
Effect on refraction of intramuscular pilocarpine in two species of monkey (*Cercopithecus aethiops* and *Macaca irus*)

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*The effect on accommodation of pilocarpine given intramuscularly was studied on two species of monkey (*Cercopithecus aethiops* and *Macaca irus*), six young individuals of each species. The results are given as dose-response curves; 0.2 mg. per kilogram of pilocarpine caused little change in refraction, generally less than 2 D., and 2.0 mg. per kilogram caused a large change in refraction in both species, always more than 12 D. The accommodation of the *Cercopithecus* seemed a little more sensitive to pilocarpine than that of the macaque. One out of four monkeys receiving very large doses behaved unexpectedly. Increasingly large doses of pilocarpine caused decreasing myopia, whereupon atropine increased the myopia. This mechanism is not understood.*

Several studies of the accommodative effect of topically administered cholinergic drugs have been reported. Reports of quantitative effects on refraction after systemically given parasympathomimetics are, however, very few and incomplete. Schmieberg and Koppe³ gave muscarine subcutaneously to human beings. In one of the cases 4 mg. caused a maximal response, with coincidence of the near and far points. Passow² administered 10 mg. of pilocarpine subcutaneously to "a few" human subjects without seeing any change in accommodation. However, in one of his subjects receiving 1 mg. of physostigmine subcutaneously, the near point moved toward the

eye by 3 cm. Unfortunately Passow does not tell the absolute values.

In a previous paper⁵ I reported the effect of intramuscular pilocarpine in a series of six monkeys, showing that the pupil and accommodation response after intramuscular administration occurred in approximately the same dose range. This was not the case when pilocarpine was given topically to the eye. Since then, Bány¹ has studied the outflow facility in two species of monkey (*Cercopithecus aethiops* and *Macaca irus*) after intramuscular pilocarpine. He found different reactivity in the two species, but also great individual differences in the same species. Some of the macaques showed little or no increase in outflow facility in spite of high doses of pilocarpine.

It thus seemed worthwhile to extend the study of accommodation after intramuscular pilocarpine to a larger series of monkeys. This paper gives the dose-response

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curves for refractive changes in the two species of monkey after intramuscular pilocarpine.

Materials and methods

Six cynomolgus monkeys (*Macaca irus*), weighing 1.4 to 3.3 kilograms, and seven African green monkeys or vervets (*Cercopithecus aethiops*), 1.6 to 3.3 kilograms, were used. Judging by weight, dentition, and general physiognomy, the monkeys seemed to be adolescents and young adults. Three monkeys of each species, that were given pilocarpine intramuscularly in an earlier study,⁵ are included in this paper.

During the measurements the monkeys were anesthetized with pentobarbital (30 mg. per kilogram body weight) given intraperitoneally.

The method used to measure the accommodation has previously been described in detail.⁵ An iridectomy was performed on the right eye, first in the 12 o'clock position and, subsequently, on another day in the 6 o'clock position. At least one month was allowed to elapse between the second stage of the iridectomy and the beginning of the experiment.

The determination of refraction was made with a Thorner⁴ optometer. The spectacle-plane refraction was read directly from the instrument. Before the pilocarpine was injected, an initial refraction value was determined as the mean of at least four successive readings. The effect of pilocarpine was followed by intermittent readings until a definite maximum was observed. This maximum (final value) was calculated as the mean of at least four successive single readings.

Pilocarpine hydrochloride was dissolved in saline solution so that 0.5 ml. of the solution was given per kilogram body weight. All pilocarpine injections were intramuscular. Every animal was used on two to three experimental occasions and one to two doses of pilocarpine were given in each experiment. Generally the second dose was not injected until the effect of the first had faded. In some instances three doses were given in the same experiment. In such cases two of the doses were large, 5 to 50 mg. per kilogram. The ratio between successive doses was never less than 5:1. Since pilocarpine often caused profuse salivation, the pharynx was cleared by suction during the experiments. At the end of an experiment the animals were given atropine sulfate, generally by the intravenous route. The doses of pilocarpine and atropine listed refer to the salts.

