COMPARATIVE MYDRIASIS:
TEMPORAL SPACING OF
DIAGNOSTIC PHARMACEUTICAL AGENTS
IN PRE-PRESBYOPES

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ABSTRACT

The rates and extent of pupillary mydriasis using three variable temporal instillation techniques were evaluated. A minimal difference in the extent of mydriasis and somewhat greater difference regarding the rate of mydriasis exist when the diagnostic pharmaceutical agents, preceeded by a topical anesthetic, are separated by thirty second, two and a half minute, and five minute intervals. The longer time interval between diagnostic pharmaceutical instillations generally produces a greater amount of dilation. This difference continues up to a point, where then all evaluated techniques of instillation demonstrate approximately the same amount of mydriasis. The differences in pupillary responses have clinical usefulness in cases where the standard of care dictates pupillary dilation.

Key Words: diagnostic pharmaceutical agents (DPAs), mydriasis, temporal instillation techniques

INTRODUCTION

With the invention of the direct ophthalmoscope and thus the advent of ophthamoscopy in the 1800's, drug induced mydriasis has been successfully used to diagnose a wide range of lenticular, vitreal, and retinal abnormalities. Presently, with such ophthalmic devices as the binocular indirect ophthamoscope, retinal camera, three-mirror fundus contact lens, and lenses used in conjuction with the biomicroscope, a complete evaluation of the retinal fundus from the posterior pole to the ora serrata is possible. The use of these new devices, and thus the diagnostic advantages, often require the pupil to be in a state of mydriasis for a full and uninhibited view. The mydriasis inducing drugs used clinically at one time were limited to the practice of ophthalmology. However, with Maryland being the most recent and final state to allow optometrists to use diagnostic pharmaceutical agents, DPAs are becoming commonplace in the optometric examination.

Many studies have been conducted to determine the best drug regime maximizing pupillary dilation while minimizing patient discomfort and adverse reactions. It is generally accepted that the best drug regime includes the initial instillation of an

anesthetic followed by a direct-acting sympathomimetic and a parasympatholytic agent.

Topical local anesthetics are frequently used when pupil mydriasis is desired. Clinically these agents are used to reduce burning sensations that arise from instillation of drops added subseqent to the anesthetic to dilate the pupil or when performing applanation tonometry. It has been observed clinically and reported in the literature by Lyle and Bobier that the speed and amplitude of mydriasis is amplified when a sympathomimetic drug is preceeded by a topical anesthetic. (1) It is generally accepted that this increase in amplitude and speed is related to an anesthetically induced change in the corneal epithelial permeability and the effect the anesthetic has on reducing reflex tearing when subsequent drugs are used.

I employed 0.5% proparacaine in my study. Proparacaine's anesthetic effects arise from its ability to stabilize the neuronal membrane and thus prevents the initiation and transmission of nerve impulses in the cornea. This particular anesthetic was chosen because of its rapid onset, short duration of action, low incidence of patient hypersensitivity, and the minimal patient discomfort experienced with instillation. Lyle

and Bobier also demonstrated that when compared to other topical anesthetics as tetracaine and benoxinate, proparacaine had the greatest effect in amplifying mydriasis. (2)

I used both a sympathomimetic and a parasympatholytic agent in my research to obtain a synergistic action for maximal mydriasis. Specifically 2.5% phenylepherine and 1.0% tropicamide were utilized.

Phenylephrine, a direct-acting alpha-adrenergic was chosen because of its relatively prompt mydriasis. It works by imitating the action of adrenaline in that it stimulates the iris dilator muscle to contract. It has been reported in the literature by Wilensky and Jackson that the 10% solution of phenylephrine can lead to adverse systemic reactions including cardiac arrhythmias and systemic hypertension. (3) Experimentation conducted by Newhouse and Hepler demonstrated that 10% and 2.5% aqueous phenylepherine have approximately the same mydriatic effects, but the 2.5% solution greatly decreases the incidence of said undisireable systemic effects. (4)

Topicamide produces pupil dilation and paralysis of accomodation by rendering the iris sphincter and cilliary muscles insensitive

to acetylcholine. I chose to use it over other anticholenergic agents such as cyclopentolate, scopolamine, or atropine because, again, of its timely dilation and for its less intense and more transient cycloplegic effects.

