DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(2), 253-282 (1989)

EFFECT OF PHENYLEPHRINE HYDROCHLORIDE ON BETAMETHASONE SIDE EFFECT IN RELATION TO VISCOSITY OF OPHTHALMIC PREPARATIONS

I - VISCOUS SOLUTIONS

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ABSTRACT

Three parameters have been utilized to assess the performance of combination preparation of betamethasone and phenylephrine hdyrochloride formulated in viscous solutions of methylcellulose, methylhydroxyethyl-cellulose or polyvinyl alcohol, PVA . The parameters were the area under the curve, AUC, the maximum response, MR, and the duration of side effect , DA, (increased in the intaocular pressure, IOP). The results demonstrate that balancing the side effect of betamethasone through combination with phenylephrine hydrochloride is highly dependent on the viscosity of the solution to the extent that the effect of the latter is insignificant in aqueous (non viscous) solutions or in a vehicle of a viscosity less than 4 cp ($D \simeq 0$ sec^{-1}). It was found that PVA seems to be the most powerful one in controlling the side effect of betamethasone.

INTRODUCTION

A major side effect of steroides in ocular therapy is their ability to elevate intraocular pressure, IOP, and even induce, in susceptible individuals, an intractable flaucoma[1]. The rise in ocular tension is marked with the potent anti-inflammatory agents dexamethasone and betamethasone[2]. It was also reported[3] that topical administration of betamethasone to the eye increases the IOP in 46% of the volunteers with 6-15mmHg. Betamethasone drops when used in one eye for 1-2 months resulted in chronic simple glaucoma.[4]

α-Sympathomimetic drugs are known to bring about the desired effect, viz. lowering of IOP[5,6]. The forgoing literature would thus justify the combination of betamethasone and phenylephrine hydrochloride for the treatment of the inflammed eye.

The effect of viscolizers on ocular drug bioavailability has been investigated most extensively with pilocarpine. It has been reported[7] that, instillation of pilocarpine nitrate solutions of increasing viscosity-using methylcellulose-resulted in higher aqueous humer drug concentration.

An attempt was carried out to verify the equal viscosity-equal activity (for pilocarpine miotic effect)

assumption, and to define species (man and rabbit) differences in the biological response to the same vehicle.[8]

Other authors[9], demonstrated that pilocarpine produces greater miosis and greater reduction in the IOP compared to the simple aqueous solution of the drug.

A study[10] in albino rabbits, proved that solution of pilocarpine nitrate containing polyvinyl alcohol have greater ocular bioavailability than simple aqueous solutions.

The aim of this work was an attempt to give an answer to the following question : How far do viscolizers influence the usefulness of the combination of betamethasone and phenylephrine hydrochloride , in other words how far does phenylephrine hydrochloride subress or inhibit betamethasone side effect (elevation of the IOP) in relation to viscosity of the ophthalmic solutions

EXPERIMENTAL

Materials:

Betamethasone (Schering), phenylephrine hydrochloride (Siegfried).

Methylcellulose 450 (BDH), methylhydroxyethylcellulose (Tylose 4000-Hoechst), polyvinyl alcohol 14000 (PVA 14000)

and polyvinyl alcohol 72000 (PVA72000) (BDH), all of reagent grade.

Methods :

Preparation of ophthalmic solutions, measurement of IOP and investigation of the rheology of ophthalmic solutions: all were carried out as previously described by the same authors[11].

The viscolizers used in ophthalmic solutions are: two grades of polyvinyl alcohol, PVA 14 and PVA72 (low and high molecular weight), methylcellulose, MC, and methylhydroxyethylcellulose (tylose) in concentration ranges : 1-3% ; 0.5-2%; 0.25-1% and 0.125-0.5% w/v respectively. Non viscous solution was used for comparison.

The combination preparations contained the two drugs in the same concentrations as those used for the individual drug, viz: 0.05% w/v betamethasone and 2.5% w/v phenylephrine hydrochloride.

RESULTS AND DISCUSSION

Betamethasone, which is a potent anti-inflammatory compound acting both as cyclo-oxygenase and lipoxygenase inhibitor has a major side effect, viz. increasing the intraocular pressure.

It is plausible that an α-adrenoreceptor stimulant, which lowers the intraocular pressure, would balance the side effect of betamethasone if administered concumittantly with betamethasone.