Calculations

The effect of pilocarpine was expressed as the largest change in refraction (difference between

final and initial values) obtained with the dose in question.

The change in refraction was plotted against the dose (in logarithmic scale), and the points of each individual monkey connected by straight lines. The log doses necessary to cause standard amounts of change in refraction were read by interpolation and averaged, giving geometric means. These are the average curves shown in the figures.

The standard deviations of single readings due to error of the method (σ_M) were calculated by means of successive differences and were for all initial values ± 0.33 D. (261 readings), and for all final values where myopia of 15 to 20 D. was obtained ± 0.83 D. (78 readings). Final values less than 15 D. gave σ_M between ± 0.33 and ± 0.83 D. No differences between the species were found in this respect. No less than four readings were ever taken for determining initial and final values. Thus the standard deviations of initial and final values due to reading errors were half the quoted values or less.

The optometer is designed for refraction values up to 20 D. myopia. In this investigation, myopia of more than 20 D. was observed in a few experiments. This means that some of the values above and just below 20 D. in the figures are more approximate. However, these values did not influence the mean curves.

Astigmatism. The mean difference of the dioptric power in the horizontal and vertical axes was 0.5 D. for the initial values. The greatest astigmatism observed was 1.5 D. Astigmatism with oblique axes was not observed. Significant changes in astigmatism during the course of an experiment were not noted.

Pupil. The diameter of the pupil was repeatedly measured during the experiments by means of a pair of vernier calipers.⁵

Results

The mean of the refractions before pilocarpine was given showed slightly myopic values in both species: -0.9 D. for cynomolgus monkeys (range $+0.3$ to -2.5) and -0.8 D. for vervets (range $+0.6$ to -3.0). After pilocarpine was administered the peak effect for both species was reached, on an average, in 13 minutes (range 5 to 22 minutes).

The course of an ordinary experiment is shown in Fig. 1. To begin with, this vervet was slightly myopic; 0.1 mg. per kilogram of pilocarpine caused a small increase in myopia. After 1.0 mg. per kilogram, myopia of -15.7 D. was recorded. Twenty-six min-

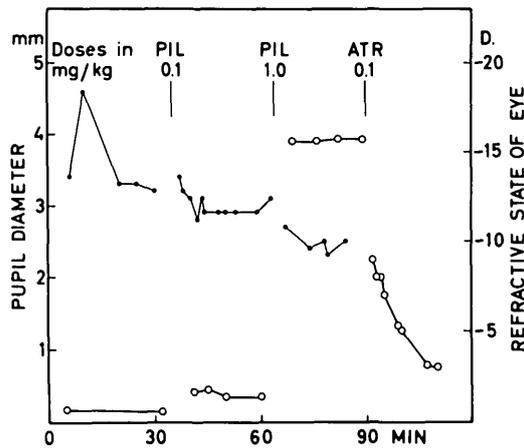


Fig. 1. Refractive state (open circles) of the right eye and pupil diameter (dots) of the left eye during an experiment with intramuscular pilocarpine and intravenous atropine.

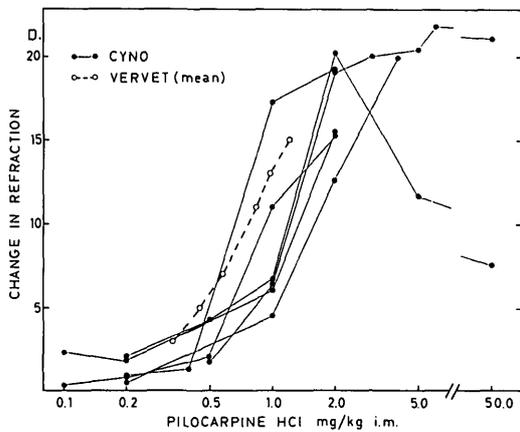


Fig. 2. Changes in refraction for six cynomolgus monkeys after intramuscular pilocarpine. The dashed curve is a geometric mean curve for six vervets.

utes after the large dose of pilocarpine, atropine (0.1 mg. per kilogram) was given intravenously. This caused an immediate decrease in myopia. In less than 5 minutes half the effect of 1.0 mg. per kilogram of pilocarpine had vanished. In Fig. 1 each point on the refraction curve is an average of at least four separate readings. (Exception: The first six points after atropine are the average of two separate readings.)

