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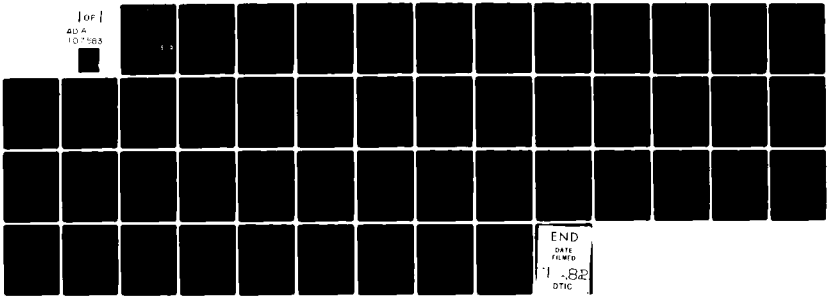

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Investigation of Visual Performance after Administration of Cholinergic Blocking Agents

I. Benactyzine.

Final Report

Brian Brown, Ph.D.
Gunilla Haegerstrom-Portnoy, O.D.
Anthony J. Adams, Ph.D.
Reese T. Jones, M.D.
Arthur Jampolsky, M.D.

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Optical Sciences Group, Inc.
(Visual Sciences Division)
24 Tiburon Street
San Rafael, California 94901

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

We have investigated the effects of 4.14 mg of Benactyzine HCl (injected I/M) on vision and vision function. We measured the time course and severity of Benactyzine effects on visual acuity for static and moving targets, amplitude of accommodation, contrast thresholds, pupil size and response, color vision, glare recovery, oculomotor

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function and intraocular pressure. Our experiments demonstrated large and significant decrements in visual function after the administration of benactyzine, especially for those functions performed at near.

Thirty minutes after injection, static distance acuity was reduced from 20/17 to 20/22, and acuity for moving targets was also reduced by an amount dependent on target velocity; for targets moving at 40°/sec acuity was reduced from 20/56 to 20/66. The mean amplitude of accommodation was reduced from 5.3to 1.5D, and the rate of change of accommodation was markedly reduced. Pupil size increased by about 0.5 mm, but pupil responsiveness was not altered. Near vision function was degraded; contrast sensitivity was reduced by about 0.25 log units over a range of spatial frequencies from 1 to 20 cycles/°. Oculomotor co-ordination was minimally affected, although one subject showed a large change in heterophoria, which led to diplopia at near.

The drug effect was rapid in onset, beginning 7 - 10 minutes after injection, peaking at approximately 30 - 40 minutes and declining to baseline values over the next two hours; most affected vision and physiological functions showed this time course. By 90 minutes post-injection substantial recovery of function had occurred.

Increases in pulse rate and blood pressure were induced by the drug treatment and an intoxicated state was also produced in nearly all of our subjects. This state, which is very rapid in onset might prove extremely disturbing to personnel who have not experienced altered states of consciousness induced by other drugs.

Implications for Performance

The changes in distance static and dynamic visual acuity which we have measured would probably have small effects on visual performance, athough under marginal visibility conditions they may be of importance. Decrements in near vision induced by benactyzine would have more severe consequences, especially for personnel in pre-presbyopic age ranges (35 - 45 yrs) or for uncorrected hyperopes. Such individuals would find themselves suddenly unable to resolve fine, low contrast detail at near. Information such as map contour lines, air space designations or data presented at low contrast on oscilloscope displays would no longer be readily visible. Under conditions of low illumination such difficulties would be increased.

Interaction of these vision function deficits may produce greater performance decrements than we have reported. Our results were produced when tasks were performed in isolation and with an experimenter present to urge maximum performance. Changes in psychological factors such as level of motivation, loss of sense of time, and diminished short-term memory performance are characteristic of bentactyzine-intoxicated subjects; these factors may interact with the vision deficits to produce more severe deficits in real world performance tasks.

SUMMARY

We have investigated the effects of an anticholinergic drug, Benactyzine HCl on vision and vision function. We conducted experiments to assess the time course and severity of Benactyzine effects on visual acuity for static and moving targets, amplitude of accommodation, contrast thresholds, pupil size and response, color vision, glare recovery, oculomotor function and intraocular pressure. A single dose of the drug (4.14 mg/70 kg body weight) was administered intramuscularly; two experiments were conducted, involving 6 and 12 subjects respectively. Our experiments demonstrated large and significant decrements in visual function after the administration of benactyzine, especially for those functions performed at near.

At the peak of the drug effect, some 30 minutes after the injection, static distance acuity was reduced from 20/17 to 20/22, and acuity for moving targets was also reduced. The amount of reduction was dependent on target velocity, with small decrements for slowly moving targets and larger decrements for targets moving at 40°/sec (from 20/56 to 20/66).

The mean amplitude of accommodation was reduced from 5.3 D to 1.5 D at the peak of the drug effect (for the 6 subjects *in Experiment* 1). The rate of change in accommodation was markedly reduced; to change focus from 1 to 2 D, benactyzine-affected subjects took approximately 1.5 seconds - 3 times as long as in the placebo condition. Concomitant with these changes in accommodation, we noted an increase in pupil size of about 0.5 mm. This increased pupil size was noted in the presence and absence of an added illumination stimulus (which was used to examine pupil responsiveness). Pupil responsiveness did not appear to be altered by the drug. Near vision function was degraded, primarily as a result of diminished accommodative amplitude; the contrast sensitivity function was reduced by about 0.25 log units across all spatial frequencies tested (1 to 20 cycles / degree). Oculomotor co-ordination was minimally affected, although one subject showed a large change in heterophoria, which led to diplopia at near.

Many vision functions did not appear to be altered by the drug treatment - color vision, glare recovery, oculomotor tracking and intra-ocular pressure showed small, statistically (and practically) insignificant changes.

The drug effect was rapid in onset, beginning 7 - 10 minutes after injection, peaking at approximately 30 - 40 minutes and declining to baseline values over the next two hours; most affected vision and physiological functions showed this time course. By 90 minutes post-injection substantial recovery of function had occurred.

Increases in pulse rate and blood pressure were induced by the drug treatment and an intoxicated state was also produced in nearly all of our subjects. This state, which is very rapid in onset might prove extremely disturbing to subjects or personnel who have not experienced altered states of consciousness induced by other drugs such as alcohol or marijuana.

Implications for Performance

The changes in distance static and dynamic visual acuity which we have measured would probably have small effects on visual performance, athough under marginal visibility conditions they may be of importance.

Decrements in near vision induced by benactyzine would have more severe conseqences, especially for personnel in pre-presbyopic age ranges (35 - 45 yrs) or for uncorrected hyperopes. Such individuals would find themselves suddenly unable to resolve fine, low contrast detail at near. Information such as map contour lines, air space designations or data presented on low contrast oscilloscope displays would no longer be readily visible to these personnel, who are in the age ranges of field commanders. Under conditions of low illumination such difficulties would be increased.

In addition to effects on purely visual performance, we have noted that changes in psychological factors such as level of motivation, loss of sense of time, and diminished short-term memory performance are characteristic of bentactyzine-intoxicated subjects. It is obvious that these factors alone or in combination could provide severe problems for personnel engaged in skilled tasks such as vehicle guidance and control, or radio and signal operations.

Interaction of the deficits we have described in contrast sensitivity, dynamic visual acuity, and static and dynamic accommodation response may produce greater decrements of performance than we have reported. Our results were produced when tasks were performed in isolation and with an experimenter present to urge maximum performance. In the real world, especially in combat conditions, there will be a great number of tasks demanding attention and parallel processing of information. The deficits which we have noted may be cumulative in their effects.

FOREWORD

This Annual Report was written for the U.S. Army Medical Research and Development Command by the investigators of a study supported by a U.S. Army Contract (No. DAMD 17-78-C-8037). This contract was awarded to the Visual Sciences Division of Optical Sciences Group, Inc., San Rafael, California, which directed, guided, and administered the research study. The experimental phases of the study were conducted at the Smith Kettlewell Institute of Visual Sciences at the Pacific Medical Center in San Francisco. We gratefully acknowledge the space, facilities, and services provided by the Institute.

We are grateful to Noah Phyllis Levin, M.A., who provided administrative and secretarial services essential to the conduct of the research.

We are pleased to acknowledge the assistance provided us by Peter Shelley, M.D., and Roy Baker, O.D., M.S., in conducting these experiments, and in analysis of the data. We are grateful to our subjects, who must remain anonymous, for cheerfully and patiently enduring many hours of testing.

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

Citations of trade names in this report does not constitute an offical Department of Army endorsement or approval of the use of such items.

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INTRODUCTION

Cholinergic blocking agents, which are antidotes to organophosphate poisoning, have systemic and ocular side effects which may be extremely debilitating. This report is primarily concerned with the visual side-effects of systemic administration of benactyzine, an anticholinergic drug which acts rapidly and has effects on central and peripheral cholinergic systems.

Benactyzine is an anticholinergic drug whose peripheral effects have been known since 1936, but whose psychopharmacological effects were first described in 1955. Peripherally it increases heart rate and blood pressure, while decreasing salivation and other secretions. It is reported to have negligible spinal/medullary effects, but apparently has effects on the reticular activating system, thus affecting concentration and attention.

It has been used in the treatment of psychoneurotic disorders, but is little used today, since it is of questionable efficacy. In a double-blind study of the effectiveness of benactyzine in outpatients suffering from anxiety, Harrington and Meyer-Gross (1959) concluded that the drug was ineffective. Himwich and Rinaldi (1957) noted that benactyzine improved Parkinson-like symptoms in 9 of 13 patients studied, and that the drug changed the EEG pattern in the rabbit in a manner consistent with depression of the reticular activating system. The doses of benactyzine used to reduce Parkinsonian symptoms were so high (up to 40mg/day) that side-effects would be unacceptable. Lathrop (1959) reported the results of a study indicating that Deprol (meprobamate 400mg and benactyzine 1mg) was ineffective in the treatment of schizophrenia.

An exaggerated idea of the central and peripheral actions seen in benactyzine intoxication can be had from consideration of a case study of a woman who ingested 1300-1400 mg in a suicide attempt (Vojtechovsky,1958). The ingestion was followed by a "delerious psychotic episode with a brief optical hallucination, followed by a secondary delusion,confusion and psychotic behavior." Other side-efects seen were ataxia, blocking of thoughts, relaxation of muscles, dull heavy feeling of the extremeties, and dryness of the mouth. Four hours after the ingestion, the patient was tired but relatively normal; one hour after this she was able to go home by bus.

Blocking of thoughts and loss of concentration lead to a loss of connected speech in many subjects, and overestimation of time, not unlike that reported in marijuana-intoxicated subjects (Melges et al, 1971).