Used as I have in my study, these three agents are extemely safe and leave very little chance of systemic reactions or toxicity.

METHODS AND MATERIALS

The study population consisted of twenty-five caucasian pre-presbyopes between the ages of eighteen and twenty-six years of age. All patients demonstrated fully intact corneal epitheliums and were free of ocular disease. Each dilated eye was subjected to the same diagnostic agents: 0.5% proparacaine hydrochloride, 2.5% phenylephrine hydrochloride, and 1.0% tropicamide.

Three techniques of drug instillation varying only in the temporal sequencing were used. Technique A involved initial anesthetic instillation followed by phenylephrine instillation thirty seconds later: tropicamide was added thirty seconds after the phenylephrine. Technique B differed from technique A only in that the time increment between the instillations of phenylephrine and tropicamide drops was increased to two and a half minutes. Technique C followed the same format as the previous two techniques except it allowed five minutes to elapse between the instillation of the second dilating drop.

The twenty-five subjects were divided into three groups. Group I had one eye dilated using technique A and the other using technique B. Group II had one eye dilated using technique A and the other

using technique C. Group III had one eye dilated using technique B and the other using technique C. In total seventeen, sixteen, and seventeen eyes were dilated using techniques A, B, and C respectively. Also, eight, nine, and eight patients participated in Groups I, II, and III respectively.

To minimize fluctuations the environment remained stable and quiet. Each drop (approximately 0.05 ml) was instilled into the conjectival cul-de-sac and the patient was advised to refrain from blinking or rubbing his eyes.

Pupillary diameters were recorded using a rule pupil measure much like the one used by Jauregui and Polse in their experimentations. (5) Initial pupillary sizes were measured as well as the pupil diameters at ten minute intervals for one hour after the last drop had been instilled. The patients were instructed to look directly at the filament of a binocular indirect ophthalmoscope while the measurements were taken.

EXPERIMENTAL RESULTS: GROUP I INDIVIDUAL PUPIL SIZES

SUB.	GRP.	TECH.	0	10	20	30	40	50	60
1	I	A	4	8	9	9	9	9	9
		B	4	8	9	9	9	9	9
2	I	A	4	5	5	5	6	7	7
		B	4	7	8	8	8	8	8
3	I	A	3	6	8	8	9	9	9
		B	3	7	8	8	9	9	9
4	I	A	4	6	7	8	8	8	8
		B	4	7	7	8	8	8	8
5	I	A	3	5	7	7	8	9	9
		B	3	5	7	7	8	9	9
6	I	A	3	5	6	7	8	9	9
		B	3	6	6	7	8	9	9
7	I	A	3	5	7	7	8	9	9
		B	3	6	7	8	8	9	9
8	I	A	3	5	7	8	8	8	8
		B	3	5	7	8	8	8	8

EXPERIMENTAL RESULTS: GROUP II INDIVIDUAL PUPIL SIZES

SUB.	GRP.	TECH.	0	10	20	30	40	50	60
9	II	A	3	5	7	8	8	9	9
		C	3	6	8	8	8	9	9
10	II	A	3	5	7	7	8	8	9
		C	3	6	8	8	8	9	9
11	II	A	4	6	8	8	8	9	9
		C	4	7	8	8	8	9	9
12	II	A	3	6	8	8	9	9	9
		C	3	7	8	9	9	9	9
13	II	A	2	4	7	8	8	8	8
		C	2	4	7	8	8	8	8
14	II	A	4	8	8	9	9	9	9
		C	4	8	8	9	9	9	9
15	II	A	3	4	7	7	8	8	8
		C	3	6	8	8	9	9	9
16	II	A	3	6	8	8	9	9	9
		C	3	7	8	8	9	9	9
17	II	A	3	6	7	8	8	8	9
		C	3	7	8	8	8	9	9