Fig. 2 shows the changes in refraction after varying doses of pilocarpine for six

cynomolgus monkeys. For comparison, a geometric mean curve for the vervets is drawn on the same figure. This mean curve is calculated from Fig. 3 where the individual responses of the six vervets are plotted. The mean curve in Fig. 3 refers to the cynomolgus species. From Fig. 4, where the two mean curves are drawn together, it can be seen that the cynomolgus in this investigation needed about 1.5 times more

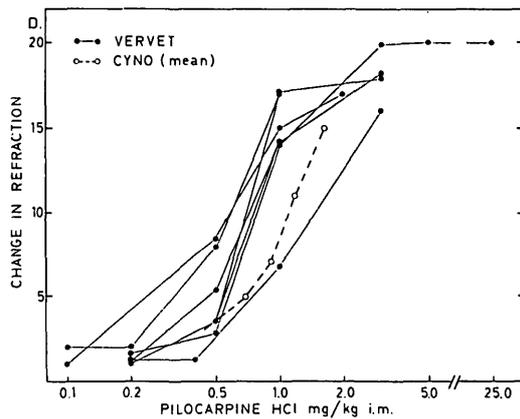


Fig. 3. Change in refraction for six vervets after intramuscular pilocarpine. The dashed curve is a geometric mean curve for six cynomolgus monkeys.

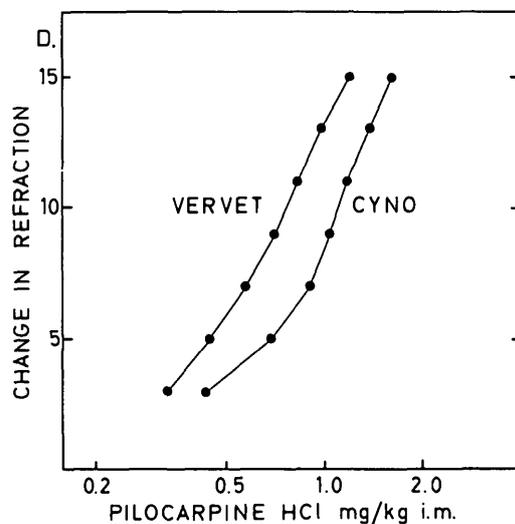


Fig. 4. Change in refraction after intramuscular pilocarpine. Geometric mean curves for six cynomolgus monkeys and six vervets.

pilocarpine than the vervets to obtain the same change in refraction. It should be observed that 2.0 mg. per kilogram of pilocarpine gives an accommodation of more than 12 D. in all monkeys.

Two monkeys of each species were given very high doses of pilocarpine, 25 or 50 mg. per kilogram. (One of the vervets receiving 50 mg. pilocarpine per kilogram was not included among the animals in Fig. 3 because it died before enough experiments were concluded.) One of the cynomolgus monkeys and both vervets reacted in an expected way and showed little or no increase in myopia after high doses, compared to doses of 2 to 5 mg. per kilogram (Figs. 2 and 3).

However, one of the cynomolgus monkeys reacted in an unexpected way. In an earlier experiment this monkey had been given 2.0 mg. per kilogram of pilocarpine, which caused a change in refraction of 20.3 D. In the present experiment the same monkey, when given a large dose (5 mg. per kilogram), showed a change in refraction of only 11.7 D. (one of the curves in Fig. 2), and an additional 50 mg. per kilogram reduced the myopia. This monkey behaved unexpectedly in another way; 24 minutes after receiving the high dose of

pilocarpine (Fig. 5), 0.45 mg. per kilogram of atropine was administered intraperitoneally. Nine minutes after the atropine, the myopia had increased and then remained high until a larger dose of atropine, 0.8 mg. per kilogram, was given. The pupil contracted maximally during the experiment, and dilated only after the second dose of atropine. The remarkable fluctuations in refraction after 50 mg. per kilogram pilocarpine (Fig. 5) were not due to errors of measurements. Each point is in fact the average of several readings in rapid succession and there is no doubt that real fluctuations of refraction took place. The same is true for the dip at 11 minutes after the first atropine dose. This was the only monkey in the present series in which there were such fluctuations and the only one which showed this paradoxical effect on refraction with pilocarpine and atropine. Fluctuations in refraction have sometimes been seen after systemic carbachol, and with this drug the paradoxical effect on refraction is constantly noted after high doses.⁶