These mental and motor effects lead to reduced

performance in tasks related to military readiness. Vojvodic et al (1972) found that benactyzine in combination with atropine and pralidoxime (3mg B,2mg A and 1000mg P) caused significant performance decrements in passing through an obstacle course and in firing a rifle. Slightly worse performance was produced by benactyzine (10mg) combined with pralidoxime (1000 mg). The effects for both treatments peaked in 40-60 minutes and persisted for 3-4 hours. This time course of the drug effect is confirmed by Hess and Jacobsen (1957,a) who report the effects of 5-6mg of benactyzine on reaction time; reaction time was increased by up to 45% after the drug. Other investigators such as Munro (1955) reported no effect "on the ordinary intelligence functions, but some highly organized functions, relating to registration of a sitation simultaneously with the attention to a task appeared somewhat impaired." A valuable annotation of an experiment involving a subject given 12mg of benactyzine subcutaneously is given in the report of Hess and Jacobsen (1957,b); effects of the drug appeared rapidly (within 4-6 minutes) and many of the signs and symptoms mentioned above are graphically reported. Hess and Jacobsen (1957,b) show changes in the EEG which parallel the drug effect; there is a marked inhibition of alpha activity in the EEG which is attributed to a "direct pharmacodynamic effect of benactyzine on the central nervous system."

The animal literature on benactyzine is fairly extensive and of less importance in the present context; the interested reader is referred to Jacobsen (1964) for a review. Jacobsen also reviews other aspects of benactyzine chemistry, central nervous system effects and clinical uses of the drug.

Thus, while there have been assessments of the effects of benactyzine on physiological functions and on some psychological functions , there has been no detailed assessment of the ocular side effects of the drug. The potential sites of action of cholinergic blocking agents within the eye and associated structures include the iris, ciliary body, retina and the extraocular muscles. Central nervous system structures which control functions such as pupil size, lens accommodation, tonus and action of the extraocular muscles, and voluntary cortical mechanisms involved in producing eye movements may also be affected. Furthermore, these drugs may have central effects such as interference with short term memory and concentration, and these effects may impact on vision performance measures.

This report describes two experiments using placebo and 4.14 mg/70 kg of benactyzine hydrochloride, injected intramusculary, using a double-blind experimental paradigm. In the first experiment we measured a wide range of vision functions; in the second phase we focussed in greater detail on those functions which were significantly altered by the drug. In both experiments, our physiological measures

(pulse and blood pressure), psychological measures (high rating) indicated that the drug preparation was effective. In the first experiment we found that static visual acuity at distance and near was degraded, dynamic visual acuity was reduced, accommodative amplitude was markedly reduced, the pupil increased in size, and the normal diurnal variation in intraocular pressure appeared to be attenuated. Large individual differences in response to the drug were noted.

In the second experiment we re-examined dynamic visual acuity and dynamics of the pupil response. We measured the contrast sensitivity function at near over a wide range of spatial frequencies and measured the dynamics of the accommodation response. Dynamic acuity was reduced, pupil size was increased, but the dynamics of the response appeared unaffected. Contrast sensitivity was diminished over the whole spatial frequency range; the accommodation response was reduced in amplitude and velocity, but the velocity of relaxation of accommodation was unaffected.

These results have important practical implications for observers in field situations where near and far visual acuity for moving and static targets are important components of performance.

GENERAL METHODS

The experiments described here were conducted double blind, using benactyzine and a placebo treatment; subjects were randomly assigned to have the drug or placebo at first visit, and on second visit received the alternate treatment. Subjects were male, between 25 and 32 years of age, who were recruited by advertisement from local college campuses. Before being accepted into the study, they filled out questionnaires on general health and drug use. They were given an optometric examination to check that their vision was adequate (vision better than 20/30 (with correction), normal ocular balance, good ocular health). Subjects with heart, respiratory, or liver problems were excluded, and subjects who were using drugs other than alcohol or marijuana at the time of the study were also excluded. The subjects all had some history of use of other "recreational" drugs. If, at the screening visit, the subject was found to be acceptable, he spent approximately one extra hour in the laboratory during which time he practiced on the entire battery to be used on the experimental days (see below).

EXPERIMENT 1

METHODS

In the first study 6 subjects were used; a further 6 subjects participated in pilot experiments in which only part of the test battery was used. Subjects reported to the laboratory on experimental days by 9:00am, and were run through the entire test battery to establish pre-drug performance levels. Heart rate and blood pressure were measured by a physician who remained on duty while the subjects were present in the laboratory. After the pre-test session, the subject was given an intramuscular injecton of benactyzine hydrochloride (using a dose equivalent to 4.14 mg/70 kg body weight) or an equivalent volume of normal saline. Fifteen minutes after injection, the subject was run through the entire test battery once more; after 5 minutes rest, the subject was again run through the test battery. He then rested for an hour and was retested, and after a further two hours was tested once more. Periodically during the day, pulse, blood pressure, and subjective "high rating" were obtained. This is a subjective report of intoxication, with a rating of 0 assigned to the unintoxicated state, and a rating of 100 being as intoxicated as the subject had ever been.

We measured the following vision functions:

a) static visual acuity - was measured at 3 meters test distance using the "S-chart" procedure, which gives a psychophysical estimate of visual acuity for Landolt ring targets (Flom, Weymouth & Kahneman, 1963)

b) dynamic visual acuity - was measured for single Landolt ring targets moving at 25°/sec. The psychophysical method of limits was used to determine the endpoint.

c) pupil size and response to light - were measured using a television-based pupillometer system, which gives a continuous readout of pupil size (Saladin, 1978). The subject maintained fixation at a distance of 3 meters while pupil size was measured. Three seconds later a peripheral light source was switched on. After a further 3 seconds the peripheral light source was switched off; pupil size was recorded continuously during this procedure.

d) amplitude of accommodation - was measured by having the subject report when a small target on a plain background became slightly blurred as the target was moved toward him. At the point of first blur, the target distance was measured and converted to a measure of amplitude of accommodation in diopters.

e) heterophoria - was measured by an experienced optometrist using the cover test and prisms to neutralize any shift of gaze. It was measured at distance (3 meters) and at near (40 cm).

f) tracking eye movements - were recorded while the subject tracked a sinusoidally moving spot; the frequency of oscillation of the spot was 0.5Hz and its amplitude 6.5^{o}.

g) color vision - was assessed by use of an anomaloscope (constructed by the Optical Sciences Group) in which a mixture of red and green is matched to a standard yellow. The subjects were requested to match the red/green and yellow test spots in both color and brightness.

h) intraocular pressure - was measured using the American Optical (air puff) tonometer. This is a non-contact device which delivers a calibrated puff of air onto the eye to flatten the cornea; the time taken for the cornea to flatten is related to the intraocular pressure. This time is measured by an electro-optical method and converted to IOP in mm. of mercury.

i) contrast sensitivity - was measured for a grating target with a sinusoidal luminance profile generated on an oscilloscope, using the method described by Campbell and Green (1965). The grating spatial frequency was 5 cycles / degree. Thresholds were determined by the method of adjustment (5 measures for each subject). The test target was at 35 cm.

j) static contrast thresholds and glare recovery - were measured using an OSG-constructed device. The static contrast threshold for a 5 min of arc spot flashing at a rate of 4 Hz was determined by the method of adjustment. Three measures of this threshold were made. The subject was then exposed to a bright light source (angular subtense 20^{o}) for 10 sec. He then looked at a uniform field with fixation markers on it; at the center of these fixation markers there was a 5 min of arc spot flashing at 4 Hz. When he had recovered visual sensitivity to the point where he could detect the spot, the subject pressed a button and this time was recorded. Simultaneously the contrast of the spot was decreased below threshold and the recovery process continued until the subject could detect the spot once more. At this point he pressed the button again. This time was recorded, and the contast of the spot was again decreased so that it was below his threshold. This procedure was repeated so that 5 glare recovery times were measured after the single exposure to the bright light source.

RESULTS

Both physiological and psychological changes were induced by the injection of the drug. Pulse rate showed a significant increase 15 minutes after the injection, and

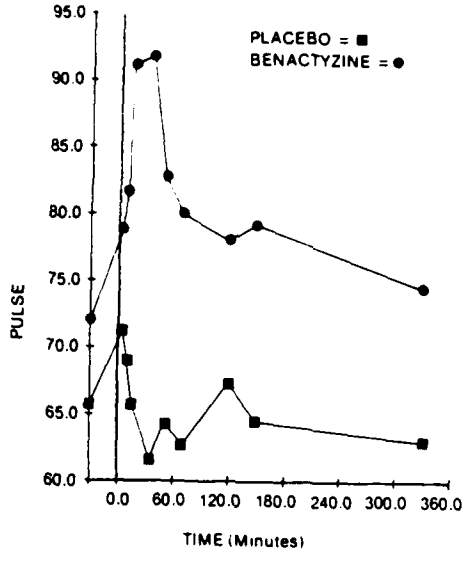


FIGURE 1. Pulse rate in beats/minute as a function of time. The vertical line at 0 minutes shows the time of injection; values left of this are pre-drug and values to the right are post-drug measures. This convention is followed in all the Figures. Table 1 in the Appendix gives the values plotted with their standard deviations. For all figures showing mean data, a table will be found in the appendix with mean, standard deviation and number of measures for each point plotted. Drug (●); Placebo (■); N=6.

remained elevated until approximately 100 minutes post-injection. These data are shown in Figure 1, and it may be noted that initial and final pulse rates for the benactyzine treatment were elevated some 7 - 10 beats per minute above the placebo. The "intoxication" induced by the drug, the so-called "high rating", closely paralleled the change in pulse rate seen in the early post-injection period. This psychological self-rating value (Figure 2) diminishes to the pre-injection value by 5 hours after injection. The high rating value is significantly elevated above the placebo levels by 35 minutes after injection, and the difference between the treatment and placebo values remains significant until some two hours after injection.

There is an overall elevation of systolic and diastolic blood pressure, which peaks 35 minutes after the injection of the drug, and at this point the blood pressure is some 16

mm of mercury above the corresponding placebo value, for both systolic and diastolic blood pressure values (Figure 3). These elevated blood pressure values show an initial

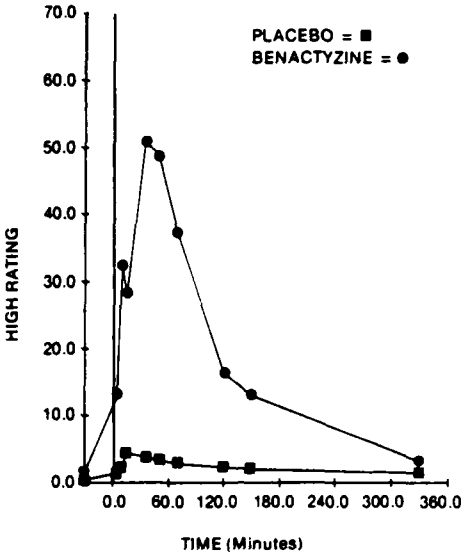


FIGURE 2. Subjective high rating as a function of time, pre- and post-drug for both benactyzine and placebo treatments. Drug (●); placebo (■); N=6.

