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Report

In Vivo Performance of Ophthalmic Preparations of Betamethasone and Phenylephrine Hydrochloride in the Rabbit Eye: Effect of Polyvinyl Alcohol

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The effect of different concentrations of polyvinyl alcohol 14000 and 72000 (PVA 14 and 72) on the activity of betamethasone and phenylephrine hydrochloride in the rabbit eye was investigated. The polymer of higher molecular weight exerts a more pronounced effect at relatively lower viscosities. Effects on the intraocular pressure are more responsive to changes in viscosity than those on pupillary response.

KEY WORDS: betamethasone, ocular effects: phenylephrine, ocular effects; polyvinyl alcohols, modulation of ocular drug effects; drug delivery, ocular.

INTRODUCTION

A substantial increase in ocular drug bioavailability can be achieved by placement of the drug in a high-viscosity vehicle prior to instillation into the eye. A study (1) in albino rabbits showed that solutions of pilocarpine nitrate containing polyvinyl alcohol (PVA) have a greater ocular bioavailability than simple aqueous solutions. The authors identified an optimum viscosity range for PVA solutions, i.e., 12–15 mPa · sec, which agrees with results from another study (2). Further, the miotic effect of pilocarpine hydrochloride in human subjects was enhanced by PVA, hydroxypropylemethylcellulose, and methylhydroxyethylcellulose already at solution viscosities as low as 4 mPa · sec or above (3). Other work (4) in albino rabbits demonstrated greater mydriasis by homatropine hydrobromide in a vehicle of 0.5% hydroxypropylmethylcellulose or 1.4% PVA, compared to the corresponding aqueous solutions of the drug.

The purpose of the present work is to clarify further the effect of viscosity on the *in vivo* performance of ophthalmic solutions. The drug examples are the antiinflammatory compound betamethasone and the α-sympathomimetic phenylephrine hydrochloride.

MATERIALS AND METHODS

Materials

Betamethasone (Schering), phenylephrine hydrochloride (Siegfried), polyvinyl alcohol 14000 and 72000 (BDH), and polyethylene glycol 400 were all of reagent grade. Albino rabbits (1.8–2.8 kg) were used.

Procedure

Ophthalmic solutions containing 0.05% (w/v) betamethasone and/or 2.5% (w/v) phenylephrine hydrochloride were prepared according to the following procedure. The polymers in question were dissolved in an isotonic phosphate buffer solution (pH 6.8). Betamethasone was dissolved in the least amount (1% of the ophthalmic solution) of polyethylene glycol 400. Solutions of betamethasone and phenylephrine hydrochloride (the latter in buffer) were mixed with the isotonic buffer solution. The pH was adjusted to 6 ± 0.2.

The concentration ranges of the polymer were 1–3 and 0.5–2% (w/v) for PVA 14000 and PVA 72000, respectively.

Investigation of the Rheology of Ophthalmic Solutions

The viscosity of the ophthalmic solutions was determined with the Ferranti Shirley cone and plate rotational viscometer at 33 ± 0.1°C.

Evaluation of the Flow Behavior

Among the equations available for the characterization of non-Newtonian flow, the Steiger-Treppi (5) equation was selected to estimate the viscosity of the system at negligible rates of shear and to calculate the apparent viscosity at any particular shearing rate, with consideration of the system's flow pattern. The viscosity was calculated at two limiting levels of shear dictated by the physiology of blinking in rabbit eye. Since the blinking rate is known to be very low in rabbit (4 times hr^{-1}) (6), the lower level of shear was a value

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near zero to represent the nonblinking condition; this was represented by the basic viscosity. The upper limit of shear was a rate similar to that calculated for the human eye during blinking (7); a value of 4500 sec^{-1} was taken.

Measurement of Intraocular Pressure (IOP) and Pupil Diameter

Test animals were kept in restraining boxes in the normal upright position during the experiments. An isotonic xylocaine solution (1%, w/v) was dropped into the rabbit's eyes to anesthetize the cornea. Each formulation was tested in each of six rabbits kept in a room with standardized illumination. The assigned formulation was applied to the right eye, while the control, nonmedicated formulation was applied to the left eye. Before and after the application of both control and test formulations, the pupil diameter and the intraocular pressure of both eyes were measured hourly using Haab's pupillometer and the Maclocof tonometer, respectively.

