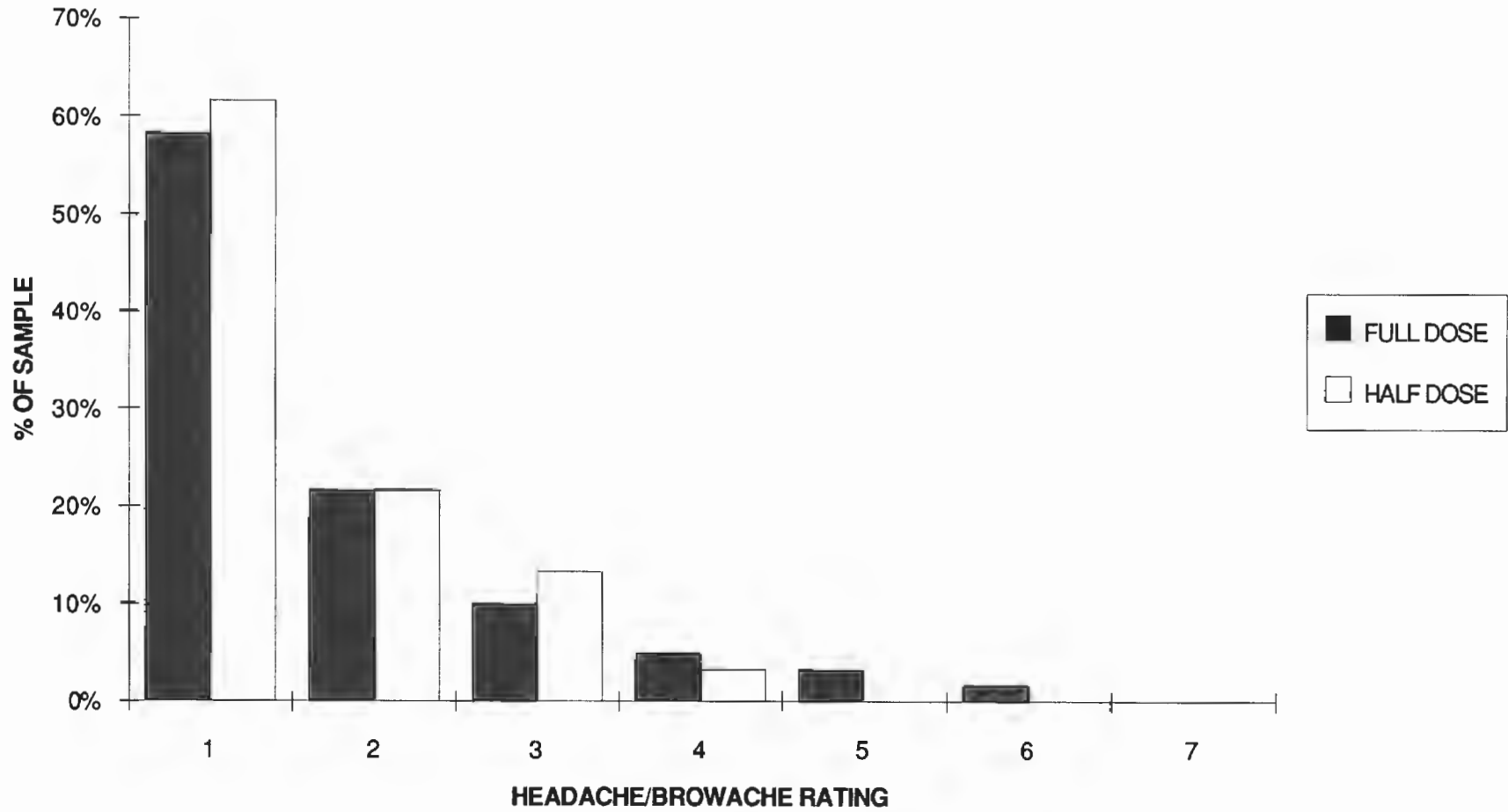


Figure 8

SUBJECTIVE RATING OF LID REACTION