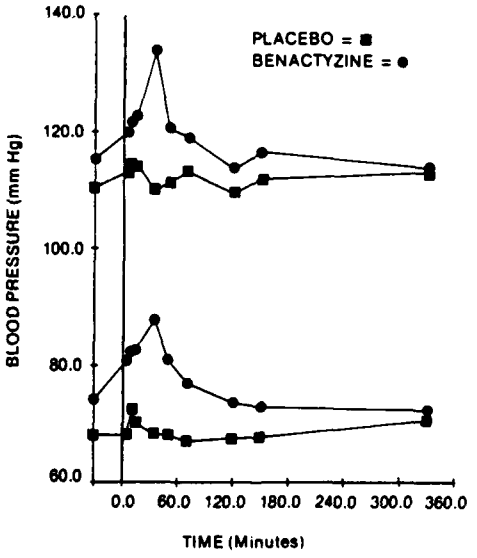


FIGURE 3. Systolic and diastolic blood pressure for benactyzine (●) and placebo (■) treatment. The two upper curves show systolic blood pressure for these treatments; the lower two curves show diastolic blood pressure; N=6.

rapid falloff and then a slow decline through the period from 60 to 300 minutes post-injection. Significant differences between the two treatments are reflected only in the diastolic values, which are significantly different for pre-test, 5 min., 15 min., 35 min., and 150 min. post-injection.

Thus, the drug was effective in producing physiological and psychological changes in this group of subjects. There was considerable variance in the measures, especially at the peak of drug intoxication-- that is, the period from about 15 min. through 35 min. post-injection. As will be noted below, this increased variance in physiological and psychological measures is also reflected in many of our measures of vision function.

Vision Function Tests

Benactyzine reduces distance static visual acuity by approximately 5% Snell-Sterling (from 102.35 - 97.7%), equivalent to reduction in Snellen acuity from 20/17 to 20/22. The effect is rapid in onset; the peak of the effect is at approximately 60 min. and recovery is not complete until some 2 to 2-1/2 hours after the drug has been injected. Figure 4 (lower part) shows these values and the corresponding placebo results.

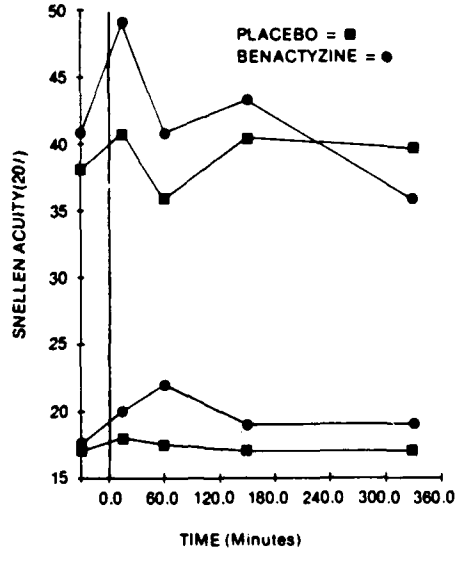


FIGURE 4. Static and dynamic visual acuity values as a function of time for both benactyzine (●) and placebo (■) treatments. The lower curves show static acuity values for both treatments. The upper curves show dynamic visual acuity for targets moving at 25 deg/sec. N=6.

As would be expected from this result, dynamic visual acuity is also reduced by benactyzine; Snellen acuity decreases from about 20/40 to 20/50. In Figure 4 (upper section) the time course of the effect is shown. The peak of the effect occurs at about 30 min. and diminishes thereafter to reach the placebo levels at about 2 to 2-1/2 hours after injection. Benactyzine has a greater effect on dynamic acuity than on static acuity immediately after injection.

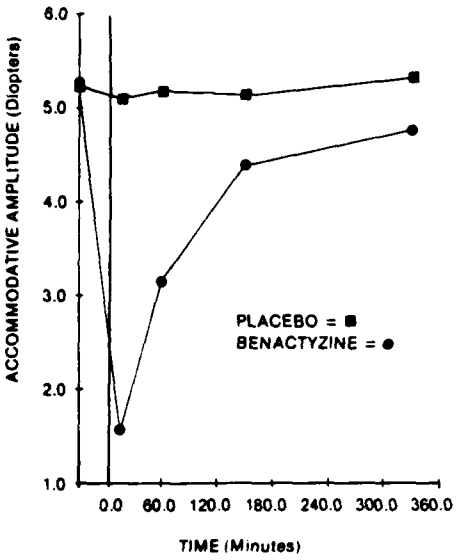


FIGURE 5. Amplitude of accommodation in diopters as a function of time for benactyzine (●) and placebo (■) treatments; N=6.

The amplitude of accommodation was dramatically reduced by the injection of benactyzine. On average, our subjects had about 5.2 diopters of accommodation in the pre-drug condition; however, by 15 minutes after injection, it was reduced to about 1.5 diopters. This reflects a shift in the near point from some 19 cm to 67 cm. This effectively made our 25-32 year old subjects presbyopic; under field conditions they would not have any optical correction available to them and near vision would be greatly reduced. The time course of the effect is very rapid, as can be seen from Figure 5, but even one hour after injection the diminution of accommodation from the pre-injection values is still approximately 2 diopters. Not until 3 hours after the injection has been administered does the accommodation system recover full function.

Concomitant with these changes in accommodative state, we measured an increase in pupil size, both before and during exposure to a small peripheral light source. Pupil size increases after the administration of the drug; prior

to and after illumination of the eye there is enlargement of the pupil. The effect seems to be somewhat slower than the accommodative change and the other changes induced by the drug, peaking at some 60 minutes after drug injection and slowly diminishing thereafter.

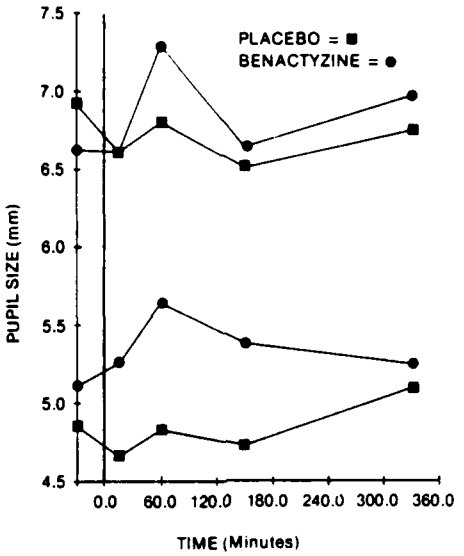


FIGURE 6. Pupil size (mm) as a function of time after administration of benactyzine (●) and placebo (■). The upper traces show pupil size before the peripheral light source was switched on, the lower traces show pupil size during illumination. N=6.

These effects are shown in Figure 6 where the pre-exposure values for pupil size are shown at the top of the figure along with corresponding placebo, and the values of pupil size during the exposure to the peripheral light source are shown in the bottom two curves. While the absolute magnitude of the change in pupil size is relatively small (about 0.5 mm) this would be expected to have a small effect on visual acuity and on contrast sensitivity measures.

In our measures of heterophoria most subjects demonstrated little or no change, either at distance or near. One of our subjects, at the peak of the drug effect, however, showed a massive esophoric shift of some 7^{Δ} at distance and 20^{Δ} at near; he complained of diplopia at near. This change in oculomotor balance slowly returned to pre-drug levels over the next five hours. These results are shown in Figure 7. There is a large amount of individual variation in oculomotor changes produced by benactyzine. Four of our subjects showed essentially no change in phoria throughout the drug or placebo trials, and one other subject showed a shift from about 4^{Δ} esophoria to 4^{Δ} exophoria at near during the course of the drug treatment.

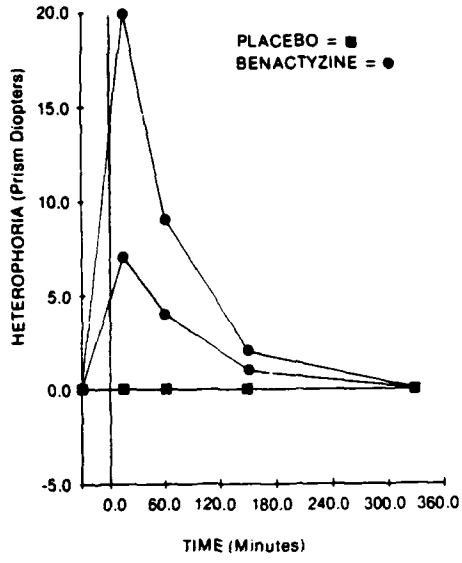


FIGURE 7. Heterophoria in prism diopters as a function of time for 1 subject. The lower curve (■) shows placebo values; the middle curve (●) shows the values for distance heterophoria in this subject. The upper curve (●) shows the value of heterophoria at near for this particular subject during the benactyzine treatment.

Tracking eye movements records were digitized and subjected to power spectrum analysis. No consistent drug effects were noted, and there was a consistent decline in performance throughout the day for both benactyzine and placebo treatments. (see Figure 8).

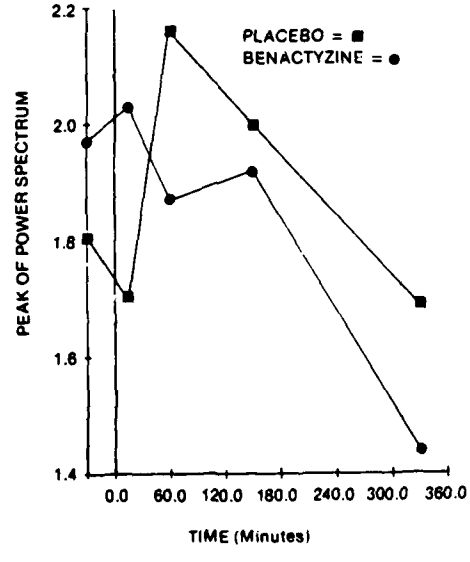


FIGURE 8. Peak value of power spectrum of sinusoidal eye movement responses as a function of time for benactyzine (●) and placebo (■) treatments. N=6.