The activity parameters are the area under (or above the curve (AUC), maximum response (MR), time of maximum response (TMR), and duration of drug action (DA).

RESULTS AND DISCUSSION

The activity of ophthalmic solutions of betamethasone or phenylephrine hydrochloride in the rabbit eye was investigated as a function of the concentration of polyvinyl alcohol. Two grades of polyvinyl alcohol were used, *viz.*, polyvinyl alcohol 14000 and 72000, to explore the effect of molecular weight of the polymer

The time course of the intraocular pressure (IOP) as a function of the PVA concentration is presented in Figs. 1. and 2. PVA of either molecular weight exerts a pronounced influence on the IOP response at rather low PVA concentrations.

Drug Response in Relation to Viscosity of Ophthalmic Solution

The area under or above the IOP/time curve is presented in Tables I and II for betamethasone and phenylephrine hydrochloride, respectively, as a function of solution viscosity for both PVA 14000 and 72000. The viscosity data represent absolute viscosities, since all ophthalmic solutions investigated were found to be Newtonian liquids in the presence of PVA 14000 or PVA 72000. In the narrow viscosity range covered by the two polymers, *viz.*, ~2–5 mPa · sec (or ~1.5–~4 mPa · sec for phenylephrine hydrochloride), the area is highly dependent on the viscosity of the ophthalmic solution. This dependency is more pronounced with the polymer of higher molecular weight.

For betamethasone, the effect of PVA begins to be statistically significant at viscosities of 2–3 mPa · sec. For phenylephrine hydrochloride, increasing the viscosity of the ophthalmic solution from ~1.5 to 2 or 2.5 mPa · sec for PVA 72 or PVA 14, respectively, causes a highly significant increase in the area above the curve.