EXPERIMENTAL RESULTS: GROUP III INDIVIDUAL PUPIL SIZES

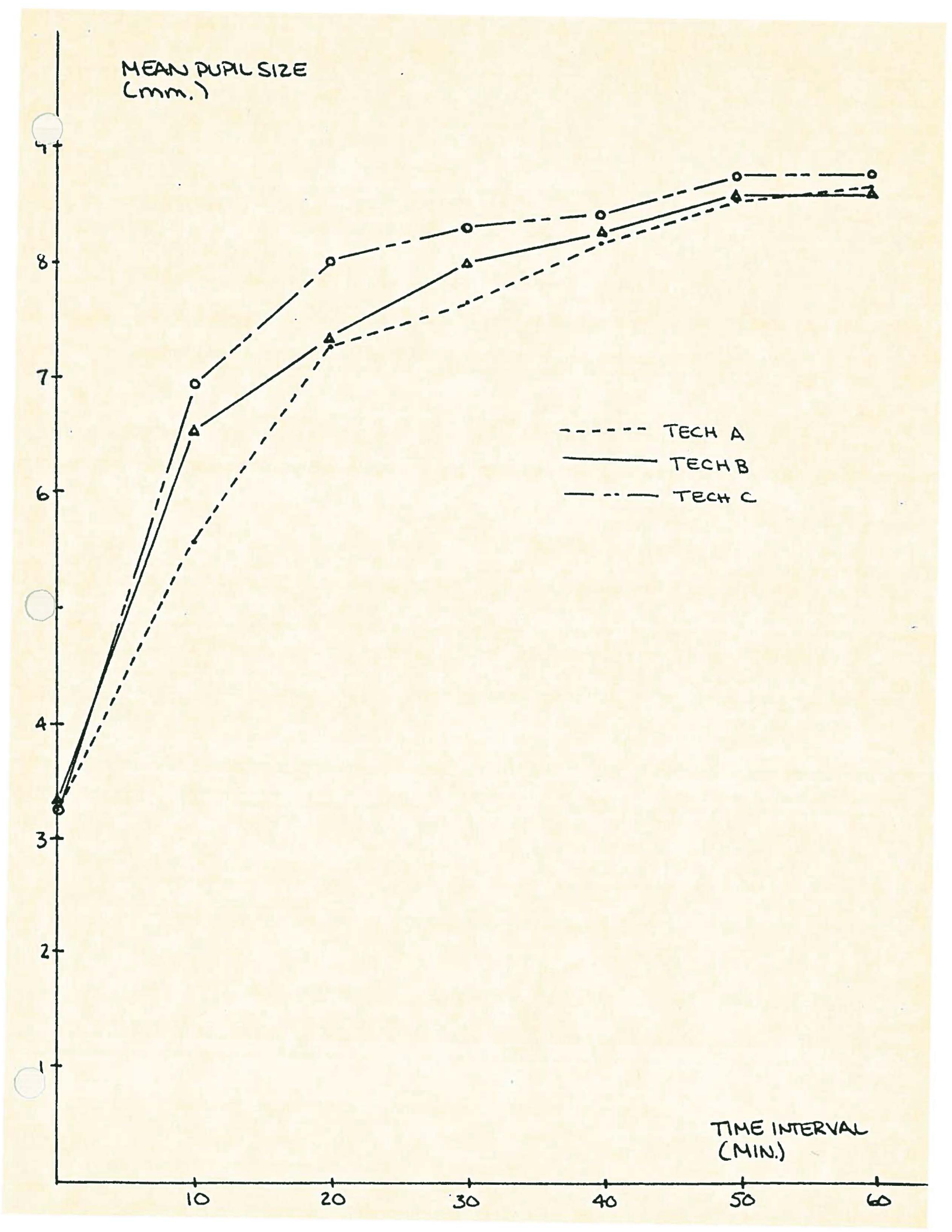
SUB.	GRP.	TECH.	0	10	20	30	40	50	60
18	III	B	4	8	9	9	9	9	9
		C	4	8	9	9	9	9	9
19	III	B	3	6	7	8	8	8	8
		C	3	8	8	8	8	8	8
20	III	B	3	6	7	8	8	8	8
		C	3	6	7	8	8	8	8
21	III	B	3	6	6	7	7	8	8
		C	3	7	8	8	8	9	9
22	III	B	4	8	8	9	9	9	9
		C	4	8	9	9	9	9	9
23	III	B	4	7	7	8	9	9	9
		C	4	8	8	9	9	9	9
24	III	B	3	6	7	8	8	9	9
		C	3	7	8	8	8	9	9
25	III	B	3	7	8	8	8	8	8
		C	3	8	8	8	8	8	8