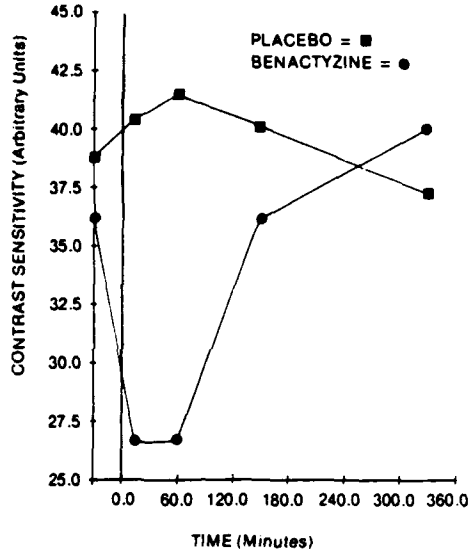


FIGURE 9. Contrast sensitivity (arbitrary units) for detection of sinusoidally modulated grating of 5 cycles/deg as a function of time for placebo (■) and benactyzine (●) treatments. N=6.

There were large changes in the contrast sensitivity measure at near (test distance was 35 cm). This effect is shown in Figure 9 where sensitivity values (arbitrary units) are shown as a function of time for both placebo and drug treatments. Contrast sensitivity recovers to normal levels by 3-4 hours after injection, after a rapid initial decline.

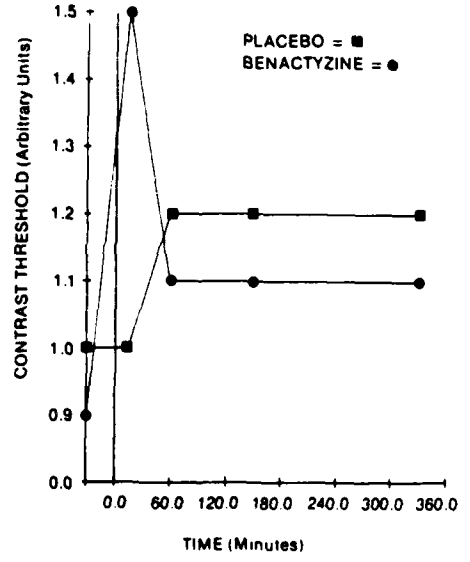


FIGURE 10. Contrast thresholds for 5 min of arc spot flashed at 4Hz after benactyzine(●)and placebo(■).N=6

The time course of these changes closely parallels the time course of the drug effect on accommodation (see Figure 5). We also showed changes in contrast sensitivity for a small (5 min of arc) spot; subjects set this spot to threshold

prior to completing the glare recovery task. These threshold measures showed marked changes with fairly rapid recovery after administration of benactyzine; the results are shown in Figure 10.

We were unable to demonstrate significant changes in color vision; intraocular pressure showed an apparent diminution of the normal diurnal variation pattern but the change was not statistically significant. Glare recovery results were impressive in their reliability but demonstrated no drug effect.

Other, less formal, observations made during the conduct of this experiment and other preliminary experiments using benactyzine indicate that there is great variability in subject response to the administration of this drug. The effects of the drug range from almost total incapacitation for structured thought or action over a period of 1 to 2-1/2 hours to almost no effect, apart from a transient increase in pulse rate. Subjects who were affected by the drug appeared to have little motiviation to perform the vision tasks which we required of them; however, when the experimenters demanded performance, the subjects were able to put aside their incapacitation and perform quite well. One of the more striking defects seen in incapaciated subjects is a marked loss of short-term memory performance, quite similar to that noted in subjects intoxicated with marijuana. Subjects may begin a sentence and be unable to complete it because they are unable to recall the words which they have just spoken and are unable to produce the next appropriate word in sequence.

This exploration of a wide range of vision functions led us to select a number of functions for further study. Dynamic visual acuity, contrast sensitivity, pupil size, an accommodation responses were all affected by benactyzine, and we examined these functions in greater detail in our second experiment.

EXPERIMENT 2

METHODS

Twelve healthy male subjects, ranging in age from 20 to 36 years were recruited by advertisement for participation in this experiment (see GENERAL METHODS above). All were in good health and had normal vision function.

On test days, subjects reported to the laboratory at 9:00 am. They had pulse and blood pressure measurements made by the attending physician and were pre-tested. After this test session, they were injected with 4.14 mg/70 kg body weight of benactyzine hydrochloride or placebo (saline) as appropriate and they were retested at 15, 90 and 270 minutes post-injection. Pulse and blood pressure were measured periodically throughout the day and subjective high ratings were also obtained.

The following procedures were used to test the various vision functions:

a) Dynamic Visual Acuity. In Experiment 1 we measured dynamic visual acuity for Landolt ring targets moving at 25°/sec. In this experiment we extended the range of target velocities to include 5° and 40°/sec. The procedure was similar to that employed in Experiment 1. The subject looked at a fixation marker on the screen 3m in front of him, and at a random time after a warning tone, the target was presented at the fixation point. It moved to the subject's right, and was exposed for .5 sec. At the end of the target exposure, the subject responded by pressing one of four buttons corresponding to the position of the gap in the presented Landolt ring. Initially the target was above threshold size, and with succeeding correct responses, the target size was reduced until the subject responded incorrectly on two successive occasions. A series of targets of increasing size was then presented until the subject responded correctly on two successive presentations. The mean of the two endpoints was taken as the subject's dynamic visual acuity for that particular target velocity.

b) Contrast Sensitivity Function. Gratings with a sinusoidal luminance profile were generated on a Tektronix 606 Display Oscilloscope positioned 57cm from the subject. The spatial frequency, contrast, and presentation time of the gratings were under computer control. Initially a grating which was above threshold for the subject was presented and the subject pressed a button indicating that he could see it. Contrast of the grating was then reduced and again the subject responded. Responses indicating that the subject could see the grating caused it's contrast to be reduced. When the subject indicated that he could not see the grating (by pressing a second button), this reversal

point was recorded; the grating contrast was then increased on successive presentations until he indicated that he could see it. This value was also recorded as a reversal point. Responses were gathered until seven reversal points had been measured and the mean of these reversal points was taken as the subject's contrast threshold. The inverse of the contrast threshold was calculated as the contrast sensitivity at a particular spatial frequency. The spatial frequencies used in this experiment were 1, 3, 5, 10 and 20 cycles/ degree. These gratings were presented in order from low to high spatial frequency. The test field was a 6^{o} circle, seen from the subject's observation position and it had a mean luminance of 11 cd/m^2.

c) Pupil Dynamics. In this experiment the subject looked at a fixation point 3 meters in front of him. A television camera with appropriate auxiliary lenses was used to obtain an enlarged TV image of his right eye. This image was processed by Saladin pupillometer which gives a continuous

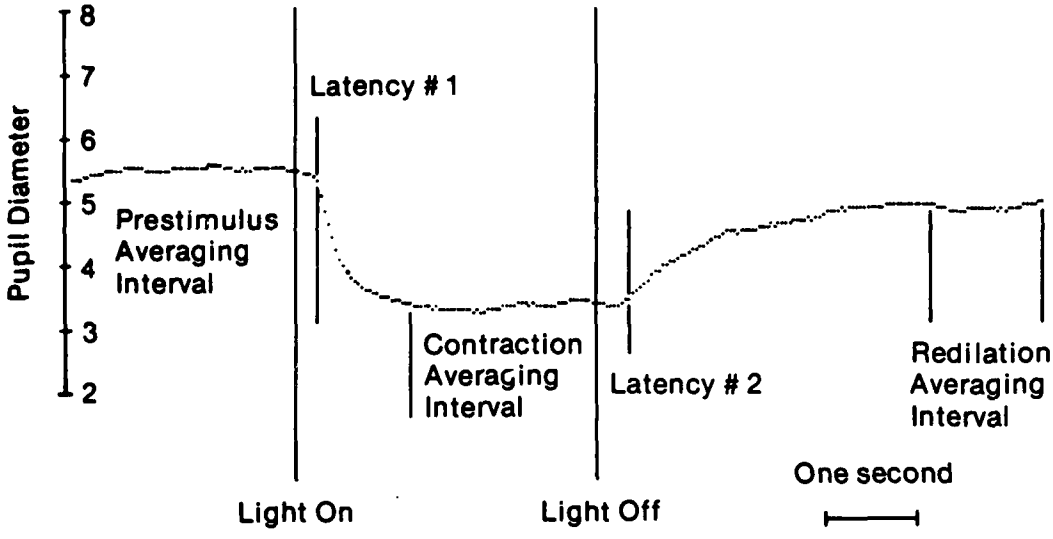


FIGURE 11. Typical output of pupillometer in Experiment 2. The labels show time of light onset and offset, and parameters measured from the records.

output of pupil diameter. (See Saladin, 1978 for a description of the device). Data from the pupillometer were input to the computer for 2.4 seconds and the computer then turned on a small light in the subject's periphery. Data was acquired for a further 3.2 seconds then the light was turned off. Data were input for a further 4.8 seconds during the relaxation phase of pupil response. These data were plotted and stored on magnetic tape to await further analysis. Figure 11 shows a typical response together with

d) Accommodation. Dynamic accommodation responses were measured using an SRI optometer, which gives a continuous readout of the state of focus of the subjects eye. It is based on a design by Cornsweet and Crane (1970). This device is a servo system which optically nulls any motion of two infrared retinal images produced by two spatially separated sources (which are pulsed in counter phase). The motion of the servo reflects the state of the eye focus, and provides an electrical signal which can be recorded.

