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Original article

Effect of potassium channel openers in acute and chronic models of glaucoma

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ABSTRACT

Purpose: Glaucoma is characterized by increased intraocular pressure (IOP). The effect of nicorandil and pinacidil on IOP in experimentally induced acute and chronic models of glaucoma and the mechanism of action involved were studied.
Methods: New Zealand white rabbits were used for the study. After the measurement of IOP, nicorandil (1%), pinacidil (1%), and pilocarpine as standard (1%) were instilled topically into the left eye. The other eye served as control. Dextrose (5%) was used to induce acute glaucoma. IOP changes were recorded every 15 minutes until the pressure became normal. Freshly prepared α-chymotrypsin solution was introduced in the posterior chamber to induce chronic glaucoma. Rabbits with ocular hypertension were selected for the study. Similar drug solutions were used to study the effect on IOP. Glibenclamide, pilocarpine, and indomethacin (1%) were used to study the mechanism of action of both drugs. The IOPs were measured just prior to drug instillation and at suitable time intervals using a tonometer.
Results: Pretreatment with topical nicorandil and pinacidil significantly lowered the rise in IOP in the acute model. Nicorandil and pinacidil initially caused rise in IOP for 15–30 minutes in chronic glaucoma. This was followed by reduction in IOP. Pretreatment with indomethacin and pilocarpine did not modify the effect of nicorandil and pinacidil on IOP. Pretreatment with glibenclamide blocked IOP from the lowering effect of nicorandil and pinacidil.
Conclusion: The oculohypotensive effect shown by these drugs appears to be attributable to enhancement of the aqueous humor outflow. This effect is perhaps mediated through potassium channels.
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1. Introduction

Glaucoma is a multifactorial disease with a number of elements contributing to its development. An elevation of intraocular pressure (IOP) is a prominent component in optic nerve damage, which is the hallmark of glaucoma. If the elevated IOP is inadequately treated, progressive blindness may result.

Various drugs used in treatment of glaucoma are parasympathomimetics, β-adrenoceptor antagonists, carbonic anhydrase inhibitors, α_2-adrenoceptor agonists, prostaglandin analogues, and angiotensin-converting enzyme inhibitors.[1,2] Timolol eye drops are the golden standard in the treatment of glaucoma. However, timolol is also known to get into the systemic circulation and causes various systemic effects.[3] Although glaucoma is known to be a serious chronic eye disease, an ideal agent to be used in this disease is still not available, and there has been a constant urge for the discovery of newer drugs.

The steady levels of IOP are the result of balanced aqueous humor formation and outflow. Calcium flux could have several effects on aqueous humor dynamics, including a hydrostatic component, a result of arterial blood pressure and ciliary body perfusion, and an osmotic component, which is a result of an effect on the active secretion of sodium, calcium, and other ions by ciliary epithelium.[4] It has been reported that functional K^+-dependent ATP channels are present in the trabecular meshwork, and their activation by potassium channel openers can increase outflow facility through the trabecular meshwork.[5] Reports have indicated the beneficial effects of diazoxide and nicorandil on K^+-dependent ATP channel-mediated IOP regulation.[6] Cromakalim and nicorandil were

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reported as occulohypotensive in normotensive, hypotensive, and hypertensive rabbits.[7] According to Food and Drug Administration reports, 0.0353% patients suffer from glaucoma after treatment with nicorandil in various disease conditions.[8] In the present study, we investigated the effect of potassium channel openers, pinacidil and nicorandil, and their interaction with a potassium channel blocker, glibenclamide, for their effect on IOP. Furthermore, the possible mechanisms of action of these agents were also studied.

2. Materials and methods

2.1. Experimental animals

New Zealand white rabbits of either sex weighing 1.5–2.5 kg (Zydus Research Center, Ahmedabad, India) were housed under well-controlled conditions: temperature, 22 ± 2°C; humidity, 55 ± 5%; and 12/12-hour light/dark cycle. They were given access to food and water *ad libitum*. The protocol of the experiment was approved by the Institutional Animal Ethical Committee as per the guidance of the Committee for the Purpose of Control and Supervision of Experiments on Animals, Ministry of Social Justice and Empowerment, Government of India.

