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Effects of Selected Antimuscarinic Agents on the Intra-Ocular Pressure in Healthy Rabbits

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Abstract: This study was designed to challenge this important issue in healthy animals. The effects of atropine, cyclopentolate and tropicamide was studied on IOP in the rabbit. For this, 12 healthy and adult white New Zealand rabbits were used. Drugs were applied topically once daily for 14 days. IOP was measured using Schiötz tonometer 5 min after surface anesthesia before the instillation of the next dose of the antimuscarinics. Three drops of a 1% concentration was applied on one eye and the other eye served as control and received saline solution only. IOP was increased during the treatment period with a peak value up to 39, 29 and 39% with atropine, cyclopentolate and tropicamide, respectively ($p<0.001$). The IOP was still high one day after cessation of the treatment and returned to the baseline levels 7 days after termination of the treatment. In conclusion, chronic administration of antimuscarinics may lead to a critically increased IOP of normotensive eyes. These agents should be considered serious risks not only for patients with glaucoma, but also for subjects with no ophthalmologic problems.

Key words: Intra-ocular pressure, eye, rabbit, atropine, cyclopentolate, tropicamide

INTRODUCTION

The impairment in outflow facility causes the high intraocular pressure (IOP) and large diurnal IOP fluctuations often found in glaucoma. Cholinergic agents like pilocarpine act primarily by improving outflow facility (Brubaker, 2003). Conversely, acute angle closure glaucoma is a potentially blinding side effect of anticholinergic agents such as atropine (Lachkar and Bouassida, 2007). Several members of this group of drugs are available in the market as eye drops with a common use in ophthalmology. There are, however, few published data to compare their effects on IOP in a long-term use.

In this experimental study, the effects of topical administration of 3 different antimuscarinic agents (atropine, cyclopentolate and tropicamide) were studied on IOP in normotensive rabbit eyes. The objective was to initiate a gateway for similar studies in clinical conditions.

MATERIALS AND METHODS

This study was performed in the year 2005 in Urmia University, Faculty of Veterinary Medicine, Urmia, Iran.

Animals

Twelve white New Zealand rabbits (1.5-2.5 kg, male) were housed under controlled conditions (room temperature and a 12 h light-dark cycle). Water and commercial chow were allowed *ad libitum*. The rabbits were free of clinically-manifested diseases, including glaucoma.

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Chemicals

Drugs used in the present study were purchased from the following manufacturers: cyclopentolate hydrochloride (Cyclolate 1%) from Tubilux Pharma S.p.A. (Rome, Italy); atropine sulphate 1%, tropicamide 1% and tetracaine hydrochloride 0.5% from Sina Darou (Tehran, Iran); saline solution 0.9% from Ghazi-Tabatabaei Company (Tabriz, Iran).

Experimental Protocol

Twelve healthy, adult rabbits, divided into three groups, were treated unilaterally with 1% solution of atropine, cyclopentolate, or tropicamide (1.5 mg in 150 μL). The contra-lateral eye served as a control, into which physiologic saline solution was administered. The treatment was performed once daily for 14 successive days. In all animals, IOP of both eyes was measured on days 0, 1, 3 and 7 before the instillation of the drugs. In addition, on days 14 (+1, i.e., 1 day after ceasing the treatment) and 21 (+7, i.e., 7 days after ceasing the treatment) the measurement was performed to observe if the effect was still remaining. IOP was measured bilaterally by means of a Schiötz Tonometer, manufactured by Rudolf Riester GmbH and Co. KG (Jungingen, Germany). This was performed 5 min after instillation of tetracaine 0.5% (0.75 mg in 150 μL) onto eyes in order to minimize pain sensation. The conversion table provided by the manufacturer was used to calculate the IOP in mmHg units. The contact time for all solutions was 60 sec.

Data Presentation and Statistical Analysis

The IOP was recorded as mmHg and the results were presented as means±SEM. The results of each set of experiments were evaluated by repeated-measures Analysis of Variance (ANOVA). If significance was achieved, post-ANOVA comparison of means was performed by using the *post hoc* Bonferroni t-test. All $p<0.05$ were considered to reflect a statistically significant difference.

RESULTS AND DISCUSSION

The Schiötz Tonometer used in this study was found to determine IOP in the rabbit in a reproducible and reliable manner. The IOP of the saline-treated eyes did not change during and after the treatment period. However, all anti-muscarinic agents used in this study increased the IOP from 1 day after the initiation of the treatment. This showed that the treatment of one eye with an antimuscarinic agent did not affect the other eye, eliminating the possibility of considerable systemic absorption of the drugs.

Atropine increased the IOP on days 1, 3, 7 and 14 by 20, 26, 26 and 39%, respectively. The effect remained still higher than the IOP before the treatment (38%) 1 day after the cessation of the treatment and returned to the normal level 7 days after termination of drug instillation. Cyclopentolate also elevated the IOP on days 1, 3, 7, 14 and +1, by 19, 19, 29, 29 and 32%, respectively. On day +7, however, there was no difference in the treated versus control eyes. Tropicamide induced an increased IOP on days 1, 3, 7, 14 and +1 by 13, 16, 18, 39 and 36%, respectively. In this case also the IOP returned back to normal level on day +7 (Table 1).