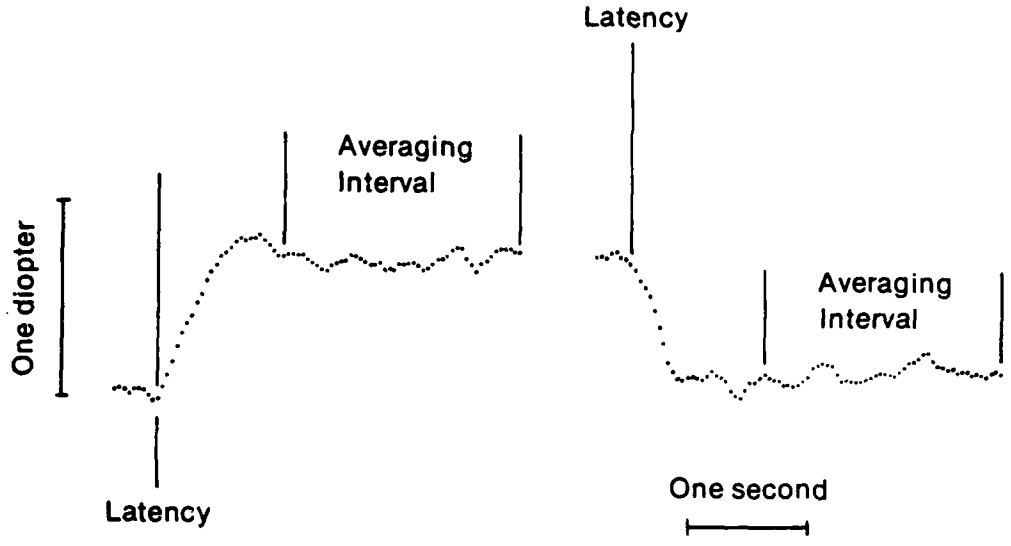
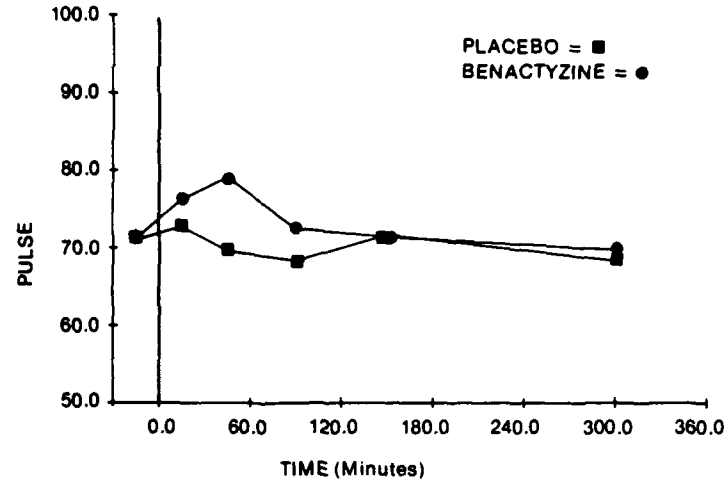
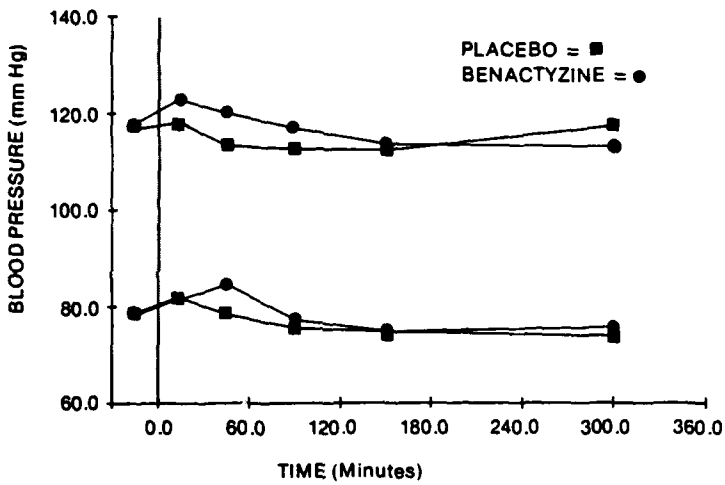


FIGURE 12. Typical optometer output, showing a change of accommodative state in response to a +1D step of vergence (left side of the Figure) and a -1D step of vergence (right side of the Figure). The labels give the various parameters and measuring intervals derived from these records.

Subjects were positioned at the optometer and viewed a target 3 meters away through a Badal focus stimulator. The computer sampled the output of the optometer at 45 msec intervals and after 3 seconds introduced a 1 diopter step in the target position. Subjects accommodated to clear the image of the target and the optometer output was sampled during this time. Further one diopter steps of target position were introduced until the target was effectively 4 diopters (25 cm) from the eye. Accommodation state was continuously monitored by the computer during this period. The target was then stepped away from the subject in 1 diopter steps at 3.5 second intervals until it reached the zero state once more. Accommodation was continuously monitored during this phase as well, and at the end of the sequence was plotted. If responses were deemed satisfactory, they were recorded on magnetic tape. Latency and absolute level of accommodation as well as velocity of the responses were measured (see Figure 12). Data were averaged across subjects, and these data are shown.





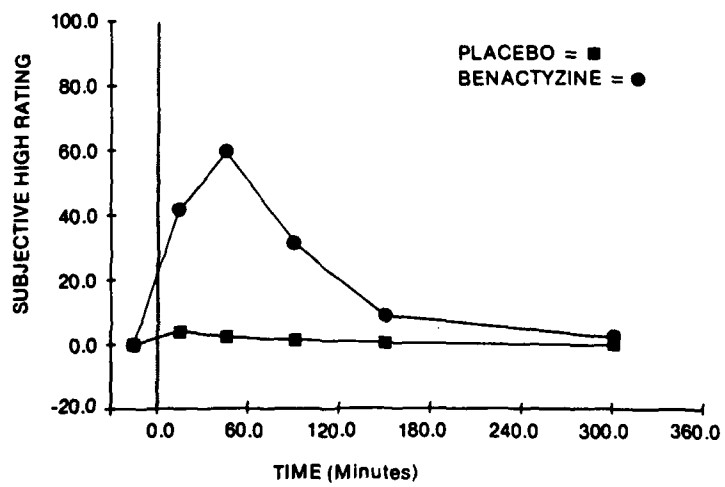


FIGURE 13. Average pulse, blood pressure (systolic and diastolic), and subjective high rating averaged across the 12 subjects used in Experiment 2 as a function of time. (Benactyzine (●); Placebo (■)).

RESULTS

Pulse, blood pressure, and high ratings all demonstrated increments over pre-drug and placebo treatments. These results are similar to those demonstrated in Experiment 1 and are shown in Figure 13. The pulse and blood pressure changes do not reach statistical significance, because of intersubject variability and presence of a fairly marked response to placebo in some subjects. The "high rating", however, is significantly elevated from 15 through 90 minutes after drug administration (Walsh test, $p < .005$).

These changes indicate that the drug preparation was effective in producing physiological and psychological changes in these subjects. As noted in Experiment 1, there was considerable variablility in individual subject's response to the drug. The duration of the drug effect was about 2 hours, which confirms our earlier findings.

Fifteen minutes after the drug was administered we found a reduction in dynamic visual acuity (relative to the placebo), which was relatively short-lived, being essentially undetectable at our second measurement time. The depression of acuity is not significant for targets moving at 5 deg/sec, but for targets moving at 40 deg/sec (see Figure 14), it is significant (Walsh test, $p < .005$).

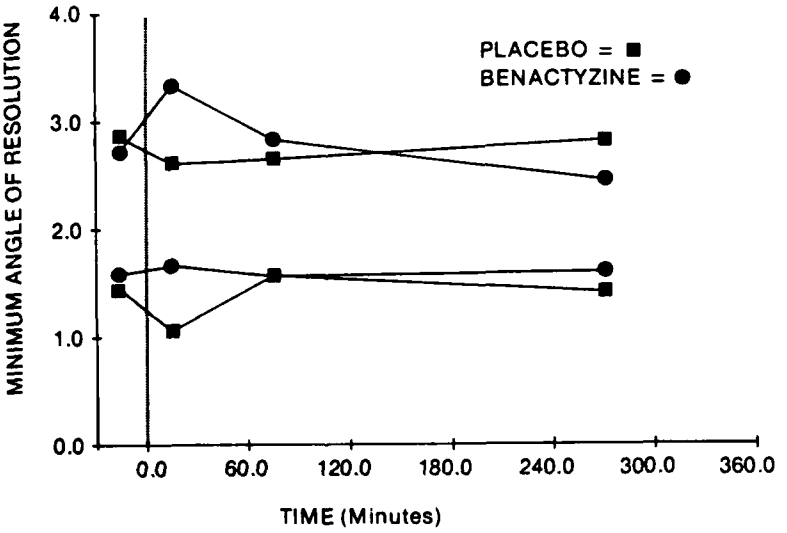


FIGURE 14. Dynamic visual acuity (as minimum angle of resolution) as a function of time. The upper set of curves show data for targets moving at 40^{o}/sec, while the lower set show data for targets moving at 5^{o}/sec. (Benactyzine (●); Placebo (■). N=12.

This result is in accord with the result reported in Experiment 1. In Figure 15 combined data from Experiments 1 and 2 are shown. Changes in acuity at the first post-drug measurement session are shown as a function of target angular velocity. Benactyzine produces a decrease in acuity at all three target velocities, while a practice effect is evident in the data of the placebo sessions, especially at 5 and 40 deg/sec.

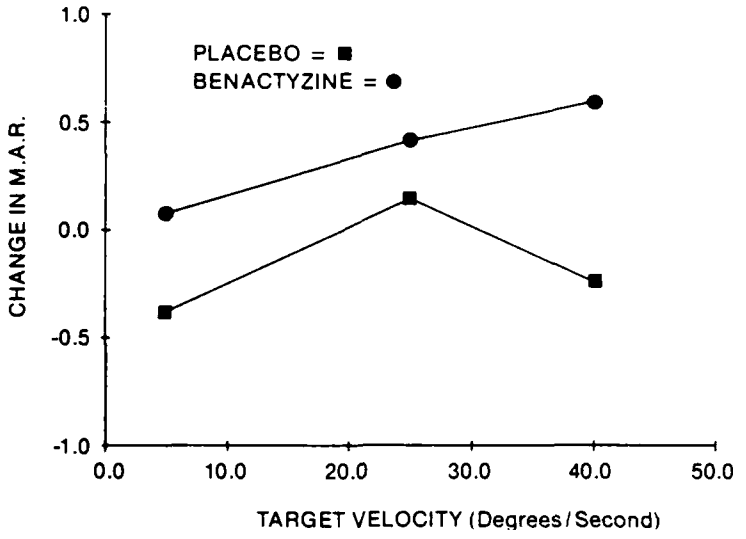


FIGURE 15. Change in minimum angle of resolution in the dynamic visual acuity experiment 15 minutes after drug injection. The data for the 25°/sec point are taken from Experiment 1; (Benactyzine (●); Placebo (■)). N=12 (Experiment 2),N=6 (Experiment 1).

It can be seen from Figure 16 that the contrast sensitivity of our subjects is depressed across the whole range of spatial frequencies used. Data for the two groups in the pre-treatment sessions are quite comparable and not statistically different; fifteen minutes after drug injection, however, the contrast sensitivity of the benactyzine subjects is depressed by some .25 to .30 log units across the whole spatial frequency range (Figure 17). The depressions of sensitivity at 1, 3, and 5 cycles/degree are significant at the .005 level (Walsh test). This reduction in contrast sensitivity is still apparent at the 90 minute test session and is still significant at the .005 level. By the last test session, there is no difference between the curves.