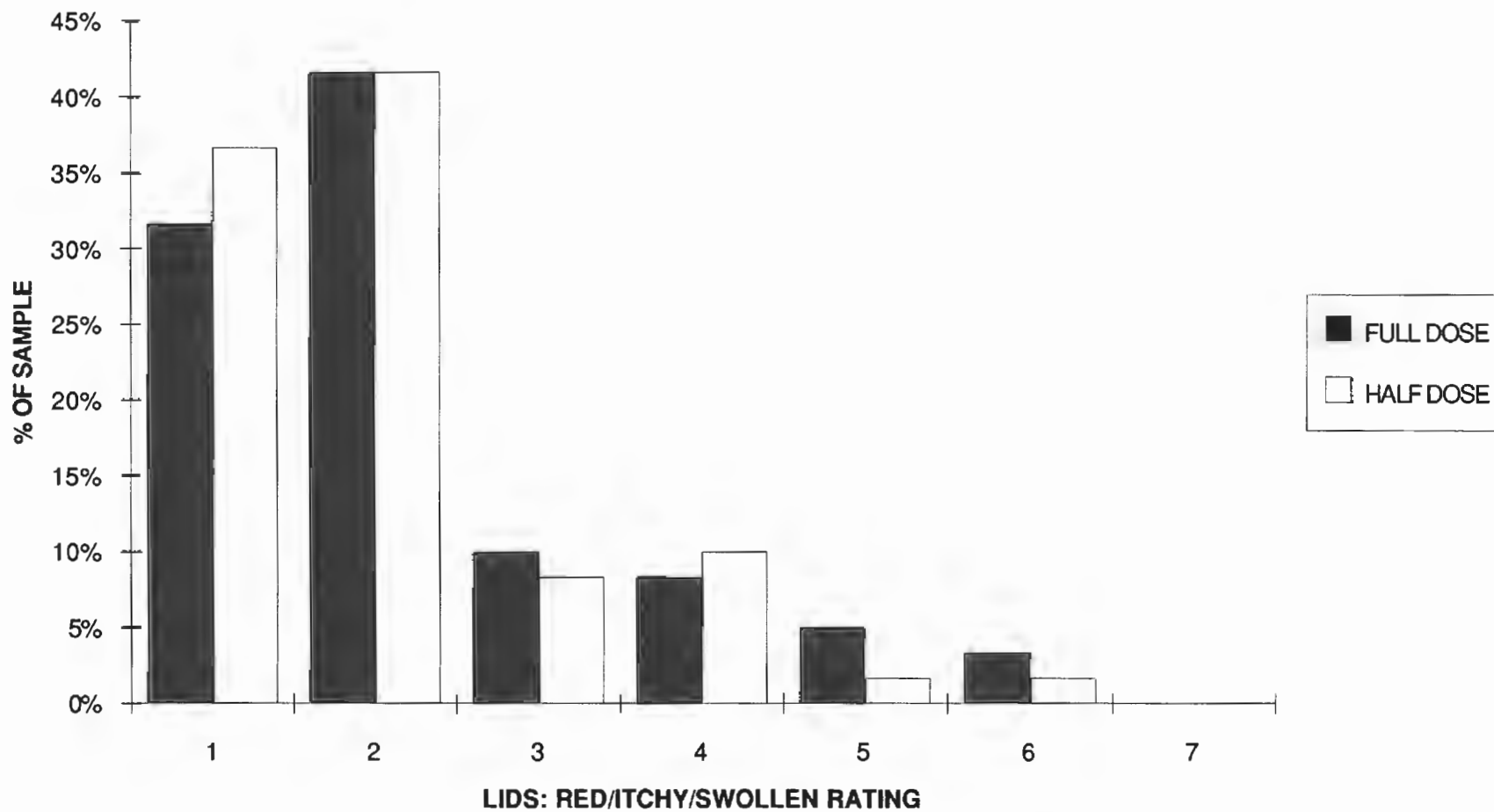


Figure 9

SUBJECTIVE RATING OF PERCEIVED REDNESS

