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PHARMACODYNAMIC EFFECTS OF PILOCARPINE EYE DROP ENHANCED BY DECREASING ITS VOLUME OF INSTILLATION

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Abstract: Previous studies have proved that as the volume of the drug solution instilled into the eye is decreased, the fraction of the dose absorbed into the ocular tissue is increased and the adverse drug reactions lowered. The present study investigated the acute effects of different drop volumes (10 µl, 20 µl, 40 µl, and 80 µl) of pilocarpine nitrate (2%) on pupil diameter, heart rate, and adverse reaction profile, in 12 healthy human volunteers. The drop volumes of 10 µl and 20 µl produced more miosis and less side effects than 40 µl and 80 µl drop volumes. This may be due to more penetration of the drug into the ocular tissue and less drainage into the nasolacrimal system.

Key words: pilocarpine pupil miosis drop size

INTRODUCTION

The topical application of ophthalmic drugs as eye drops is a major technique in use. Pilocarpine eye drops are commonly used in glaucoma (1). It has been estimated that the tear film of the eye has a capacity of holding only 7 ml to 10 ml of the fluid (2, 3), whereas the drop volume of the commercial eye drops available is more than 40 µl (4). When an eye drop is instilled into the eye, only a small part of it actually penetrates the ocular tissue (2). A little fraction of the administered dose flows on to the cheeks causing some nuisance to the patients. A major portion of the drug so instilled is also lost into the nasolacrimal system, from where it is absorbed into the systemic circulation, causing systemic adverse reactions (2). In the animal studies it has been observed that this rate of drainage of fluid into the nasolacrimal duct, which is a direct function of its systemic toxicity, is dependent on the volume of the instilled drug solution (2). A variety of systemic side effects have been reported with the use of pilocarpine eye drops (5). These adverse reactions could be lowered by decrease in the nasolacrimal fluid drainage, which is possible by minimising the drop volume of administered drug.

The ocular therapeutic effect of a drug solution occurs when the instilled drug is actually absorbed into the ocular tissue. In rabbits it has been observed that as the volume of the instilled drug solution is decreased, the fraction of the drug penetrating into the eye is increased (6, 7). The smaller drop volume is thus expected to enhance the therapeutic effects in the eye.

The present study, was therefore planned to investigate the acute effect of different drop volumes of pilocarpine, on pupil diameter heart rate, and side effect profile in healthy human volunteers.

METHODS

The study design, was controlled, randomized, double masked and cross over. Twelve healthy human volunteers were enrolled in the trial. They had no history of any intraocular surgery, glaucoma, diabetes mellitus, bronchial asthma, cardiovascular disease or any allergy to parasympathomimetics. They were also not on drugs affecting the pupil size. An

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informed written consent was obtained from each subject.

The commercial preparation of pilocarpine nitrate (Pilocar 2%) eye drop, having the pH of 4.5 and containing chlorbutol 0.5 w/v as preservative, was used in the present investigation.

Single instillation of different drop volumes (10 µl, 20 µl, 40 µl and 80 µl) of pilocarpine nitrate (2%), was done into the lower conjuctival sac of the eye, on separate occasions. After the drop administration, the inner punctum was pressed for 1 min. A wash out period of 7 days was kept between the two doses. The drop volumes were delivered by the micropipette, which had been checked for accuracy, by weighing the drop in the balance.

The pupil diameter and heart rate were measured at 0 min for the baseline value and at 15 min, 30 min, 45 min, 60 min, 90 min, 120 min, 180 min, 240 min, and 300 min after the drug instillation. The pupil size was measured with a Manual pupillometer, under a constant room illumination, with the subject focussing a pre-fixed point at a distance of 2.50 meter. This was done to rule out the effect of light intensity and accommodation on the pupil diameter. The heart rate was measured manually for 1 min.

The adverse drug reactions were monitored by following a check list. The objective parameters of systemic reactions (excitement, sedation and effect of salivation), were studied by using a visual analog scale (VAS). These side effects were noted at the baseline level, during and at the end of the trial.

The experiments were performed at the same time (9.30 A.M.) of the day to rule out the effects of circadian variation on the results. The decrease in the pupil diameter from the baseline value, at the different time intervals, was measured for each subject.

The results were analysed using paired 't' test for intra-group and Wilcoxon Rank test, for inter-group comparisons. The value of P less than 0.05 was kept as the level of significance.

RESULTS

There was no drop out in the present study. At the baseline level, there was no difference in the pupil diameter, between the different groups. The pupil sizes were, 4.08 ± 0.23 mm in 10 µl group, 4.17 ± 0.15 mm in 20 µl group, 4.12 ± 0.13 mm in 40 µl group, and 4.08 ± 0.19 mm in 80 µl group.

The decrease in the pupil diameter from the baseline, with the instillation of different drop volumes of pilocarpine, at different time intervals is shown in Fig 1. There occurred a significant decrease in the pupil diameter with the instillation of various drop sizes, as compared to their respective baseline values ($P < 0.001$). The peak effect was achieved at 90 min. The 10 µl drop volume of pilocarpine produced more miosis than 20 µl, 40 µl and 80 µl, at the respective time intervals. The 20 µl drop volume also caused more constriction of pupil than 40 µl and 80 µl drop volumes. There was a significant decrease in the pupil diameter, with 10 µl drop volume (from 15 min to 300 min) and also with 20 µl drop volume (from 45 min to 300 min), as compared to 40 µl drop volume of pilocarpine ($P < 0.05$).