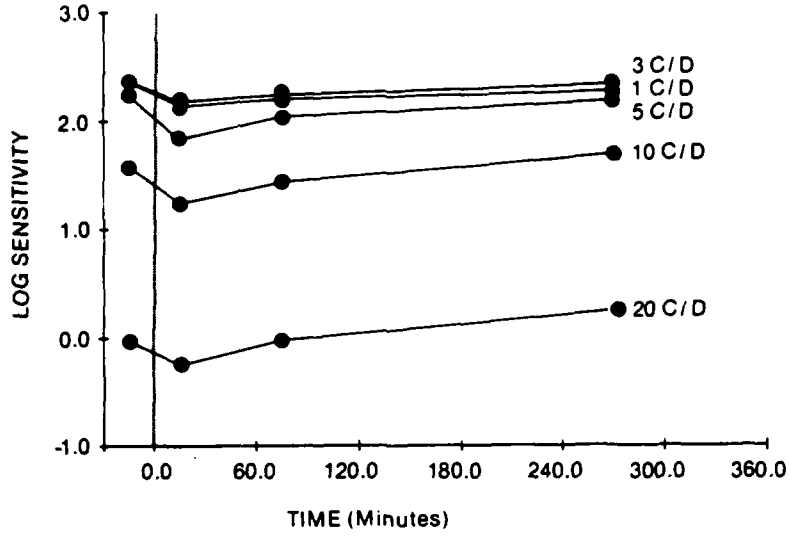


FIGURE 16. Contrast sensitivity as a function of time after drug injection. The parameter is spatial frequency of the display in cycles/degree. Note that on this figure no placebo data are shown. N=12.

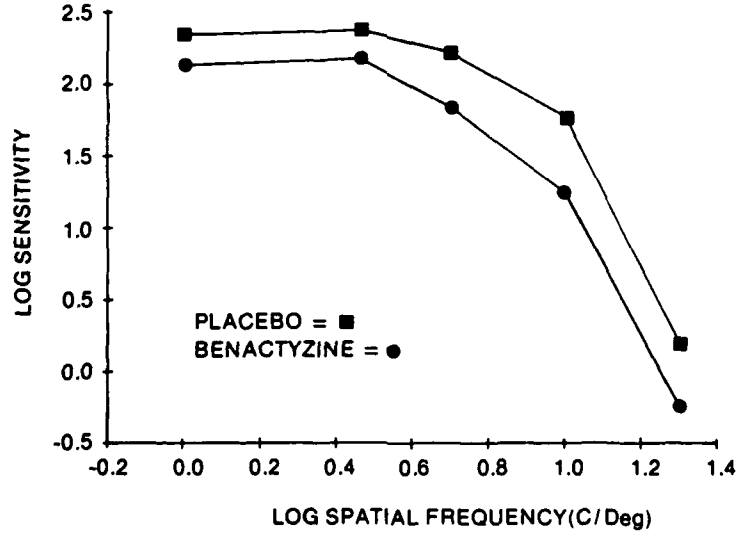


FIGURE 17. Contrast sensitivity as a function of spatial frequency 15 minutes after drug injection for benactyzine (●) and placebo (■); N=12.

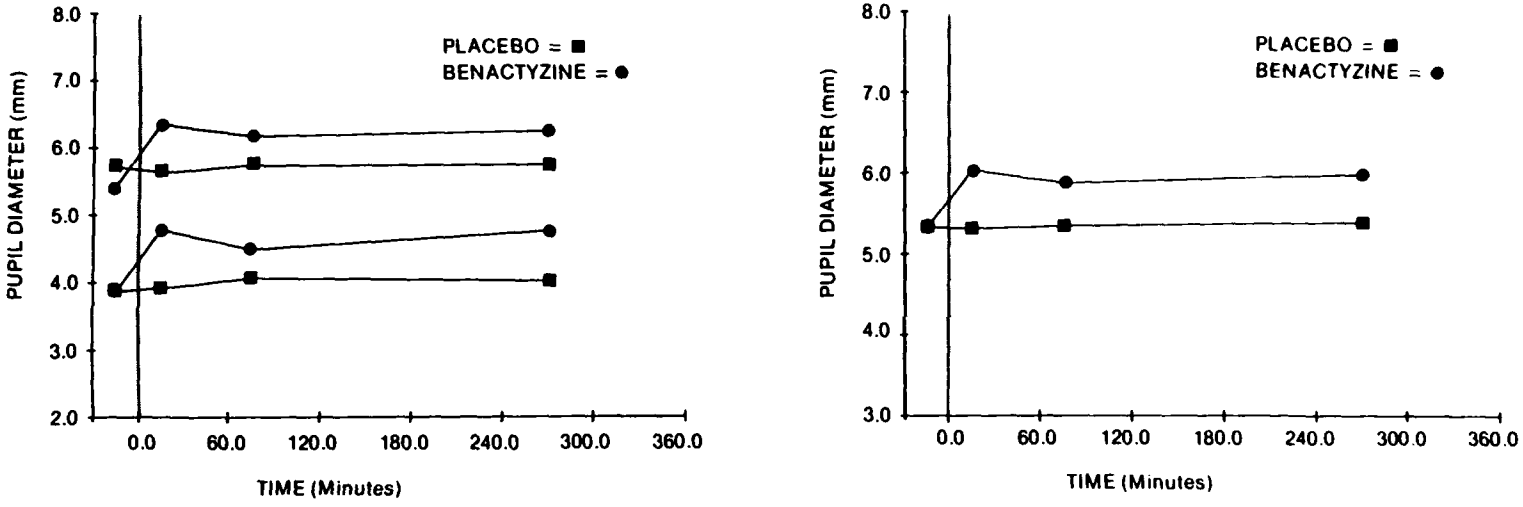


FIGURE 18. Pupil diameter as a function of time after injection of benactyzine or placebo. The upper set of curves on the left show mean pupil diameter before onset of the stimulus light while the lower set shows pupil diameter during the "contraction averaging interval" (see Figure 11). The curves on the right show mean pupil size after the pupil recovered, during the "redilation averaging interval", after the peripheral light has been turned off. (Benactyzine(●); Placebo (■)); N=12.

Pupil size was increased after benactyzine in this group of subjects, a result which confirms the result of Experiment 1 ($p < .005$, Walsh test). The pupil is larger before, during, and after exposure to a peripheral light source (see Figure 18). In this experiment we measured the latency of pupillary constriction and found it to be unaffected by benactyzine. However, the latency of dilatation of the pupil, when a peripheral light source is turned off, appears to be increased by the drug ($p < .047$, Walsh test, at post-15 minutes measurement time. Other aspects of dynamic pupil function appear unaffected. Benactyzine apparently has no effect on the velocity of the constriction response or the dilatation response.

The reduction in accommodative amplitude which we found in Experiment 1 is confirmed by the data presented in Figure 19. The amplitude of the accommodative response averaged across subjects' responses are comparable to those of the placebo group when up to 2 diopters of accommodation is demanded; when the demand is 3 diopters, the placebo group

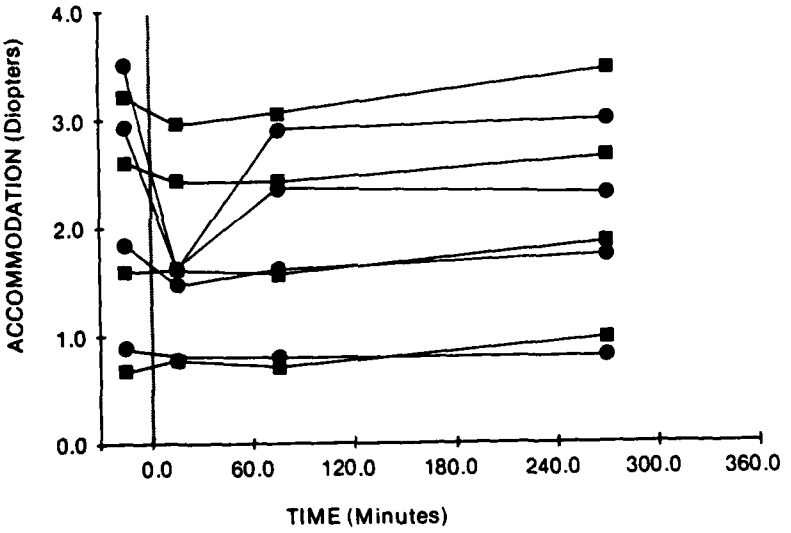


FIGURE 19. Accommodation as a function of time after drug injection. Each pair of curves shows the response to a stimulus of (from the bottom) 1, 2, 3 and 4 diopters. Note that at the 15 minute measuring point the responses for benactyzine and placebo are comparable for the 1 and 2 diopter stimuli while the 3 and 4 diopter stimuli, the benactyzine response does not exceed that for the 2 diopter stimulus. (Benactyzine (●); Placebo (■)); N=6-10.

accommodate on average 2.5 diopters; however, the benactyzine group appears unable to accommodate beyond the level which they attained for the 2 diopter stimulus. Similar findings are present when the accomodative demand is 4 diopters. The accommodative response appears to have recovered to near normal limits by 90 minutes post-

injection. The wave forms of the averaged accommodation responses for the two groups are shown in Figure 20. Responses of the benactyzine group, especially at higher accommodative demands, appear to exceed those of the placebo group in the pre-drug session; however, immediately after injection it is clear that the responses of the benactyzine subjects are diminished in absolute accommodative amplitude (being restricted to about 1.5 diopters), and it is further evident that the velocity of the remaining accommodative response is considerably reduced. In the placebo group

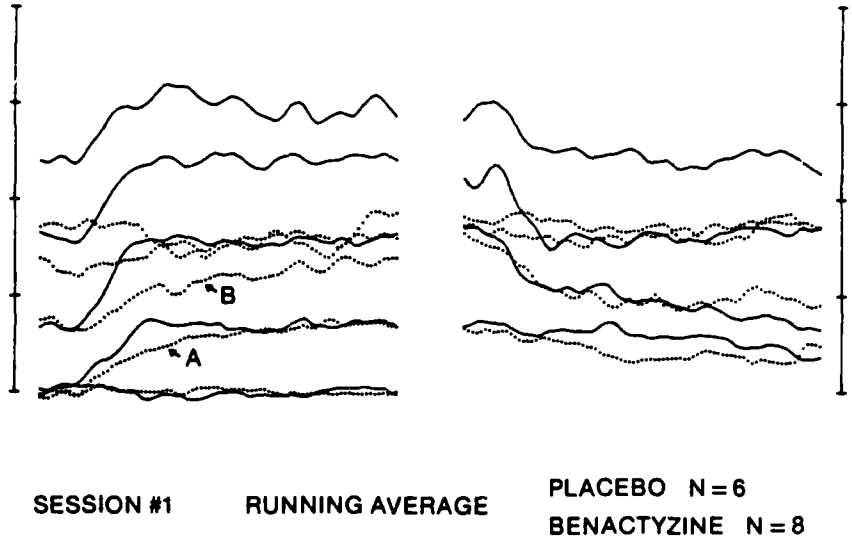


FIGURE 20. Averaged accommodation waveforms in response to 1 diopter increments of stimulation (left side) and 1 diopter decrements of stimulation (right side), for placebo (continuous lines) and benactyzine (dotted lines). Note the delayed response to stimulation, marked by A and B. N=6(placebo);N=8(drug).

accommodation responses are completed by approximately 1.1 seconds, while the bentactyzine group do not obtain maximum accommodative response until 2 seconds after the stimulus step (marked A in Figure 20). Response to the 2 diopter step (marked B in Figure 20) reaches almost the same level as the placebo only at the end of the target step interval, an almost three-fold increment in response time. It is apparent from the right-hand side of Figure 20 that relaxation of accommodation from maximum level exerted takes about the same time in both of the groups.

