The effect of topical administration of sildenafil in acute ocular hypertension model in rabbits.

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Summary:

Background: Nitric oxide (NO) is a physiological mediator of many processes in the eye including regulation of aqueous humor dynamics. Compounds acting via NO dependent mechanisms may enhance aqueous humor outflow and reduce intraocular pressure (IOP) .

Objective: Sildenafil a cGMP specific phosphodiesterase 5inhibitor that potentiates NO production and increases cyclic GMP is tested in this study for its effects on intraocular pressure in an acute ocular hypertension model in rabbits.

Materials and methods: Newzealand albino rabbits of either sex weighing 2–2.5 Kg , were used in this study. Sildenafil was prepared in a vehicle of phosphate buffer and diluted to the required strength of 0.5%. Intraocular pressure (IOP) was measured after 45 seconds of one drop of proparacaine topical anesthesia by using schiotz indentation tonometer. Basal IOP was obtained for both eyes using 12 rabbits .One drop of sildenafil (0.5%) was then topically instilled in the left eye while the right eye received the vehicle and served as a control. After 30 minutes of drug and vehicle administration the IOP was measured in both eyes and acute ocular hypertension was induced by the administration of 15ml/kg 5% glucose. The IOP was then recorded every 15 min for 180 minutes.

Results: Topical 0.5% sildenafil administration had no effect on the basal IOP levels. However sildenafil significantly ($p < 0.05$) attenuated the acute rise in IOP induced by 5% glucose infusion. The IOP levels returned to their basal values in shorter time with sildenafil compared to the control

Conclusion: Topical sildenafil pretreatment reduces IOP in acutely induced intraocular hypertension.

Key words: Topical sildenafil , oculohypotensive effect

Introduction:

Elevation of intraocular pressure (IOP) from the individual normal level has consistently been considered to be one of the most important risk factors in glaucoma (1, 2). It has also been demonstrated that lowering of IOP would be protective (3) . It is no surprise therefore that all current pharmacological treatments of glaucoma are designed to reduce IOP and maintain it at levels presumed to prevent deterioration of the visual field and alteration in the optic nerve (3) . In the anterior segment of the mammalian eye nitric oxide (NO) is involved in the regulation of aqueous humor dynamics and there is now substantial evidence that compounds acting via NO – dependant mechanisms may enhance aqueous humor outflow and reduce IOP (4, 5) .However , there is no drug in the market at present that utilizes this property of these compounds in the treatment of glaucoma(6) . In this study sildenafil a cyclic cGMP specific phosphodiesterase 5 inhibitor that potentiates NO production and increases cyclic GMP (7, 8,9) is tested for its effects on intraocular pressure in an acutely induced intraocular hypertension in rabbits.

Materials and methods:

Newzealand albino rabbits of either sex weighing 2–2.5 Kg, were acclimated to the laboratory environment at least one week prior to experimentation . They were individually housed in metallic cages in well ventilated rooms under hygienic conditions . Rabbits were given water ad libitum and fed with green leafy vegetables.

Sildenafil citrate, pure powder was a gift sample from the national center for drug researches and control. Sildenafil was prepared in a vehicle of phosphate buffer and diluted to required strength of 0.5%. Phosphate buffer solution was prepared from chemicals obtained from British Drug House (BDH) company , and was used as a vehicle. IOP was measured after 45 seconds of one drop (50 µL) of proparacaine (from Alcon)

topical anesthesia by using schiotz indentation tonometer which was previously calibrated by an open manometric calibration procedure . Three reading were recorded for each IOP measurement and their mean was calculated. Basal IOP was obtained for both eyes using 12 rabbits . One drop of sildenafil (0.5%) was then topically instilled in the left eye while the right eye received the vehicle and served as a control. After 30 minutes of drug and vehicle administration the IOP was measured in both eyes and acute ocular hypertension was induced by administration of 15ml/kg 5% glucose through the marginal ear vein (10). The IOP was then recorded every 15 min for 180 minutes.

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Experiments were scheduled for the same time at each day of experimentation .

Statistical analysis:

The data were analyzed using SPSS version 13 (SPSS, Inc, Chicago, IL, USA). The IOP values were expressed as mean ± SEM . Student t-test was used for comparison between means of treated and control groups. All statistical tests were two-tailed with p value of < 0.05 deemed statistically significant.

Results:

The Figure depicts the IOP levels of both topical 0.5% sildenafil and control treated eyes before and after the induction of acute glaucoma. Basal IOP levels were not affected by sildenafil treatment. However, sildenafil significantly ($p < 0.05$) attenuated the acute rise in IOP induced by 5% glucose infusion when compared with the control . The IOP levels returned to their basal values in a shorter time with sildenafil compared to the control .

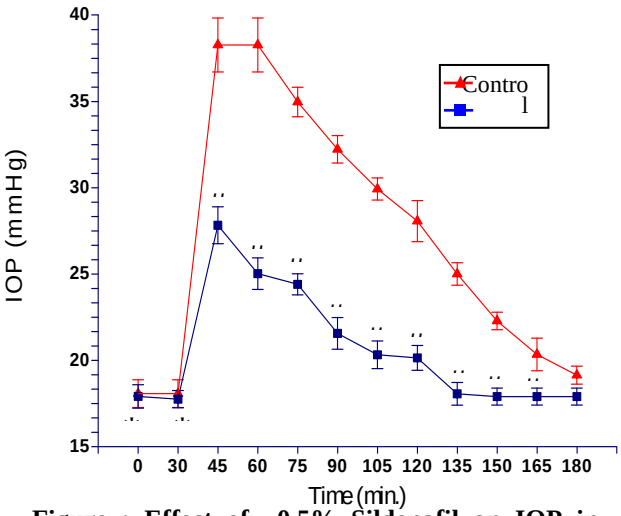

Figure : Effect of 0.5% Sildenafil on IOP in acute ocular hypertension model in rabbits. Each point represents the mean +SEM of twelve observations.

# P< 0.05 when compared with control group.

***** : Drug administration and baseline reading of IOP at zero time .

****** : The time of induction of acute glaucoma

Discussion:

We have studied the ocular hypotensive effect of sildenafil in experimentally induced acute model of glaucoma using 5% glucose infusion . This model is one of the easiest, fastest , and most reliable technique to screen antiglaucoma agents (11). A 5% glucose infusion leads to reduction in the blood osmolality , which leads to transfer of water into the eye , causing elevation of IOP (10) . In this study topical sildenafil administration had no effect on normal tension of the eye. However, Sildenafil (0.5 %) attenuated the acute rise in IOP due to 5% glucose infusion. The IOP lowering effect achieved by sildenafil in this study is in accordance with the results of other studies on acute ocular hypertension using NO donors or cGMP analogues (12, 13, 14). It has been reported that compounds affecting the NO – cGMP pathway cause relaxation of the ciliary muscle leading to increased uveoscleral outflow and also to decreased trabecular meshwork resistance and thus alteration of aqueous humor dynamics resulting in decreased IOP(15). There is also evidence that the trabecular meshwork has an intrinsic contractile element which can be relaxed by NO leading to increased aqueous humor outflow (16, 17) .These effects on the trabecular meshwork cells could be amplified by sildenafil because of the drug's ability to potentiate endogenous NO production which in turn stimulates the synthesis of cGMP in the target cells by directly activating the soluble isoform of the enzyme guanlylate cyclase (18) . Moreover these increased levels of cGMP could escape degradation by PDE5 enzyme due to its inhibition by sildenafil (19).

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