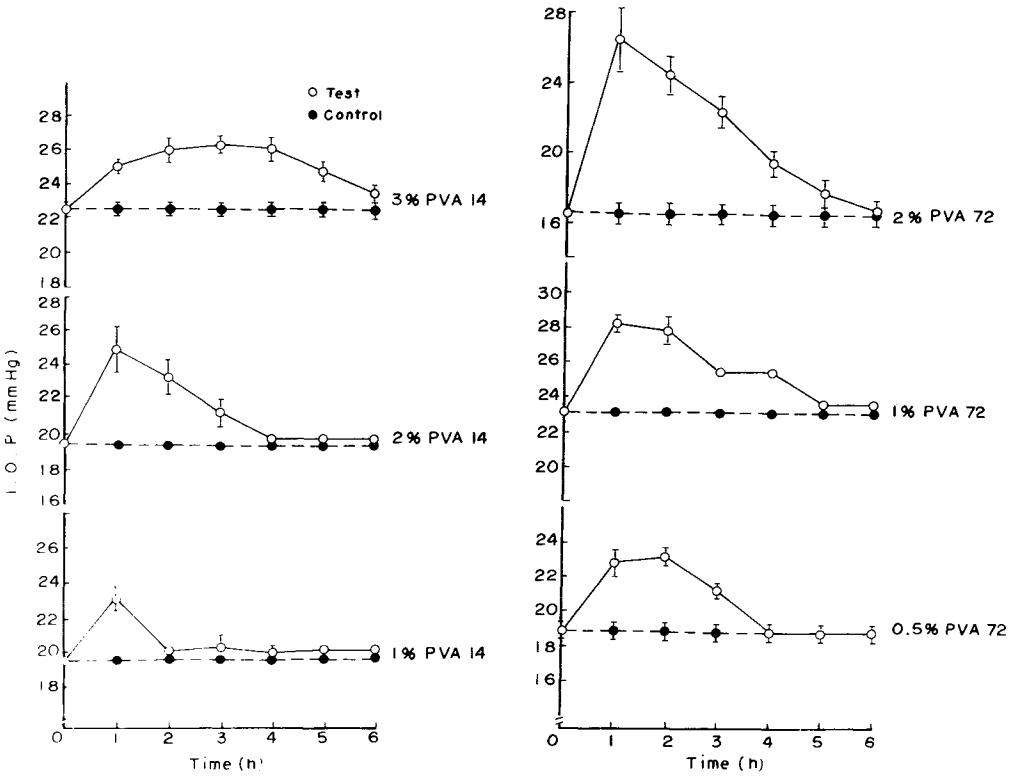

Fig. 1. Intraocular pressure (mm Hg) of rabbit eye postinstillation of 0.05% (w/v) betamethasone ophthalmic solutions containing different concentrations of polyvinyl alcohol 14000 (PVA 14) and 72000 (PVA 72).

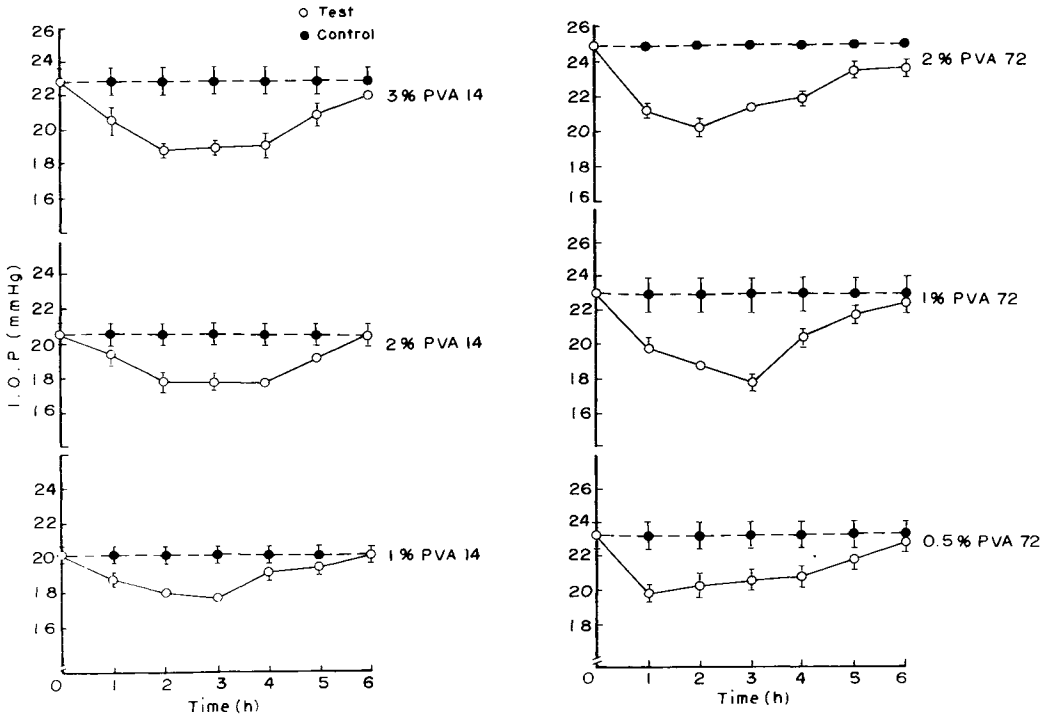

Fig. 2. Intraocular pressure (mm Hg) of rabbit eye postinstillation of 2.5% (w/v) phenylephrine hydrochloride ophthalmic solutions containing different concentrations of polyvinyl alcohol 14000 (PVA 14) and 72000 (PVA 72).

Maximum Response in Relation to Viscosity of Ophthalmic Solution

The maximum response to both drugs is presented in Tables I and II as a function of the viscosity of the ophthalmic solution in the presence of either PVA 14000 or PVA 72000. The intensity of drug action markedly depends on the solution viscosity in the experimental viscosity range, *viz.*, ~2–~5 mPa · sec for betamethasone, which is more pronounced with PVA 72000. Phenylephrine hydrochloride demonstrates a gradual increase in the maximum response with increasing viscosity for solutions containing PVA 14000 (Table II). In PVA 72000 solutions the maximum response increases markedly in the lower viscosity range and approaches an asymptotic value already at viscosities of about 3 mPa · sec.