DISCUSSION

We have noted performance decrements in many aspects of the visual function in our subjects. In particular, their acuity for static and moving targets was reduced, and these effects would act to impede the detection, tracking, and identification of distant targets. Contrast sensitivity at near is reduced (this is produced in part by effects on the accommodative mechanism and by changes in pupil size). Benactyzine produces changes in concentration, motivation, and time sense which are important in determining performance levels.

The drug-induced reduction of dynamic visual acuity appears to be velocity dependent, showing greater reduction at 25^{o}/sec and 40^{o}/sec than at slower velocities. In view of our inability to demonstrate changes in pursuit eye movements in subjects under the influence of benactyzine this result is somewhat surprising. However, these eye movements were measured for stimuli moving in a predictable and continuous manner. It may be that benactyzine-induced alterations in attention to the dynamic visual acuity task (in which the targets are presented only intermittently), produced this result.

Our results indicate that in near visual tasks, personnel in critical command positions who are in the pre-presbyopic and presbyopic age ranges (and who do not have spectacle correction) would have serious difficulty performing tasks such as reading and interpreting maps or changing focus from distant to near targets. The near vision of these subjects would be extremely blurred and under reduced illumination conditions there may be a risk of total breakdown of binocular vision resulting in double vision. One important aspect of the results of our second experiment is the alteration in the velocity of the accommodation response. Normally a change of accommodation of some 2 diopters takes about 0.5 sec. Subjects who were at the peak of benactyzine intoxication needed approximately 3 sec to achieve this response. In dynamic tasks such as driving or flying this is a significant amount of time subtracted from the time available for other aspects of task performance. It may result in neglect of tasks such as search of the external environment, or may result in neglect of monitoring of instruments which provide crucial information regarding vehicle performance and guidance. The consequences of neglect of these important functions in a military environment may be disastrous.

We have noted important reductions of performance in the contrast sensitivity function and in detection of low contrast single objects (the 5 min cf arc spot in our glare recovery pre-test). These functions are of course most

dramatically affected at near. Since this result was produced using a threshold task, one would expect that in the real world, detection would be diminished for targets with low contrast; i.e., those whose visibility and conspicuity is marginal at best.

Our contrast sensitivity function measures were decreased at all spatial frequencies tested. This result may be produced by a number of factors, including optical, neural, and motivational (criterion shift). Optical factors such as reduced amplitude of accommodation and increased aberrations (resulting from increased pupil size) would be expected to affect the higher spatial frequencies tested; we do not expect these effects to be large since the target was at 57 cm (demanding 1.75 diopters of accommodation). Many of our subjects were able to accommodate to this distance. An indirect mechanism by which cholinergic blocking agents may affect low spatial frequency contrast sensitivity is by reduction of tear flow. If reduced tear flow leads to drying and slight edema of the cornea, low as well as high spatial frequency response would be diminished.

Neural factors which may be influenced by benactyzine include the cholinergic mechanisms within the retina--acetylcholine is known to be a transmitter within the retina although its exact function in determining vision performance is unknown. (Masland, 1979; Redburn and Chentanez, 1979) Alterations at the low spatial frequency end of the contrast sensitivity curve are generally attributed to neural and not to optical factors. The way in which our experiment was conducted (sudden onset of the stimulus after blank field presentation) may indicate that benactyzine affects transient retinal mechanisms at low spatial frequencies.

It is also possible that our result was produced by a criterion shift in our observers after administration of benactyzine. Such an effect would probably act across all spatial frequencies to produce a uniform depression of sensitivity. Without extensive further testing this possibility cannot be excluded.

From a practical point of view, reduction of contrast sensitivity is of importance. Reduction of contrast sensitivity at high spatial frequencies (as may be expected from optical blur) will render fine detail more difficult to resolve; reduction of contrast sensitivity at low spatial frequencies may mean that relatively large objects have their visibility reduced below threshold. Furthermore, changes in contrast sensitivity of low spatial frequency mechanisms may have an interacting effect with accommodative control; recent evidence suggests that relatively low spatial frequency information is necessary to provide adequate control in the accommodation system (Owens, 1980).

Some aspects of vision function appear to be entirely unaffected by benactyzine. We were unable to demonstrate changes in color vision or tracking eye movements for predictable targets. The relatively small changes that we have seen in intraocular pressure appear to attenuate the normal diurnal variation. It may be that the tissue of the iris impinges slightly on the angle of the anterior chamber of the eye and thus impedes the outflow of aqueous humor to some extent.

Could our subjects perform complex tasks of any kind after administration of the drug? Many of our subjects, when asked this question, felt they would be unable to perform tasks such as riding a bicycle, or driving a car. Indeed, some of them felt that they would be unable to walk; however, with encouragement and appropriate motivation, all were able to perform at some minimal level. All subjects but one were able to walk from the test laboratory after the first test session (about 40 minutes post-injection). We were able to test our subjects on all of our tasks; some of the tasks call for complex interactions of sensory, oculomotor, and general motor performance. However, it should be noted that these tasks were performed singly. Had our subjects been required to process information from more than one source, or to perform a continuous tracking task as well as our other test protocols, the results may well have indicated much greater performance decrements.

On the other hand, in military combat situations it is likely that the level of self-motivation would be relatively high (presumably higher than we could provide in the laboratory), and we feel that it is likely that in a group situation, some individuals would be relatively unaffected by the drug. Such individuals would probably be able to perform at adequate levels, and may also be capable of motivating their colleagues to perform at a level which an affected individual may feel he is unable to reach.

CONCLUSION

Our experiments demonstrated large and significant decrements in visual functions after the administration of benactyzine, especially for those vision functions performed at near. Dynamic acuity, static acuity, contrast thresholds at near and pupil size were most dramatically affected.

The onset of the drug effect is rapid, with maximal effects on vision and other physiological and psychological parameters reached in 30 - 40 minutes post-injection. Substantial effects are present for about 2 hours and by 3 - 5 hours performance has improved to pre-drug levels.

In addition to effects on purely visual performance, we have noted that psychological factors such the level of motivation, loss of sense of time, and diminished short-term memory performance are characteristic of benactyzine-intoxicated subjects. It is obvious that these factors alone or in combination could provide severe problems for personnel engaged in skilled tasks such as vehicle guidance and control, or radio and signal operations. There is a wide range of individual variation in response to this drug.

We caution that the results we have described were produced when tasks were performed in isolation. In the real world, especially in combat situations, there will be a great number of tasks demanding attention and parallel processing of information. Thus, the deficits which we have noted may be cumulative in their effects. That is to say, interaction of these various deficits of contrast sensitivity function, dynamic visual acuity, and alteration of dynamic accommodation response may produce large deficits in target detection and tracking, and in search and monitoring behaviors.

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APPENDIX

THIS APPENDIX INCLUDES THE MEAN VALUES, STANDARD DEVIATIONS AND NUMBER OF VALUES CONTRIBUTING TO THESE DATA FOR EACH OF THE FIGURES IN THE MAIN BODY OF THIS REPORT. TIMES ARE IN MINUTES PRE AND POST-DRUG INJECTION. OTHER UNITS ARE NOTED IN EACH TABLE.

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	72.0	11.0	6	63.7	9.0	6
+5	78.7	12.6	6	71.2	7.7	5
+10	81.6	16.6	5	69.0	6.0	4
+15	91.1	23.7	6	65.7	9.2	6
+35	91.7	11.3	6	61.6	3.3	5
+50	82.8	3.4	5	64.3	8.2	6
+70	80.0	5.1	6	62.7	6.7	6
+120	78.0	4.0	4	67.3	6.7	4
+150	79.2	1.8	5	64.5	5.0	6
+330	74.5	7.8	6	63.0	6.0	4

FIGURE 1 (PAGE 6) PULSE RATE (BEATS/MIN)

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N.
PRE	1.7	2.6	6	0.5	1.2	6
+5	13.0	23.2	6	1.4	2.0	5
+10	32.5	30.3	6	2.3	2.9	4
+15	28.0	27.8	5	4.4	3.1	5
+35	50.8	27.0	6	3.8	3.5	4
+50	48.8	34.4	5	3.4	3.1	5
+70	37.2	30.7	6	2.8	2.8	5
+120	16.3	23.6	4	2.3	2.9	4
+150	13.0	17.9	5	2.0	2.8	5
+330	3.3	5.2	6	1.5	3.0	4

FIGURE 2 (PAGE 7) SUBJECTIVE HIGH RATING

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	115.3	6.8	6	110.3	8.8	6
+5	119.7	10.7	6	113.0	7.8	5
+10	121.8	17.6	6	114.5	9.2	4
+15	122.5	18.4	6	114.0	8.6	6
+35	133.7	22.0	6	109.8	6.6	5
+50	120.4	11.3	5	111.1	7.2	6
+70	119.0	9.4	6	113.0	6.7	6
+120	113.5	9.3	4	109.3	9.4	4
+150	116.4	7.1	5	111.8	4.9	6
+330	113.8	5.3	6	113.0	8.1	4
PRE	74.0	9.6	6	68.0	8.7	6
+5	80.7	13.2	6	68.0	9.8	5
+10	82.3	16.0	6	72.5	9.9	4
+15	82.7	17.2	6	70.0	9.2	6
+35	87.7	6.0	6	68.2	9.7	5
+50	80.8	11.7	5	68.0	9.1	6
+70	77.0	10.6	6	67.0	9.4	6
+120	73.5	11.7	4	67.5	8.5	4
+150	72.8	10.8	5	67.7	8.1	6
+330	72.3	9.1	6	70.5	8.2	4