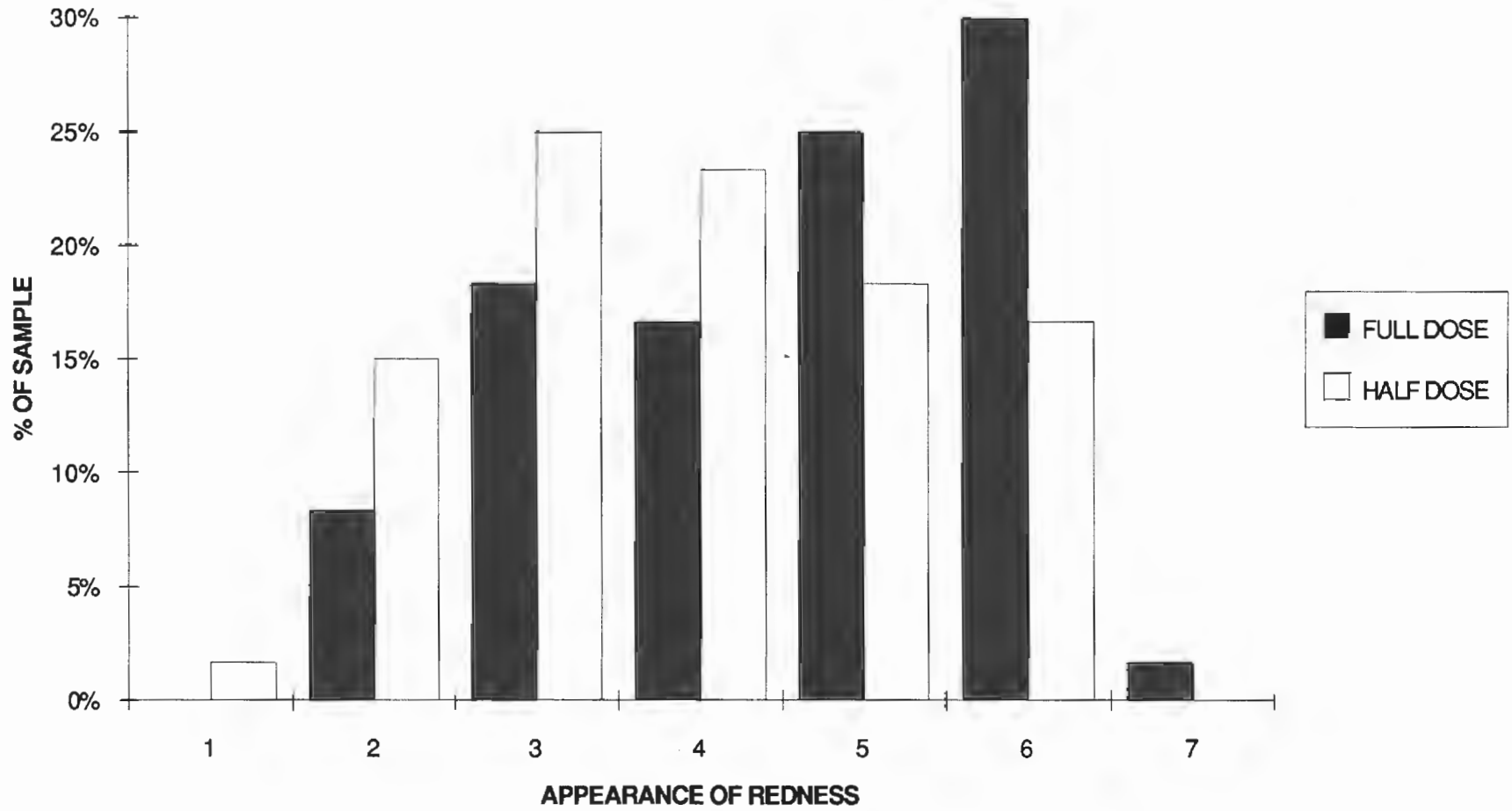
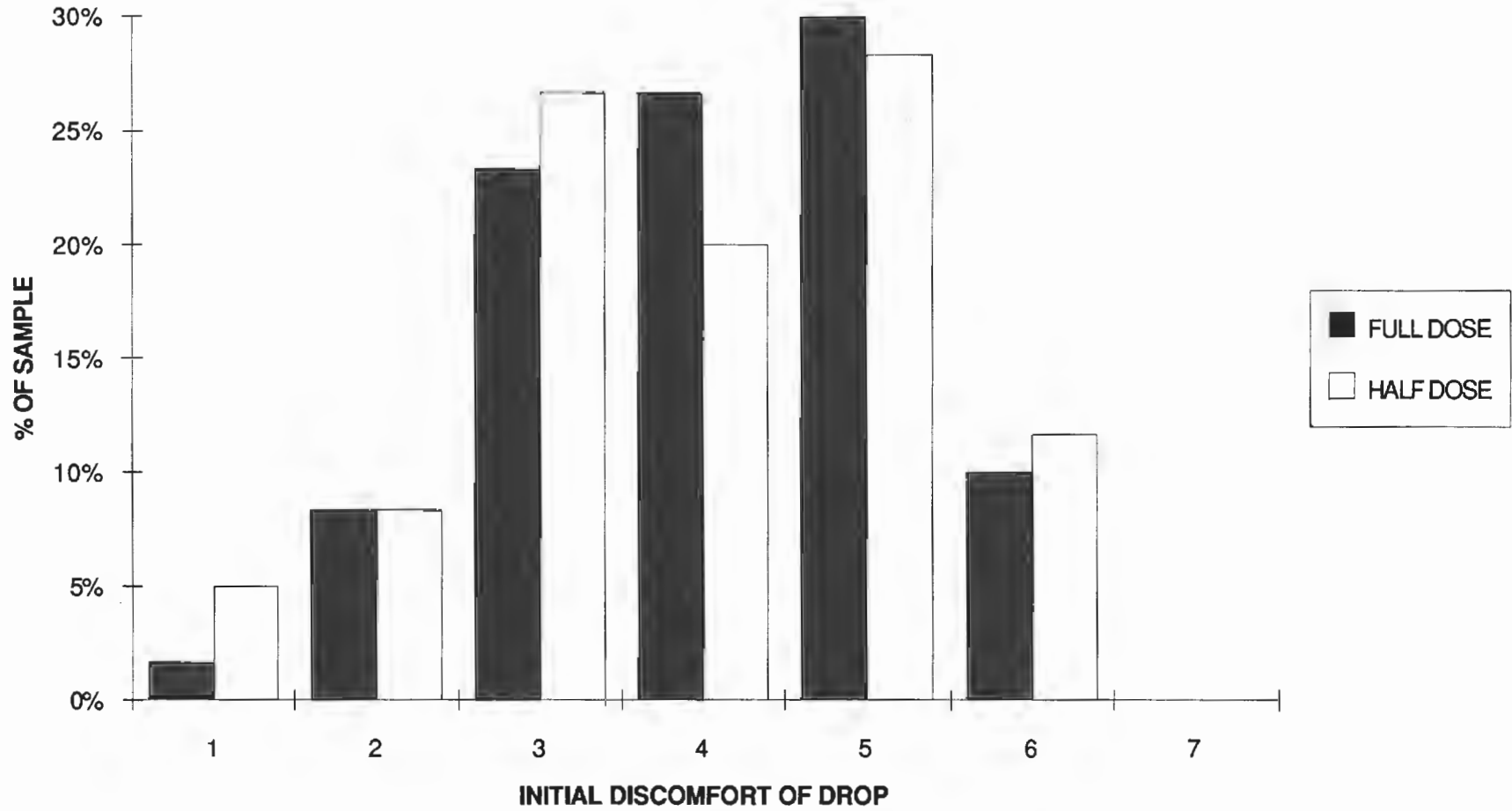