Statistical analysis of the data reveals that the effect of PVA 14000 begins to be significant at a viscosity approaching 3 mPa · sec. For PVA 72000, on the other hand, the effect is already significant at 2 mPA · sec.

Table I. Correlation of the AUC, MR, TMR, and DA to the Viscosity of Ophthalmic Solutions of Betamethasone Containing Polyvinyl Alcohol 14000 (PVA 14) and 72000 (PVA 72)

Polymer type	Concentration (%)	Absolute viscosity (cP)	Parameter of activity			
			AUC[a] (mm Hg · hr)	MR (mm Hg)	TMR (hr)	DA (hr)
PVA 14	0	1.6	4.3 (0.7)[b]	2.6 (0.4)	1.5 (0.2)	2.0
	1	2.3	5.0 (0.5)	3.9 (0.3)	1.3 (0.3)	2.6 (0.6)
	2	2.8	12.1 (1.7)	5.5 (0.9)	1.0	3.1 (0.6)
	3	3.8	16.4 (1.1)	5.2 (0.2)	2.8 (0.4)	6
PVA 72	0.5	2	10.5 (1.9)	5.0 (0.8)	1.83 (0.2)	3 (0.2)
	1	3.2	14.7 (1.1)	5.3 (0.4)	1.33 (0.2)	4.8 (0.1)
	2	4.6	28.2 (2.5)	10.5 (1.0)	1.73 (0.8)	5.1 (0.1)

[a] In excess to the corresponding control, *viz.*, corresponding solution without drug.
[b] The values in parentheses in this and subsequent tables represent the standard errors.

Table II. Correlation of AAC, MR, TMR, and DA of the IOP to the Viscosity of Ophthalmic Solutions of Phenylephrine Hydrochloride Containing Polyvinyl Alcohol 14000 and 72000 as Viscolizers

Polymer type	Concentration %	Viscosity (cP) $D = 0$ (sec^{-1})	Viscosity (cP) $D = 4500$ (sec^{-1})	Viscosity (cP) AAC (mm Hg · hr)	Parameter of activity MR (mm Hg)	Parameter of activity TMR (hr)	Parameter of activity DA (hr)
PVA 14	0	1.6	1.4	2.1 (0.3)	1.4 (0.1)	2.3 (0.2)	2.6 (0.2)
	1	2.3	2.3	8 (1.7)	2.7 (0.6)	2.2 (0.4)	4.3 (0.4)
	2	2.8	2.8	10.3 (2.1)	3.6 (0.5)	3.2 (0.4)	4.6 (0.2)
	3	3.8	3.8	15.8 (4.1)	4.5 (0.9)	2.2 (0.6)	5.3 (0.3)
PVA 72	0.5	2	2.0	13.5 (3.8)	4.1 (0.6)	1.5 (0.3)	4.6 (0.4)
	1	3.2	3.1	16.3 (4.3)	5.2 (0.8)	2.3 (0.4)	4.8 (0.4)
	2	4.6	4.6	16.9 (2.3)	4.7 (0.5)	1.6 (0.2)	5.5 (0.3)

Time of Maximum Response in Relation to Viscosity of Ophthalmic Solution

Tables I and II summarize the dependency of the TMR on the viscosity of the ophthalmic solution in the presence of PVA 14000 or PVA 72000. For betamethasone the correlation between TMR and viscosity is very poor, with one minor change in TMR in the presence of PVA 72000. In the case of PVA 14000, the only marked change was observed at a viscosity approaching 4 mPa · sec. Moreover, there is no clear correlation between TMR and solution viscosity for phenylephrine hydrochloride with either PVA 14000 or PVA 72000.