FIGURE 3 (PAGE 7) PHASE I BLOOD PRESSURE (mm Hg)
(UPPER: SYSTOLIC; LOWER: DIASTOLIC)

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	20/40.8	9.8	6	20/38	11.4	6
+15	49.0	10.6	6	40.8	11.4	6
+60	40.8	9.8	6	35.8	9.2	6
+150	43.2	12.8	6	40.4	12.4	6
+330	35.8	10.2	6	39.6	10.6	6
PRE	20/17.5	0.4	6	20/17.0	0.4	6
+15	20.0	0.8	6	18.0	0.7	6
+60	22.0	1.0	6	17.5	0.6	6
+150	19.0	0.6	6	17.0	0.6	6
+330	19.0	0.6	6	17.0	0.7	6

FIGURE 4 (PAGE 8) STATIC & DYNAMIC VISUAL ACUITIES (SNELLEN NOTATION)

(UPPER: DYNAMIC VISUAL ACUITY, $25^{O}/S$;
LOWER: STATIC VISUAL ACUITY)

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	5.3	2.0	6	5.2	1.5	6
+15	1.6	1.3	5	5.1	1.4	6
+60	3.2	2.5	6	5.2	1.6	6
+150	4.4	2.7	6	5.1	1.7	6
+330	4.8	2.2	6	5.3	1.6	6

FIGURE 5 (PAGE 9) AMPLITUDE OF ACCOMMODATION (DIOPTERS)

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	6.6	0.7	6	6.9	0.8	6
+15	6.6	1.3	6	6.6	0.7	6
+60	7.3	0.7	6	6.8	0.6	6
+150	6.6	0.7	6	6.5	1.0	6
+330	7.0	0.8	6	6.8	0.7	6
PRE	5.1	0.4	6	4.9	0.6	6
+15	5.3	0.8	6	4.7	0.5	6
+60	5.6	0.8	6	4.8	0.5	6
+150	5.4	0.6	6	4.7	0.6	6
+330	5.3	0.9	6	5.1	0.6	6

FIGURE 6 (PAGE 10) PUPIL DIAMETER (mm)

(UPPER: PERIPHERAL LIGHT OFF
LOWER: PERIPHERAL LIGHT ON)

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	2.0	0.2	5	1.8	0.3	5
+15	2.0	0.6	5	1.7	0.4	5
+60	1.9	0.6	5	2.2	0.9	5
+150	1.9	0.4	5	2.0	0.6	5
+330	1.4	0.5	5	1.7	0.2	5

FIGURE 8 (PAGE 11) POWER OF SINUSOIDAL EYE MOVEMENTS
(ARBITRARY UNITS)

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	36.3	13.5	6	38.8	12.6	6
+15	33.0	16.2	6	40.4	10.5	6
+60	26.7	18.0	6	41.5	10.8	6
+150	36.2	19.2	6	40.1	12.2	6
+330	40.0	9.4	6	37.2	11.4	6

FIGURE 9 (PAGE 12) CONTRAST SENSITIVITY
(ARBITRARY UNITS)

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	0.9	0.4	6	1.0	0.5	6
+15	1.5	1.1	6	1.0	0.4	6
+60	1.1	0.3	6	1.2	0.4	6
+150	1.1	0.3	6	1.2	0.4	6
+330	1.1	0.5	6	1.2	0.4	6

FIGURE 10 (PAGE 12) CONTRAST THRESHOLDS
(ARBITRARY UNITS)

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	118.0	16.6	12	116.9	8.8	12
+15	123.0	14.3	12	118.2	10.1	12
+60	120.2	9.6	10	113.5	7.3	12
+90	117.1	12.2	12	112.8	7.2	11
+150	113.7	13.7	12	112.5	7.4	12
+330	113.3	9.8	12	117.6	6.8	10
PRE	78.4	9.1	12	78.5	6.2	12
+15	81.8	8.2	12	82.1	10.2	12
+60	84.8	6.6	10	78.6	5.9	12
+90	77.4	5.7	12	75.8	6.9	11
+150	75.1	8.8	12	75.0	6.7	12
+330	75.9	5.5	12	74.2	9.5	10
PRE	71.2	10.5	12	71.0	8.7	12
+15	76.2	12.7	12	72.7	7.9	12
+60	79.1	10.4	10	69.6	8.9	12
+90	72.5	10.7	12	68.4	6.5	11
+150	71.3	13.1	12	71.7	7.8	12
+330	69.8	6.5	12	68.4	6.2	10
PRE	0.4	1.4	12	0	0	12
+15	41.8	24.6	12	3.8	9.3	12
+60	59.4	24.9	12	2.1	5.8	12
+90	31.3	22.5	12	1.4	3.2	11
+150	8.9	17.1	12	0.4	1.4	12
+330	2.1	5.8	12	0	0	10

FIGURE 13 (PAGE 17) FROM TOP DOWN, SYSTOLIC & DIASTOLIC BLOOD PRESSURE (mm Hg), PULSE (BEATS/MIN) AND HIGH RATING FOR EXPERIMENT 2.

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	2.7	0.8	12	2.9	1.1	12
+15	3.3	0.7	12	2.6	0.6	12
+75	2.8	0.6	12	2.7	0.6	12
+270	2.5	0.7	12	2.8	0.4	12
PRE	1.6	0.6	12	1.4	0.6	12
+15	1.7	0.8	12	1.7	0.2	12
+75	1.6	0.7	12	1.6	0.5	12
+270	1.6	0.6	12	1.4	0.3	12

FIGURE 14 (PAGE 18) DYNAMIC VISUAL ACUITY (MINIMUM ANGLE OF RESOLUTION, MIN OF ARC) FOR 40^{O}/SEC (UPPER) AND 5^{O}/SEC (LOWER).

	BENACTYZINE		PLACEBO	
TARGET VEL (^{O}/SEC)	MEAN	N	MEAN	N
5	+.08	12	-.38	12
25	+.41	6	+.14	6
40	+.59	12	-.24	12

FIGURE 15 (PAGE 19) CHANGE IN M.A.R. VERSUS TARGET VELOCITY

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	2.4	0.1	12	2.3	0.1	11
+15	2.1	0.1	12	2.4	0.1	11
+75	2.2	0.1	12	2.3	0.1	11
+270	2.3	0.1	12	2.4	0.1	11
PRE	2.4	0.2	12	2.4	0.2	11
+15	2.2	0.2	12	2.4	0.1	11
+75	2.2	0.2	12	2.4	0.1	11
+270	2.3	0.2	12	2.4	0.1	11
PRE	2.2	0.1	12	2.3	0.1	11
+15	1.8	1.0	12	2.2	0.3	11
+75	2.0	0.3	12	2.3	0.1	11
+270	2.2	0.2	12	2.2	0.1	11
PRE	1.6	1.8	12	1.8	0.2	11
+15	1.2	1.9	12	1.8	0.2	11
+75	1.4	0.6	12	1.8	0.2	11
+270	1.7	0.2	12	1.7	0.5	11
PRE	-0.03	1.51	12	0.24	0.52	11
+15	-0.25	0.47	12	0.19	0.84	11
+75	-0.02	0.87	12	0.20	0.92	11
+270	0.25	0.63	12	0.23	0.65	11

FIGURE 16 (PAGE 20) CONSTRAST SENSITIVITY FUNCTION (CSF)
FOR BENACTYZINE AND PLACEBO
FOR SINUSOIDAL GRATINGS OF 1, 3, 5, 10 AND 20CYCLES/DEGREE

	BENACTYZINE			PLACEBO		
LOG S.F	MEAN	S.D.	N	MEAN	S.D.	N
0	2.14	0.12	12	2.35	0.11	11
0.462	2.18	0.17	12	2.38	0.14	11
0.699	1.84	1.03	12	2.22	0.27	11
1.000	1.24	1.89	12	1.77	0.18	11
1.301	-0.25	0.47	12	0.19	0.84	11

FIGURE 17 (PAGE 20) CSF AT FIRST POST-DRUG MEASURMENT TIME

	BENACTYZINE			PLACEBO		
TIME	MEAN	S.D.	N	MEAN	S.D.	N
PRE	5.4	0.9	12	5.7	0.7	12
+15	6.3	0.7	12	5.6	1.0	12
+75	6.2	0.9	12	5.7	0.8	12
+270	6.2	0.9	11	5.7	0.8	12
PRE	3.9	0.8	12	3.9	0.7	12
+15	4.8	0.9	12	3.9	0.7	12
+75	4.5	1.0	12	4.1	0.7	12
+270	4.8	0.9	11	4.0	0.6	12

FIGURE 18 (PAGE 21) (LEFT SIDE) MEAN PUPIL DIAMETER (mm)
BEFORE (UPPER) AND DURING (LOWER)
EXPOSURE TO PERIPHERAL LIGHT.

PRE	5.3	0.9	12	5.3	0.6	12
+15	6.0	0.6	12	5.3	1.0	12
+75	5.9	0.8	12	5.4	0.8	12
+270	6.0	0.9	11	5.4	0.8	12

FIGURE 18 (PAGE 21) (RIGHT SIDE) MEAN PUPIL DIAMETER (mm)
AFTER PERIPHERAL LIGHT SOURCE IS TURNED OFF

	BENACTYZINE			PLACEBO		
TIME (MIN)	MEAN	S.D.	N	MEAN	S.D.	N
PRE	0.88	0.05	7	0.67	0.06	8
+15	0.81	0.06	8	0.77	0.08	6
+75	0.79	0.05	9	0.71	0.06	8
+270	0.80	0.08	9	0.98	0.08	8
PRE	1.84	0.08	7	1.59	0.09	8
+15	1.47	0.09	8	1.60	0.05	6
+75	1.61	0.06	9	1.57	0.07	8
+270	1.74	0.08	9	1.86	0.08	8
PRE	2.93	0.12	7	2.60	0.09	8
+15	1.63	0.07	8	2.42	0.06	6
+75	2.36	0.10	9	2.42	0.06	8
+270	2.31	0.10	9	2.65	0.13	8
PRE	3.51	0.13	7	3.21	0.10	8
+15	1.62	0.13	8	2.95	0.10	6
+75	2.91	0.12	9	3.06	0.11	8
+270	2.99	0.15	9	3.46	0.13	8

FIGURE 19 (PAGE 22) MEAN ACCOMMODATION RESPONSES TO STIMULUS STEPS OF 1, 2, 3 AND 4 DIOPTERS (FROM TOP, DOWN)

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