Figure 10

SUBJECTIVE RATING OF DROP DISCOMFORT



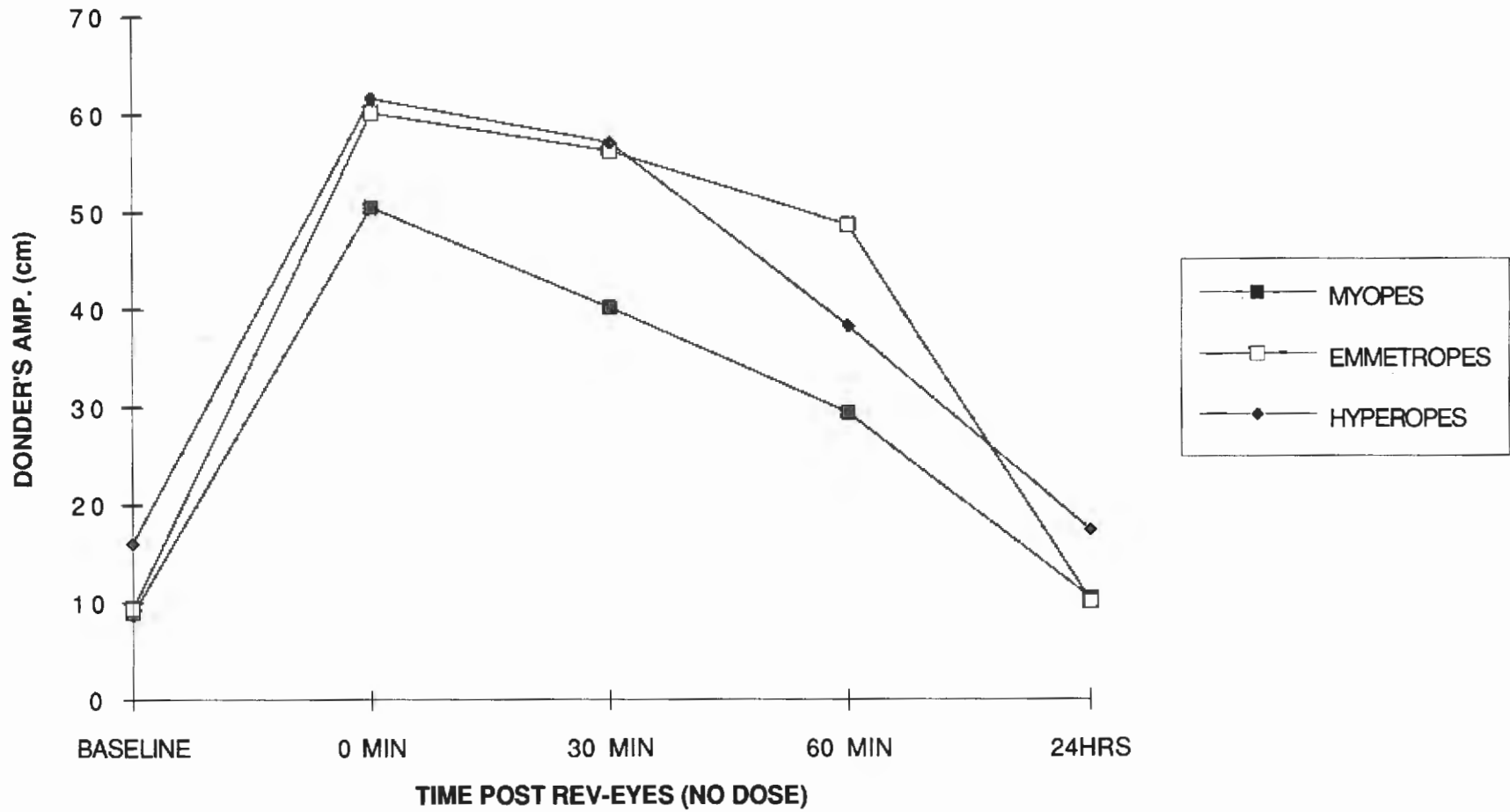