2.2. Acute glaucoma model

The basal IOP was measured using a Schiotz-type indentation tonometer. The drug solutions were prepared in suitable solvents and were instilled topically into the left eye. The drug solutions used in the study were nicorandil (1% in phosphate buffer, pH 7.4), pinacidil (1% in PEG 400), glibenclamide (1% in PEG 400), and pilocarpine (1%; FDC Ltd., Maharastra, India). The right eye, which served as control, received the vehicle. After 15 minutes of drug administration, 5% dextrose solution (15 mL/kg) was intravenously (i.v.) infused through the marginal ear vein up to 15 minutes. Six rabbits (of either sex) were taken to study the effect of each drug. A 5% dextrose infusion induced an acute increase in IOP in both eyes of all rabbits under study. IOP was recorded every 15 minutes until the pressure became normal.[9]

2.3. Chronic glaucoma model

Albino rabbits were sedated with diazepam (1 mg/kg, i.v.) and anesthetized with ketamine (25 mg/kg, i.v.). Fresh α-chymotrypsin (50 units; Sigma Life Sciences, Missouri, USA) solution prepared in 0.1 mL of sterile saline was irrigated through the cannula into the posterior chamber.[9] The debris of tissue blocked the pathway of the aqueous humor outflow in the trabecular meshwork to induce ocular hypertension.[10] α-Chymotrypsin was administered in 36 rabbit eyes. From this, we have successfully increased IOP in 27 eyes. Rabbit with increased IOP above 30 mmHg were selected and used to determine the effect of drugs on IOP. After a steady elevated IOP was achieved, similar drug solutions as in acute glaucoma model were administered topically into the left eye, whereas the right eye served as control. The IOPs were measured at time 0 (just before eye drop instillation), 15, 30, 45, 60, 75, 90, 120, 180, 240, 300, and 360 minutes using a tonometer.

2.4. Studies on interaction of glibenclamide with nicorandil and pinacidil in acute glaucoma model in rabbits

The basal IOP was measured in both eyes. After 15 minutes of glibenclamide instillation in the left eye, nicorandil or pinacidil were instilled topically. The right eye served as control. The acute glaucoma model was produced using the procedure described above.[9] IOP was recorded with a tonometer every 15 minutes until the pressure became normal.

2.5. Studies on interaction of glibenclamide with nicorandil and pinacidil in chronic glaucoma model in rabbits

Rabbits with α-chymotrypsin-induced glaucoma were selected for the study. The IOP was initially recorded with the help of a tonometer. The interaction study was carried out similarly as in the acute model.

2.6. Studies on interaction of indomethacin and pilocarpine with nicorandil and pinacidil in chronic glaucoma model in rabbits

Rabbits with α-chymotrypsin-induced glaucoma were selected for the study. The IOP was initially recorded with the help of a tonometer. Indomethacin (1%; Sterfil Laboratories Pvt. Ltd., Maharastra, India) prostaglandin inhibitor was topically administered to the left eye. The right eye served as control. After 45 minutes of administration of indomethacin, nicorandil or pinacidil was instilled topically. The changes in IOPs were recorded at suitable time intervals using a tonometer. Indomethacin was replaced with pilocarpine to study the interaction of pilocarpine with nicorandil and pinacidil.

These formulations were first tested in rabbit's eyes for ocular safety. No ill effects were observed.

2.7. Statistical analysis

Paired Student *t* test was used for determining the statistical significance of most of the data at the probability level of 95%. A split-plot analysis of variance was carried out for studying the time-dependent interaction between the drugs under study and other drugs.

3. Results

An acute elevation in IOP of up to 30–35 mmHg was observed when 5% dextrose (15 mL/kg) was administered intravenously. Potassium channel blocker, glibenclamide (1%) partially reversed IOP lowering effect of nicorandil (1%) and pinacidil (1%) in acute glaucoma in rabbits (Figures 1 and 2, respectively).

The topical administration of nicorandil in animals with α-chymotrypsin-induced ocular hypertension produced a significant drop in IOP (from 33.67 ± 0.31 mmHg to 20.10 ± 0.01mmHg) after an initial rise (from 33.67 ± 0.31 mmHg to 42.17 ± 0.07 mmHg), and the topical administration of pinacidil in rabbits with α-chymotrypsin-induced occular hypertension produced a significant drop in IOP (from 33.93 ± 0.43 mmHg to 21.30 ± 0.30 mmHg) after an initial rise (from 33.93 ± 0.43 mmHg to 38.77 ± 0.84 mmHg) in IOP (Figures 3 and 4, respectively).

Glibenclamide reversed the OP-lowering effect of nicorandil and pinacidil in rabbits with α-chymotrypsin-induced chronic glaucoma (Figures 3 and 4, respectively). Interaction with indomethacin (1%) or pilocarpine (1%) did not produce a significant change in the IOP-lowering effect of nicorandil and pinacidil (Figures 3 and 4, respectively).

4. Discussion

Glaucoma is an eye disease with elevated IOP as a prominent and hallmark component. It has been reported that glaucoma has vascular roots, as it is more prevalent in cardiovascular and cerebrovascular diseases,[11,12] and in Raynaud-like peripheral circulation disease.[13]

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