REFRACTIVE STATE AFTER INSTILLATION OF PAREDRINE AND NEOSYNEPHRINE*†‡

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In ophthalmic practice, drugs such as hydroxyamphetamine hydrobromide (Paredrine) and phenylephrine hydrochloride (Neosynephrine) are commonly used to produce mydriasis without alteration of refractive state. There is, however, no definite evidence that the refractive state is completely unaffected by these drugs, and experimental information on this subject is limited. Of some interest in this regard is the report of Campbell and Robson (1959) that after instillation of Paredrine (1 per cent.) into the conjunctival sac: "the drug takes about 20 to 40 minutes to produce mydriasis and thereafter there is a period of about one hour when a fixed dilated pupil is obtained without a detectable effect on the ciliary muscle. After this period, some subjects show a slight diminution in the amplitude of accommodation". Thus, the effect of Paredrine on accommodation is small or absent, but still unanswered is the question of a possible effect of this drug on the resting refractive state.

One way by which a mydriatic might affect the resting refractive state is through a significant direct action on the ciliary muscle such as occurred after conjunctival instillation of 10 per cent. phenylephrine hydrochloride in rabbits by Roth (1965).

A less obvious possibility is that decreased depth of focus, increased image degradation, and raised retinal illuminance resulting from pupil dilatation may be responsible for a shift in the resting refractive state.

The purpose of this investigation was to learn if the results of customary (clinical) refractive examination can be affected by instillation of a mydriatic that presumably does not exert a direct influence on the ciliary muscle.

In the following section, some aspects of the test procedure, because of their fundamental importance to the experimental design, are described in considerable detail. For example, a study like this must give careful attention to instillation of the test drug, measurement of the resting refractive state, and stabilization of head and eye position to reduce the possibility of artefacts.

Material and Methods

The drugs Paredrine (1 per cent.) and Neosynephrine (2.5 per cent. and 10 per cent.) were tested for refractive effects in five white male students between 19 and 28 years of age. Their refractive errors were between +0.50 and −1.00 D (spherical equivalent), maximum astigmatism was 0.50 D, and corrected visual acuity was 20/20 or better. The students had no known ocular
pathology. One subject (R.M.S.) wore contact lenses throughout the experiment and these brought his refractive errors and acuities within the desired range. The remaining subjects wore no optical corrections during the experiment.

The apparatus used to measure the resting refractive state is shown diagrammatically in Fig. 1. The source (S) is a small tungsten lamp (GE No. 14) that illuminates a target (T) consisting of a translucent sheet of plastic on which is printed a reduced Snellen chart. Target position can be changed by means of a rack and pinion controlled by the experimenter. The subject sees an image of the target formed by a convex lens (L, +10·00 D). The subject’s eye (E) is positioned to place the centre of the entrance pupil at the focal point of L, providing a linear relationship between target position and ray vergence referred to the plane of the entrance pupil (Campbell and Westheimer, 1960).

Because S is stationary, some variation in target luminance occurs with a change in the position of T, but this is of little consequence since the required changes in position of T for any given trial are small relative to the distance between S and T (7 cm. when T is at the focal point of L). Average variation in target luminance for twenty trials (five subjects) was ±7 per cent. over the range of target positions employed. Target luminance was 2·7 foot-lamberts with T at zero position, as measured with a Photo Research Corp. UB-1-1/2 photometer.

Since the experiment demanded regular trials of at least 2½ hours’ duration, the subject could not comfortably remain fixed in the apparatus without rest periods between measurements. A constant head and eye position relative to the apparatus was achieved by having each subject use a permanently moulded bite-rest. The angular relation of the visual axis to the measuring device was kept constant by using the same target letter for fixation during the course of the entire trial.

The target was viewed through a beam splitter (PR) with its plane 45° to the visual and optometer axes. The beam splitter served to reflect light beams from the optometer (R) into the test eye (E), and also provided a return path to the optical system of the optometer by which the experimenter viewed the image of the source on the fundus of E to measure the refractive state. The position of the source image on the fundus was adjusted to be approximately 3° from the foveal centre. All refractive measurements were made in the 180° meridian with a Hartinger Refractionometer, a double-beamed coincidence optometer that functions on the Scheiner principle. The optometer lamp (6-volt rating) was run at 6·5 volts to compensate for losses through the beam splitter.

Since the experiment was concerned with possible refractive effects associated with pupil dilatation, the natural entrance pupil of the test eye constituted the limiting stop of the accommodative stimulus system, i.e., no artificial pupil was used.

Each subject was given at least two 30-minute training sessions on different days to familiarize him with the apparatus and test procedure. In addition, each was tested for 1 hour as a control
REFRACTIVE STATE AFTER PAREDRINE AND NEOSYNEPHRINE

before the start of the actual test series. All training and control sessions began with a series of ten refractive measurements spaced 3 minutes apart, followed by the instillation of one drop of 0·9 per cent. saline into the lower cul-de-sac of the right eye. (The left eye was occluded.) After instillation of saline, the trial was completed with a final series of refractive measurements carried out for 30 minutes if the trial was intended for training, or for 1 hour if the trial was intended for control.