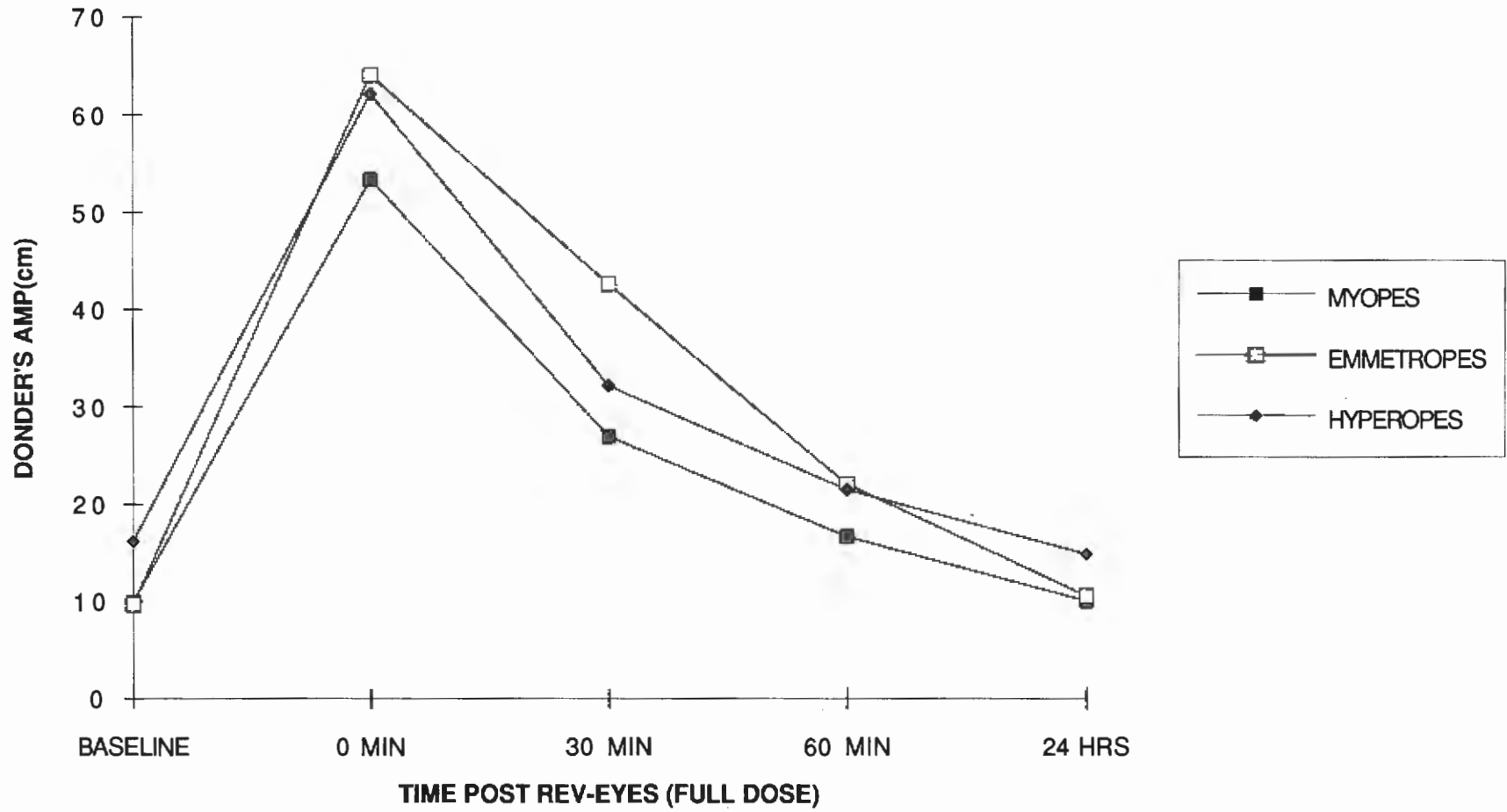