How far this balance may be achieved and to what extent is this dependent on the viscosity of the ophthalmic preparations are questions awaiting an answer in the scientific literautre. This part of the work is a contribution to this.

Three parameters have been utilized to assess the performance of combination preparations of betamethasone and phenylephrine hydrochloride. These were the area under the curve, AUC, the maximum response MR, and the duration of side effect (increased in I O P). The above mentioned parameters are those found-in the light of the foregoing investigations-most indicative of drug effect for the individual drugs.

Effect of Methylcellulose.

Figure (1) shows the time course of that intraocular pressure for combination preparations as a function of polymer concentration in the opthalmic solution. It is obvious that deviation of the IOP from normal is not only a function of the two drugs, but also depends to a marked extent on the polymer concentration.

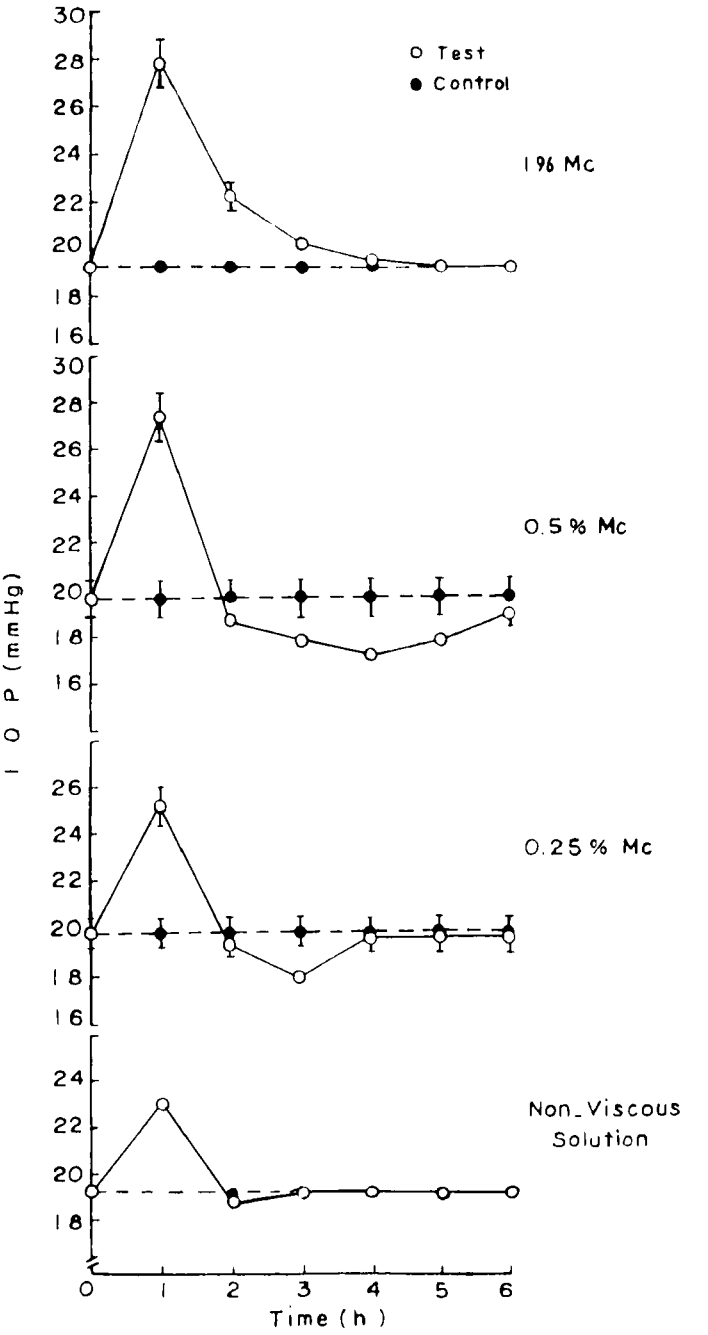


Fig. (1): Intraocular Pressure (in mm Hg) of Rabbit's Eye Post-Instillation of Ophthalmic Solutions of Betamethasone and Phenylephrine Hydrochloride Containing Methylcellulose (MC).

To find out the optimum conditions for a balance of the side effect of betamethasone and in the mean time a fair effect of the drug, it would be appropriate to compare the values of the parameters AUC, DA and MR for combination preparations and betamethasone preparations of similar viscosity.

AUC .