During training sessions the subject was familiarized with the criterion to be used for deciding when the target appeared clear or blurred. He was told to look at a letter “P” and to detect the presence of blur by noting whether the black part of the letter seemed to spill over into the hole in the “P”.

A typical trial was conducted as follows:

The target was first placed at the far point as determined previously by subjective examination. The subject was instructed to look at the target and to signal with a buzzer whether the target was clear or blurred. If blurred, the target was moved slowly towards E until “clear” was signalled, at which time the direction of target movement was reversed until it appeared blurred. If the target was initially clear, however, it was moved away from E until the subject signalled “blur”. The subject was told that the slightest blur was sufficient to warrant the appropriate signal.

The above-described procedure had two purposes:

1. To encourage the relaxation of accommodation.
2. To supply information on the location of the far point under experimental conditions by a method analogous to that used in subjective refractive examination of the eye.

(Physical movement of the target behind a lens in order to change image location does not differ in principle from the usual clinical method used to find the far point by moving the image of a fixed target optically, i.e., by changing lenses in the spectacle plane.)

With the target image slightly blurred, three successive (accommodative response value) measurements of refractive state were made with the Hartinger Refractometer, followed by a reading of the target location (accommodative stimulus value). As an indicator of far point location, the stimulus value shown by target location is likely to be somewhat higher in convex power than clinical findings because the present method requires the target to appear slightly blurred at the end-point of the determination.

The test sequence just described was completed in less than 1 minute. For the first half-hour of the trial, sequences were spaced approximately 3 minutes apart, after which one drop of the test drug (approx. 0·04 ml.) was instilled into the lower cul-de-sac of the right eye. To minimize the passage of drug through the nasolacrimal duct, the subject tilted his head to the right while forming a pool for the instilled drug by maintaining traction on his lower lid. After drug instillation, the observer watched the subject continuously for 2 minutes to ensure that the trial would not be invalidated by loss of fluid from the cul-de-sac. As a further precaution against fluid loss, the subject was asked to try to inhibit blinking by rotating his eyes when he felt compelled to blink. For an additional 2 hours, series of measurements were made continually in sequences spaced at approximately 4-minute intervals.

Each subject was tested at intervals of at least 2 days with one of four preparations: 2·5 per cent. Neosyphrine; 10 per cent. Neosyphrine; 1 per cent. Paredrine; and 0·9 per cent. saline. Thus, each subject participated in four trials.

Drug identity was coded by an assistant so that experimental results would not be influenced by personal bias of the investigator or of the subject. However, because of the differences in the amount and kinds of reaction caused by drugs (e.g., irritation, vasoconstriction, etc.), some clues to drug identity were inevitable and no anaesthetic could be used to obviate these reactions for fear of introducing unknown factors into the experimental situation.

Results

As expected, far point locations indicated by final test target positions (stimulus values)
were generally higher in plus values than the response values measured with the optometer.

Short-term variations in refractive state occurred in different degrees among the subjects and from one trial to the next in the same subject, but the variations had a random appearance (Fig. 2, subject A.D.) and did not differ from variations occurring in the controls (0-9 per cent. saline).

Long-term (approximately 2-hour period) refractive drifts (both stimulus and response values) were evident in some trials, but these were not large (0.50 D max.) and did not show internal consistency from one drug to another. For example, a slight, apparently myopic drift occurred with both 1 per cent. Paredrine and 2.5 per cent. Neosynephrine, but no drift occurred with 10 per cent. Neosynephrine (Fig. 3, subject B.R.). (Compare also saline data with mydriatic data, Fig. 2.) Data on the three remaining subjects were more scattered than those presented in Figs 2 and 3 and showed no signs of systematic variation in refractive state.

![Fig. 2. Accommodative stimulus and response data v. time for three test drugs plus control (subject A.D.).](image)

![Fig. 3. Accommodative stimulus and response data v. time for three test drugs plus control (subject B.R.).](image)

Two of five subjects thus showed signs of systematic refractive changes after instillation of the test drugs, but these changes were no greater than 0.50 D, which was only slightly larger than the apparently non-systematic refractive changes (see Fig. 3, especially response records after 2.5 per cent. Neosynephrine and 1 per cent. Paredrine).

**Discussion and Conclusions**

If changes in resting refractive state of 0.50 D or more were attributable to conjunctivally-instilled mydriatics, the use of these mydriatics before a non-cycloplegic refractive examination would be contraindicated. Results of the present study, however, demonstrate that significant refractive changes do not regularly follow the instillation of a single drop of 10 per cent. Neosynephrine or 1 per cent. Paredrine. In fact, the changes observed in
REFRACTIVE STATE AFTER PAREDRINE AND NEOSYNEPHRINE 767

refraction after instillation of these drugs were infrequent and hardly greater in magnitude than seemingly random variations.

The present findings contrast markedly with those reported for the rabbit by Roth (1965), wherein significant changes regularly followed conjunctival instillation of 10 per cent. Neosynephrine and were obviously greater in magnitude than chance variations. This difference in drug response may be due to species difference, to a difference in drug dosage, or to other factors. Among the latter is a significant difference in the physiological state of the subject. Specifically, the rabbits were under general anaesthesia, while the human subjects were unanaesthetized.

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Refractive state after instillation of paredrine and neosynephrine.

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