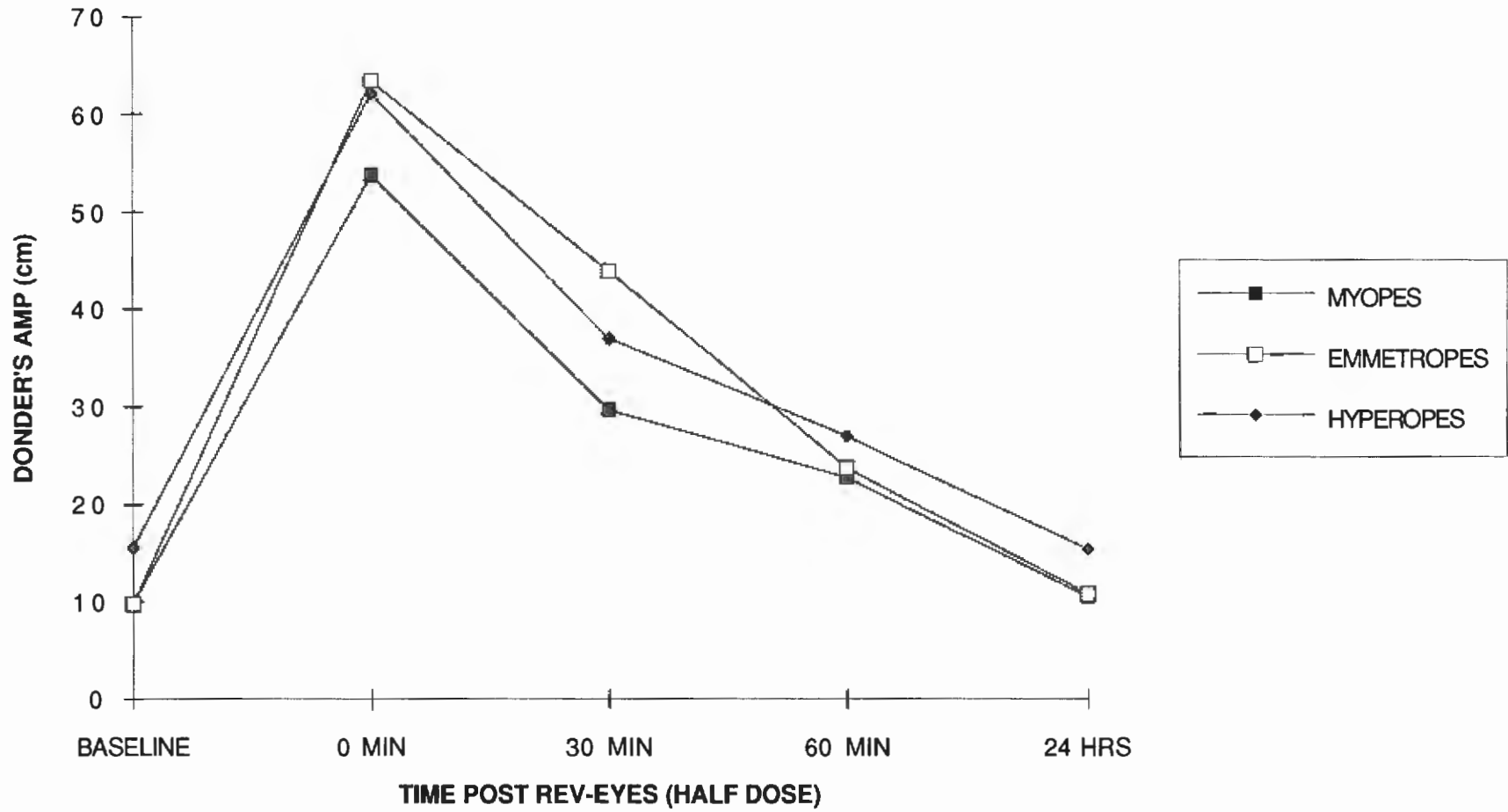
DONDER'S AMP. vs TIME WITH NO DOSE (REFRACTIVE STATUS)