Figure (2) and table (1) shows the AUC of combination preparations expressed as percent of that for the corresponding betamethasone preparation i.e. solutions of the same viscosity.

It is obvious that increasing the viscosity, even by small increments, favours a reduction of the AUC for the combination preparation relative to that of corresponding betamethasone preparations. Relative to the latter, the area markedly decrease already in the viscosity range 4-9 cP and approaches a plateau afterwards. In the viscosity range 4-9 cP, the area for the combination preparations is only 30% that of the corresponding betamethasone preparations. This would mean a marked reduction of the side effect.

Statistical analysis of the data of table (2)reveals that, while the differences in the AUC are insignificant for the non viscous preparations (combination versus betamethasone aqueous solutions), they are highly to

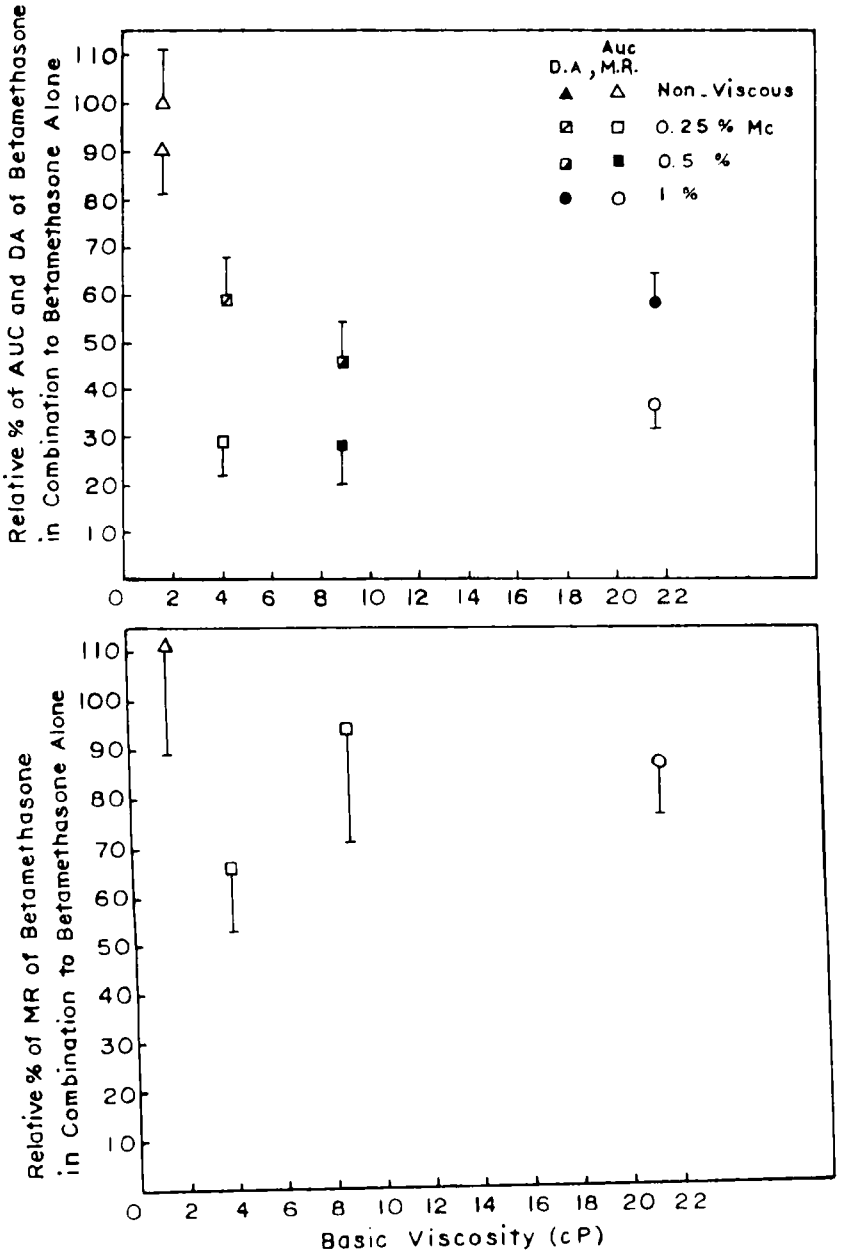


Fig.(2): Influence of Viscosity of Ophthalmic Solutions Containing Methylcellulose (MC) on the Counter Effect of Phenylephrine-HCl with Regard to the Relative % of AUC, DA and MR.