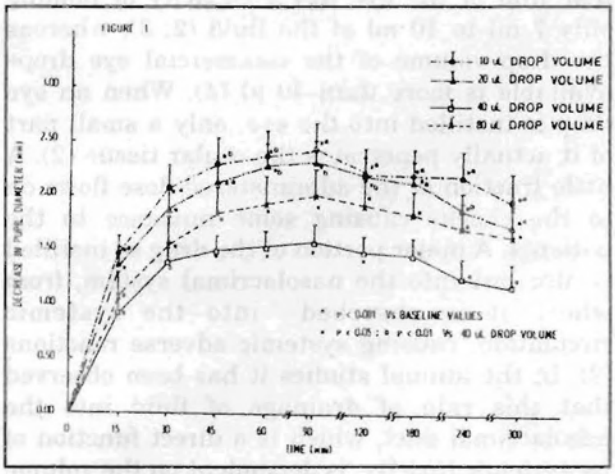

Fig. 1 : Effect of different drop volumes (10 µl, 20 µl, 40 µl , 80 µl) of pilocarpine nitrate 2% on pulpil diameter, at different time intervals.

The effect of different drop volumes of pilocarpine on the heart rate, at different time

TABLE I : Effect of different drop volumes (10 µl, 20 µl, 40 µl, 80 µl) of pilocarpine 2% on heart rate. (Data are $\bar{X} \pm$ SEM of 12 subjects).

Time (hr)	*Drop volumes*			
	10 µl	*20 µl*	*40 µl*	*80 µl*
0.00	92.86 ± 3.49	90.00 ± 2.26	92.00 ± 1.71	91.83 ± 1.73
0.25	89.42 ± 3.11	88.83 ± 1.86	90.67 ± 1.76	94.00 ± 1.84
0.50	88.86 ± 2.55	87.30 ± 0.72	90.67 ± 1.29	91.00 ± 2.17
0.75	86.43 ± 2.86	88.33 ± 0.93	89.33 ± 1.14	88.00 ± 1.97
1.00	88.29 ± 2.74	88.33 ± 1.37	88.33 ± 0.88	88.67 ± 1.29
1.50	85.71 ± 2.84	89.33 ± 1.54	85.67 ± 1.01	91.33 ± 1.73
2.00	85.14 ± 2.09	85.33 ± 2.35	88.00 ± 1.04	88.67 ± 2.02
3.00	84.57 ± 2.07	82.83 ± 2.18	88.00 ± 1.56	88.67 ± 1.33
4.00	87.71 ± 2.23	88.33 ± 1.76	90.67 ± 1.14	90.67 ± 1.29
5.00	87.57 ± 2.41	91.67 ± 1.23	88.00 ± 1.21	91.67 ± 1.01

intervals is shown in Table I. There was no difference in the heart rate, among different groups, at the baseline levels. There was also no marked effect of different drop volumes of pilocarpine, on the heart rate at different time intervals.

While monitoring the adverse drug reactions, 7 subjects has frontal headache after the instillation of pilocarpine. Four volunteers, out of these, belonged to 80 µl drop volume group whereas the other 3 belonged to the 40 µl drop volume group. The headache persisted for 4 h. Ten subjects complained of some irritation in the eye after the administration of pilocarpine eye drop. Five subjects, out of these, belonged to 80 µl drop volume group, 4 subjects to 40 µl drop volume, and only 1 subject to 20 µl drop volume group. The irritation persisted for 30 min. There was no marked effect of drug on any of the objective parameters (excitement, sedation and salivation) of adverse effects monitoring. No other untoward effect was reported by any of the volunteers.

DISCUSSION

Pilocarpine is effective in glaucoma, through its property of constricting the pupil which opens the cannal of Schlemm. This facilitates the drainage of aqueous humor, thereby decreasing the intraocular pressure. Clinically, large amounts of eye drops are being instilled into the eye which can produce some systemic side effects.

The present study clearly indicates that the drop volume of 10-20 µl of pilocarpine produced more miosis and less side effects than 40 µl or 80 µl drop volumes. In other words, the 10 µl and 20 µl drop volumes of pilocarpine possess a higher therapeutic index, the ratio of the therapeutic effect and toxicity. Since less drug is consumed by instilling the smaller drop volume, the drop volume of 10 µl and 20 µl will also increase the cost-effectiveness (4).

Previously, it had been observed that 10 µl drop volume of phenlyephrine hydrochloride (10%), when administered into the eye, caused more mydriasis than that with 80 µl drop, both in the rabbits (8) as well as humans (9). It has also been reported that 15 µl volume of clonidine hydrochloride produced ocular hypotension, similar to that produced with 70 µl drop volume, without causing any systemic fall in the blood pressure (10). With the use of the tropicamide eye drop, it was seen that the therapeutic effect (pupillary dilation and the receding to near point of vision) was much more with the use of 10 µl and 20 µl drop sizes as compared to the large drop volume (11).

There was no marked effect of any drop

volume of pilocarpine nitrate on heart rate. Though, there was a slight decrease in the heart rate after instillation of different drops of pilocarpine, the results were not statistically significant.

In the present study the cross over design was used which would eliminate the inter subject variability among the different groups. Furthermore, the double mask pattern and prior randomization of the study, eliminated the chances of bias affecting the study results.

The mechanism by which the smaller drop volumes of pilocarpine nitrate produced higher therapeutic index, can be due to greater intraocular penetration (6) and decreased drainage into the nasolacrimal system (2, 3).

It is concluded that to get the desired pupillary constriction along with the decrease in the side effects. The drop volume of pilocarpine nitrate 2% eye drop volume should be in the range of 10-20 µl. The drop volume of the commercial pilocarpine 2% eye drops available in India, ranges from 41.0 µl to 54.5 µl (4). The current problem of large drop volume of the market preperation can be circumvented by changing the surface tension of the eye drop solution and also by decreasing the dropper tip dimension. This technique may produce the drops with smaller volumes, the use of which will not only be cost-effective but be the therapeutically beneficial too.

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