Figure 12

DONDER'S AMP. vs TIME WITH FULL DOSE (REFRACTIVE STATUS)



DONDER'S AMP. vs TIME WITH HALF DOSE (REFRACTIVE STATUS)



DISCUSSION

Evaluation of our data showed that for the most part, there was no significant difference between the full and half doses of REV-EYES, and those differences that did exist were not clinically significant when comparing the subjects' visual performance and physiological response. However, in our subject sample, the half dose achieved equivalent reversal results as the full dose with overall statistically and clinically significant fewer side effects. Since the purpose of drug treatment is to achieve the desired effect while avoiding as many side effects as possible, the use of the half dose would be beneficial to both the practitioner and the patient. The patient would return to his or her pre-dilated state with less discomfort, and the practitioner would both reduce the time needed to retain the patient for administering the full sequence of REV-EYES, and would increase the number of patient doses per bottle.

When comparing the effects of the full and half dose of REV-EYES on pupil diameter, we found that there were significant differences at 30 minutes ($df=59, p=0.0001$) and at 60 minutes ($df=59, p=0.0001$) following REV-EYES administration with a two tailed t-test, but there was no significant difference found with the two-way ANOVA at any time interval. These differences were only 0.2 mm at time 30 minutes and 0.324 mm at time 60 minutes. Clinically, these differences are very small and would be unnoticeable to patients.

Near visual acuity was also found to be significantly different between the full dose and the half dose at 30 minutes and 60 minutes

post REV-EYES with the t-test, but not with the ANOVA. Thirty minutes following instillation, the average near acuity of the half dose eyes was 20/47, whereas, the acuity of the eyes with a full dose was 20/42. At 60 minutes, near acuity with a half dose was 20/28, and with a full dose was 20/26. These differences do not represent even one line of acuity on a reduced Snellen acuity card and are, therefore, irrelevant clinically.

There was a significantly different Donders accommodative amplitude at 60 minutes between the full and half dose eyes when analysis was done using a two tailed t-test ($p=0.0196$). The mean Donders amplitude at time 60 minutes with the full dose was 18.12 cm, and with the half dose was 23.32 cm. Both amplitudes are within a comfortable near working distance range. There was no significant difference in Donders amplitude at time 30 minutes between the full and half doses. Two- way ANOVA with repeated measures showed that there was no significant differences with respect to accommodative amplitude and dosage over time.

There were no differences found between the full dose and half dose with respect to recovery of distance visual acuity with either t-test analysis or with the two-way ANOVA. Dilation with a phenylephrine and tropicamide combination caused most subjects to lose about one of line of acuity on a distance Snellen chart. Moreover, return to pre-dilation distance acuity levels was not enhanced by any amount of REV-EYES, as there was no significant

difference between the natural reversal process of dilation and a drug-induced reversal for this variable.

We also wanted to establish whether dark or light irides reacted differently to the two doses of REV-EYES examined in this study. In the first phase baseline dilation, our sample showed no significant difference in any of the variables between subjects with light or dark irides. Our findings do not support the observed clinical tendency for light and dark irides to dilate at different rates and magnitudes. This may be due to the fact that subjects in our study designated as having dark irides were predominantly (67.8%) caucasian subjects with darkly pigmented eyes. The tendency for differing dilation rates pertains more specifically to black or darkly pigmented people with dark irides¹⁶. In our study, the remaining 32.2% of the dark iris subjects were Asian, Hispanic, and Indian.

From the results of our sample, it appears as though iris color alone is not a sufficient consideration when clinically determining whether to use the full or half dose.

Our second phase data also revealed that regardless of whether the full or half dose of REV-EYES was used, subjects with light irides demonstrated a faster rate of reversal from dilation. Subjects with light irides showed a faster return to baseline with near acuity as well as with pupil diameter. *See Table 4, Figures 5a and 5b.* Thirty minutes following the instillation of the half dose of REV-EYES, subjects with light irides were able to read two lines better near

acuity than subjects with dark irides, although this was not statistically significant due to high intersubject variability. At this point these subjects also had a 0.5mm smaller pupil diameter. These two differences remained the same at the one hour interval after REV-EYES.

The full dose did not return either of these variables to baseline any faster than the half dose. A patient with light irides could be expected to return to baseline equally fast with either the full or half dose.

No difference in accommodative amplitude, or distance visual acuity was found between light and dark irides with either dose.

One of the most significant variables involved in the decision whether or not to use REV-EYES as an anti-mydratic may be the patient's response to its side effects. The side effects in our study that showed a significant difference in subjective ranking between the full and half dose were: (1) tearing , (2) headache/browache , (3) puffy/red/itchy lids, and (4) perceived redness of the eyes. *See Table 5.*

The most significant side effect was how red the subjects perceived their own eyes to be when comparing between the eye with the full dose and the eye with the half dose. Without knowing which eye had received which dose, 66.7% of the subjects rated their full dose eye to be moderately to severely red (grade four to seven out of seven),

whereas, only 34.9% of the subjects rated their half dose eye to be as red.

The modal value (representing 30% of the subjects) for redness rating for the full dose eyes was a grade six out of seven. With the half dose eye the modal value (25% of the sample) of redness was a grade two out of seven. This represents a significant difference in the perceived redness of the subjects' eyes, and represents an important variable for the practitioner to consider before administering the full dose of REV-EYES.