Therefore, maximal increase in IOP in the treated eyes occurred by 39, 29 and 39% by atropine, cyclopentolate and tropicamide, respectively ($p<0.001$). In brief, the magnitude of the effects was as: Atropine = tropicamide >> cyclopentolate. Detailed data are showed in Table 1.

Estimation of IOP in rabbits is often done by indentation tonometry using Schiotz tonometer. The use of Schiotz tonometer for estimation of IOP requires the use of topical anesthesia and may pose risk of infection and injury to cornea and puts the animal under stress (Gupta *et al*., 2007). Nevertheless, our experience with this device accompanied a reliable and reproducible IOP estimation in this animal species.

Table 1: Effect of local instillation of antimuscarinic agents on the IOP (mm Hg) of rabbits[1]

	Atropine	Cyclopentolate	Tropicamide
Basal IOP on day 0 (before treatment)			
Control	25.65±0.20	25.68±0.26	25.73±0.22
Treated	25.78±0.29	25.60±0.21	26.33±0.65
Change in IOP after starting daily treatments[2]			
Day 1			
Control	+0.20±0.96	+0.07±0.17	+0.02±0.09
Treated	+5.28±0.87[3]	+4.76±0.15[3]	+3.48±0.79[3]
	(↑ 20%)	(↑ 19%)	(↑ 13%)
Day 3			
Control	+0.25±0.15	+0.17±0.49	+0.13±0.29
Treated	+6.58±0.56[3]	+4.80±0.21[3]	+4.13±1.35[3]
	(↑ 26%)	(↑ 19%)	(↑ 16%)
Day 7			
Control	-0.05±0.10	-0.03±0.19	-0.08±0.29
Treated	+6.83±0.64[3]	+7.40±0.76[3]	+4.73±1.16[3]
	(↑ 26%)	(↑ 29%)	(↑ 18%)
Day 14			
Control	+0.05± 0.10	-0.03±0.25	+0.63±0.84
Treated	+10.03±0.31[3]	+7.53±0.14[3]	+10.23±0.22[3]
	(↑ 39%)	(↑ 29%)	(↑ 39%)
Change in IOP after ceasing daily treatments[2]			
Day +1			
Control	-0.05±0.18	+0.02±0.14	+0.07±0.17
Treated	+9.80±0.36[3]	+8.10±0.97[3]	+9.48±0.72[3]
	(↑ 38%)	(↑ 32%)	(↑ 36%)
Day +7			
Control	+0.12±0.23	+0.15±0.32	-0.10±0.24
Treated	+0.03±0.07	+0.10±0.47	-0.35±0.73

[1]A 1% Concentration was used once daily, starting on day 0 and ending on day 14. IOP was measured before instillation. Left eye was taken as control and the right one was treated. Data are expressed as means±SEM, [2]Increase (+) or decrease (-) in IOP compared to the basal IOP of the same group on day 0, [3]$p<0.001$; the difference in the change of IOP was statistically significant in comparison to the corresponding control eyes

Present findings suggest that atropine, tropicamide and cyclopentolate increase the IOP in normotensive eyes of the rabbit. The latter has a slightly weaker effect. Following cyclopentolate application, some, but not all, glaucoma patients with open angles may develop a clinically important (>10 mmHg) sustained rise in IOP requiring treatment (Hancox *et al*., 2002). However, in patients with open-angle glaucoma, who were under pilocarpine treatment, cyclopentolate increased the IOP dramatically. In normal eyes as well as those with untreated open angle glaucoma, it is believed that this cycloplegic has a relatively small effect on the IOP (Portney and Purcell, 1975).

It appears that a short time elapsed after application of a cycloplegic drug may not lead to an increased IOP. As reported by Cozanitis, in doses suitable for pre-anaesthetic medication, intramuscular injection of glycopyrrolate and atropine to healthy volunteers caused no significant change in either intraocular pressure at 45 min after drug administration (Cozanitis *et al*., 1979). No significant changes in intraocular pressure occurred as a result of the treatment with 1% atropine during a 2 day period of treatment in four healthy adult horses; pupil diameter increased significantly after atropine was applied (Mughannam *et al*., 1999). These discrepancies may be explained simply by the fact that the closure of the openings of the angular aqueous plexus/sinus for such a short time may not be enough for the accumulation of aqueous humor in the eye chambers. For this reason, we decided to measure the IOP for a much longer period following repeated administration of the cycloplegic agents. Indeed, a sustained increase occurred in the IOP when these agents were applied for successive 14 days. Species differences should also be taken into account.

In the present study, one eye of each animal served as the control for the other, treated eye. While a significant rise was observed with all anticholinergic agents used, the control eyes presented no

change in their internal pressure. This is in contrast with a previous study in cat, where topical 0.5% tropicamide in one eye caused an elevation of IOP not only in the treated but also in the untreated eye (Stadtbaumer *et al*., 2002). Here we should not only consider the species difference, but also should pay attention to the fact that in that study the authors found a very large variation in the responses, so that the SEMs were larger than the mean values. The same research group found comparable results in feline eyes treated with atropine, cyclopentolate and tropicamide (Stadbaumer *et al*., 2006).

In conclusion, chronic topical administration of antimuscarinic agents may lead to a critical increase in the IOP of normotensive eyes. Therefore, these agents should be considered serious risks not only for patients with closed-angle glaucoma, but also for subjects that bear no ophthalmologic problems.

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