STATISTICAL RESULTS: MEAN PUPIL DIAMETERS

INTERVAL	0	10	20	30	40	50	60
TECH. A	3.24	5.59	7.24	7.65	8.18	8.53	8.65
TECH. B	3.37	6.56	7.38	8.00	8.25	8.56	8.56
TECH. C	3.24	6.94	8.00	8.29	8.41	8.76	8.76

STATISTICAL RESULTS: SIGNIFICANT TWO-TAIL PROBABILITIES

TECH. A	VS	TECH. B	at 10	0.012
TECH. A	VS	TECH. C	at 10	0.001
TECH. A	VS	TECH. C	at 20	0.005
TECH. B	VS	TECH. C	at 20	0.017
TECH. A	VS	TECH. C	at 30	0.015


MEAN PUPIL SIZE
(mm.)
9
8
7
6
4
3
2
1
TECH A
TECH B
TECH C
TIME INTERVAL
(MIN.)
10
20
30
40
50
60

RESULTS

Figure 1 represents the dose-response curves for the three techniques I employed. As illustrated by the graph, there is a difference in the rates of mydriasis between techniques A, B, and C. These differences are greatest in the early part of the experiment, but note that 40 minutes after the instillation of the last dilating drop, all mean pupil sizes are within 0.3 mm. of each other. Furthurmore, there are no statistical differences using a two tailed unpaired T-test model between pupil sizes at a given time interval between the three techniques at and beyond the 40 minute interval.

What can be deemed even more important than the individual comparison of mean pupil sizes at given time intervals, is the actual time at which the different techniques produce a specific amount of pupillary mydriasis. Kubo et. al. has stated that a 2.5 mm increase in pupil diameter will facilitate most ophthalmoscopic procedures. (6) Using their hypothesis, we find that all procedures tested here reach this point by the 10 minute interval. More dramatically illustrated is the time it takes for each technique to produce an 8 mm pupil diameter. Technique C reaches the 8 mm measure at the 20 minute interval, where as techniques

B and A need an additional 10 and 20 minutes respectively to reach this same point. This can become a significant factor in dictating dilation regimes if the clinician decides to implement an examination routine such as the "round robin" procedure. This procedure has been advised by Gottschalk (7) and also Bartlett (8) as a way to implement routine dilation in the optometric practice by starting a cyclical examination series with a group of paients. The optometrist performs an examination on the first patient and instills drops to dilate the pupil, the patient is then proceeded to the frame selection or the dilaing area while the O.D. examines the second patient. After the second patient has been examined and has received mydriatic drops the optometrist completes the examination of the first patient with ophthalmoscopy and other indicated procedures. The cycle then can continue with subsequent patients.

CONCLUSION

To appreciate the results obtained in this study one must have a basic understanding of the drug delivey kinetics involved when using topically applied ophthalmic solutions.

It has been determined that the normal volume of precorneal tear film is between 0.007 - 0.01 ml,the conjunctival cul-de-sac is capable of holding approximately 0.025 - 0.03 ml of fluid, and the drop obtained from commercially available droppers can range from 0.05 - 0.075 ml. (9) When a drop is instilled in the manner as I have used in my study, much of the solution overflows out of the eye or is lost through the nasolacrimal duct, most of the drug will be gone within thirty seconds and all within twenty minutes. (10)

The volume instilled and the rate of drainage are closely related. The rate of drainage increases with larger volumes instilled, therefore technique A in my study resulted in a faster drainage rate than the other two techniques. Larger instilled volumes also result in a higher concentration of drug in the precorneal tear film. This will also effect the results because higher concentrations in the precorneal tear film produce more

drug available to penetrate the cornea. Taking these two effects into account we can surmise that although technique A initiated greater drainage rates it also resulted in higher precorneal drug concentrations, and the inverse is applicable to technique C.

I believe the individual optometrist must decide what routine will best suit his needs best when picking a dilating regime. His choice will be determined by extraneous factors such as what procedure is needed and time constraints on the doctor.

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