The conjunctival injection of the subjects' eyes was also evaluated by the researchers before REV-EYES instillation, and at 30 minutes, 60 minutes, and 24 hours after the instillation of REV-EYES (see Table 6). A significant difference in conjunctival injection was found between the eye receiving the full and the half doses at all time intervals with T-test analysis ($p=0.0001$), and with ANOVA across time ($p=0.0008$). The comparative injection of the eyes showed the most difference one hour after REV-EYES, however, there was still a significant difference in injection between eyes the next day.

Subjects also responded that there was a significant difference between the full and half dose on the comfort of their lids. Of the subjects, 8.3% rated a strong lid reaction (grade four to seven) on the eye which received the full dose, whereas, only 3.2% rated an equally strong reaction with the eye which received the half dose.

While the majority of the sample rated their reflex tearing to be minimal in both eyes (grade one or two), 5% of the subjects rated the full dose eye as having moderate to severe tearing. No subjects rated their half dose eye to be tearing as severely.

The majority of the subjects felt no related onset of browache or headache with either the full or half dose, and rated this side effect to be grade one or two. However, 5% of the sample felt a moderate to severe browache (grade four to seven) occurred over the eye that received the full dose. There were no subjects who rated a grade four to seven browache over the half dose eye.

Objectively, each subject was also examined for corneal staining before instillation of REV-EYES, and at 30 minutes, and 60 minutes after instillation of REV-EYES . *See Table 6.* There was a significant difference in staining both at 30 minutes, and at 60 minutes, with the full dose eye staining more than the half dose eye. These results may indicate a difference in overall subject comfort experienced as a result of the drug instillation, and may also relate to the difference found between the tearing and comfort of the full and half dose eyes (that is, the more irritated eye tearing more).

Subjective side effects which did not differ by dosage were: eye itching, eye dryness, sensitivity to bright lights, and initial discomfort of the drops.

Although the subjects found no difference between the two doses on these side effects, their overall ratings were still important. On overall subjective rating of the discomfort of the drops, 71.7% of the subjects gave stinging a moderate to severe rating (grade four to seven out of seven), whereas, only 28.3% felt the stinging was mild (grade one to three).

All subjects (100%) rated the eye itching to be mild (grade one to three), and almost all subjects (96.4%) felt there was only mild dryness related to the drops of either of their eyes (grade one to three). Also, 63.3% of the subjects felt a moderate sensitivity to lights (grade three to five) which was equal whether the half or full dose was used.

Due to the range of responses on the subjective survey, it is apparent that each patient will respond differently to REV-EYES. Therefore, it is critical to involve the individual patient in the decision of whether or not to use REV-EYES. It is important that the practitioner evaluate the patient to determine how sensitive to other procedures and ophthalmic drugs he or she may be. A patient who is extremely sensitive in most instances will probably be bothered by the side effects of this drug.

Many subjects in our study had strong opinions of the drug, whether they felt the benefits outweighed the side-effects or not. One subject reported an intense browache that kept him awake for a part of that night, and which was not relieved with aspirin. Another subject had

a strong hyperemic and edematous reaction beyond that which might be considered appropriate to iatrogenically induce. However, there were subjects who were very pleased with the effects of REV-EYES, and would not want to be dilated again without the option of using this drug. All in all, when subjects were asked if they would want to use REV-EYES again, 75% of the 48 subjects responding said that they would.

CONCLUSIONS

In conclusion:

1. We determined REV-EYES to be effective in accelerating the physiological and functional recovery from dilation with 1% tropicamide and 2.5% phenylephrine, measured by near visual acuity, pupil size, and accommodative amplitude.
2. There were no clinically important differences between the full and half doses of REV-EYES, although statistically significant differences existed.
3. There were clinically and statistically significant differences in subjective discomfort and side effects; subjects tolerated the half dose better than the full dose.
4. In our sample, the half dose was found to be equally effective to the full dose with fewer side effects regardless of iris color.

From the evaluation of our data, it became apparent that there are certain patients that would benefit most from the use of REV-EYES. These include:

1. Hyperopic patients. REV-EYES may act as an important drug for reversing the effects of dilation/cycloplegia in patients who are moderate to significant uncorrected or partially corrected hyperopes. Functionally, this means that the use of REV-EYES following dilation of hyperopic patients may ease the transition in returning to work or a task where a near point demand is required.

2. Patients who have to perform visually dependent tasks requiring near work.

3. Those patients that are apprehensive about, or have a history of having difficulty driving following dilation.

4. Patients with narrow angles or shallow anterior chambers where dilation is necessary, but where quick reversal is desired. REV-EYES can be used to pass more quickly through the most dangerous mid-dilated state. This may also decrease the time that these patients need remain in the office to be monitored.

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