Systemic effects of pilocarpine. The monkeys started to salivate after 0.1 mg. per kilogram of pilocarpine. At 0.5 to 1.0 mg. per kilogram the salivation was profuse and

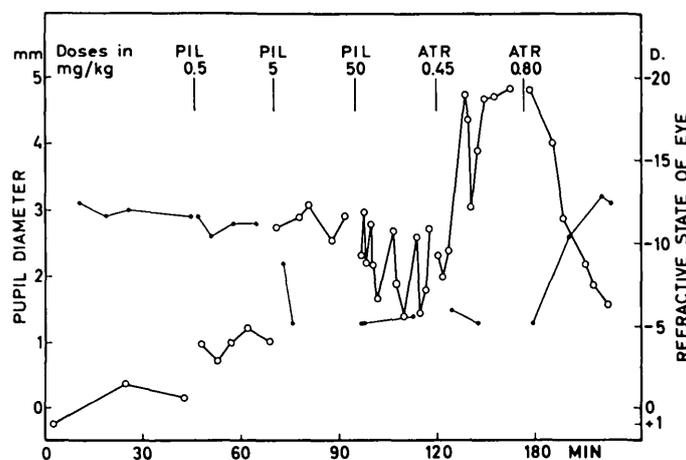


Fig. 5. Refractive state (open circles) of the right eye and pupil diameter (dots) of the left eye during an experiment with intramuscular pilocarpine in high doses. The first dose of atropine was injected intraperitoneally; the second dose was given intravenously, but there was some extravasation.

with 1 to 5 mg. per kilogram vomiting, defecation, and urination occurred.

Discussion

In this investigation measurements of the pupil were made in all experiments mainly as a control. These data, though not accounted for, confirmed earlier results,⁵ i.e., the pupil size and the state of accommodation showed approximately the same sensitivity to intramuscular pilocarpine. Though not studied in detail, it was obvious that the effects of intramuscular pilocarpine on the eye occurred in the same dose range as those on the salivary glands and gastrointestinal tract.

In this investigation the accommodation of vervets appeared a little more sensitive (1.5 times) to intramuscular pilocarpine than that of cynomolgus. This is so, when the results are given in diopters, though it is not necessarily the case if the responses are given in per cent (maximal response = 100 per cent). The latter method could not be used here because the monkeys could not stand high doses of pilocarpine very well, and, moreover, how could a maximal response be determined if a monkey reacts with decreasing myopia after increasingly high doses of pilocarpine? One cannot be sure that the highest myopia (peak of the curve) is an absolutely maximal response, because the inhibiting (myopia-decreasing) effect of the drug can start already with a smaller dose.

In this discussion I have referred to sensitivity of accommodation rather than to the ciliary muscle. It must be pointed out that it is quite possible the ciliary muscle contracts before any change in refraction

is recorded, and it is equally possible the muscle increases its contraction isometrically or isotonicly also when a maximal response of accommodation is already obtained. Thus, the dose-response curves are valid for accommodation but not for the ciliary muscle of the monkeys examined.

It is evident that 2.0 mg. per kilogram of pilocarpine gave high accommodation in all monkeys examined. It is puzzling that Bárány¹ found individuals among the cynomolgus species that showed no facility increase at all when they were given the same dose (2 mg. per kilogram).

One of the four monkeys receiving very high doses (5 to 50 mg. per kilogram) of pilocarpine reacted unexpectedly, i.e., higher doses of pilocarpine caused less myopia and, when a small dose of atropine was given subsequently, the myopia increased. This effect is not understood. I hope to discuss it in detail when publishing results of corresponding experiments with carbachol, where a similar effect appeared more uniformly.

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