Duration of Drug Action in Relation to Viscosity of Ophthalmic Solution

The duration of drug action greatly depends on the viscosity (~2–~5 mPa · sec). This dependency seems to be more pronounced for lower concentrations and lower viscosities of PVA 72000 than PVA 14000. The increase in effect duration of betamethasone is statistically significant for PVA 14000 only as the viscosity approaches 4 mPa · sec. In the case of PVA 72000, on the other hand, the increase is statistically significant already at viscosities as low as 2 mPa · sec.

Effect of Phenylephrine Hydrochloride in Relation to Viscosity of Ophthalmic Solution

In the investigated viscosity range of ~2–~5 mPa · sec is a limited increase in the AUC, using either PVA 14000 or PVA 72000 (Fig. 3). The increase in the AUC does not become apparent unless the viscosity exceeds 3 mPa · sec. Beyond a viscosity of ~3 mPa · sec, the viscous solutions are significantly different ($P = 0.01$) from the nonviscous solution. The maximum pupillary response to phenylephrine hydrochloride and the time of maximum response depend on the viscosity of the ophthalmic solution only to a very limited extent. The increase in the maximum response does not become evident unless the viscosity of the solutions reaches values of approximately 4 mPa · sec. The only significant differences are those observed between the PVA 14000 solution of a viscosity of 4 mPa · sec and the other solutions of lower viscosities.

The duration of drug action (Table III) significantly increases with increasing viscosity of the ophthalmic solution above a value of about 2 mPa · sec, which is more pronounced for PVA 72000.

These results show that the area under (or above) the curve is the parameter most sensitive to changes of viscosity. This is followed by the maximum response and the duration of drug action. Further, the IOP response is more sensitive to viscosity changes than the pupillary response.

Comparison of PVA 14000 and PVA 72000 reveals that the effect of both polymers is dictated largely by the viscosity of the solution, irrespective of the molecular weight. The only difference is the greater effect of the high molecular weight polymer in the lower viscosity range of 2 mPa · sec.

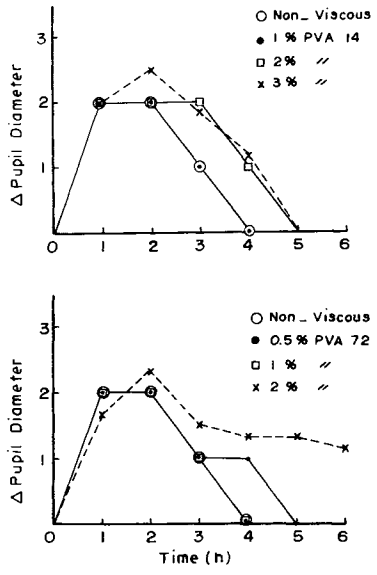

Fig. 3. Pupil diameter (mm) of rabbit eye postinstillation of 2.5% (w/v) phenylephrine hydrochloride ophthalmic solutions containing different concentrations of polyvinyl alcohol 14000 (PVA 14) and 72000 (PVA 72).

Table III. Correlation of the AUC, MR, TMR, and DA of the Pupil Diameter to the Viscosity of Ophthalmic Solutions of Phenylephrine Hydrochloride Containing Polyvinyl Alcohol 14000 (PVA 14) and 72000 (PVA 72)

		Viscosity (cP)		Parameter of activity			
Polymer type	Concentration %	$D = 0$ (sec^{-1})	$D = 4500$ (sec^{-1})	AUC (mm · hr)	MR (mm)	TMR (hr)	DA (hr)
PVA 14	0	1.7	1.4	5.0	2.0	1.0	3
	1	2.4	2.3	5.0	2.0	1.0	3
	2	2.8	2.8	7.0	2.0	1.0	4
	3	3.8	3.8	7.5 (0.4)	2.5 (0.2)	1.5 (0.2)	4
PVA 72	0.5	2	2.0	5.0	2.0	1.0	3
	1	3.2	3.1	6.0	2.0	1.0	4
	2	4.6	4.6	8.7 (1)	2.3 (0.2)	1.6 (0.2)	6

These findings indicate that there may be no need to increase the viscosity of ophthalmic solutions containing PVA to values much higher than 2 mPa · sec.

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