Table (1): Correlation of AUC, DA and MR to the Viscosity of Ophthalmic Solutions of Betamethasone and Phenylephrine Hydrochloride Containing Methylcellulose (MC).

Concentration	Viscosity of D=0 $sec.^{-1}$	Parameters of Activity		
		AUC (mmHg.h)	DA (h)	MR mmHg
0 %	1.67	90.44 (9)*	100 (11.2)*	112.4 (23.5)*
0.25 %	4.00	28.06 (6.9)	59.33(9)	65.60 (13)
0.50 %	8.87	27.65 (7)	46.44(8.6)	94.04(22.8)
1.00 %	21.46	36.66 (5)	58.31(5.6)	87.3 (10.9)

* The Figures between parenthesis represent the standard error.

very highly significant for the preparations containing methylcellulose. The table reveals also that the differences observed in figure (2) for different viscosities are highly significant for comparisons between the non viscous solutions and any of the viscous ones. Differences amongst the latter are insignificant.

Duration of Side Effect .

The duration of side effect is also found to depend on the viscosity of the solution in a manner very similar to that of the AUC. Also here, the duration of side effect is drastically reduced (40-55%) already in the viscosity range ~ 4-9 cP (Table 1).

Table (2): Significance Level (Value of P) of Differences in the Parameters of Activity for Ophthalmic Solutions of Betamethasone and Phenylephrine Hydrochloride Containing Methylcellulose (MC)

Pairs of Comparison	Parameters of Activity		
	AUC (mm Hgh)	DA (h)	MR mmHg
0 % with 0.25%	0.01	0.01	0.1
0 % with 0.5 %	0.01	0.01	0.1
0 % with 1 %	0.01	0.01	0.1
0.25% with 0.5 %	0.1	0.1	0.1
0.25% with 1 %	0.1	0.1	0.1
0.5 % with 1 %	0.1	0.1	0.1
0 % with 0 %	0.1	0.1	0.1
0.25% with 0.25%	0.01	0.01	0.05
0.5 % with 0.5 %	0.01	0.001	0.1
1 % with 1 :	0.001	0.001	0.1

Statistical analysis of the data reveals that while the differences between the non viscous solutions (combination preparation versus betamethasone aqueous solutions) are insignificant, those between the corresponding viscous solutions are highly to very highly significant (table 2).

Analysis of differences in the duration of side effect in relation to viscosity of the solution reveals

highly significantly levels for comparisons between the non viscous solutions, on one hand, and any of the viscous ones, on the other hand. Differences in the latter group are insignificant (table 2).

Maximum Response.

The maximum response for the combination preparation in percent of that for the corresponding betamethasone preparation is presented in figure (2).

It is obvious that the dependency of the MR parameter on solution viscosity is less pronounced, compared to other parameters. The figure depicts that the presence of viscolizers favours, to a certain extent, lowering of the MR parameter.

Statistical analysis of the data reveals that any differences observed either as a function of the presence or absence of phenylephrine hydrochloride or as a function of viscosity of solution are statistically insignificant for the MR parameter (table 2).

These findings demonstrate that balancing the side effect of betamethasone through combination with phenylephrine hydrochloride is highly dependent on the viscosity of the solution to the extent tha the effect of phenylephrine hydrochloride is insignificant in aqueous (non-viscous) solutions and highly to very highly significant

in presence of a viscolizer specially with regard to AUC and DA. In presence of methylcellulose the effect is highly significant already at viscosities around 4 cP.

The above mentioned phenomenon, viz, controlling drug/drug interactions in ocular application via controlling the viscosity of the ophthalmic preparation is unprecedented and represents a new dimension that worths-further investigation on the example of other viscolizers.

Effect of Methylhydroxyethylcellulose (Tylose)

Figure (3) shows the time course of the IOP for combination preparations as a function of Tylose concentration in the ophthalmic solution. It is evident that the presence of Tylose influences the time-course of the IOP to a marked extent.

AUC .

Figure (4) and table (3) depict the AUC for the combination preparations expressed as percent of that for the corresponding, viz, of same viscosity, betamethasone preparation.

It is obvious that the value of the above mentioned area parameter is a function of the viscosity of the ophthalmic solution. It decreases with increasing viscosity to reach values as low as 50% at ~ 16 cP.

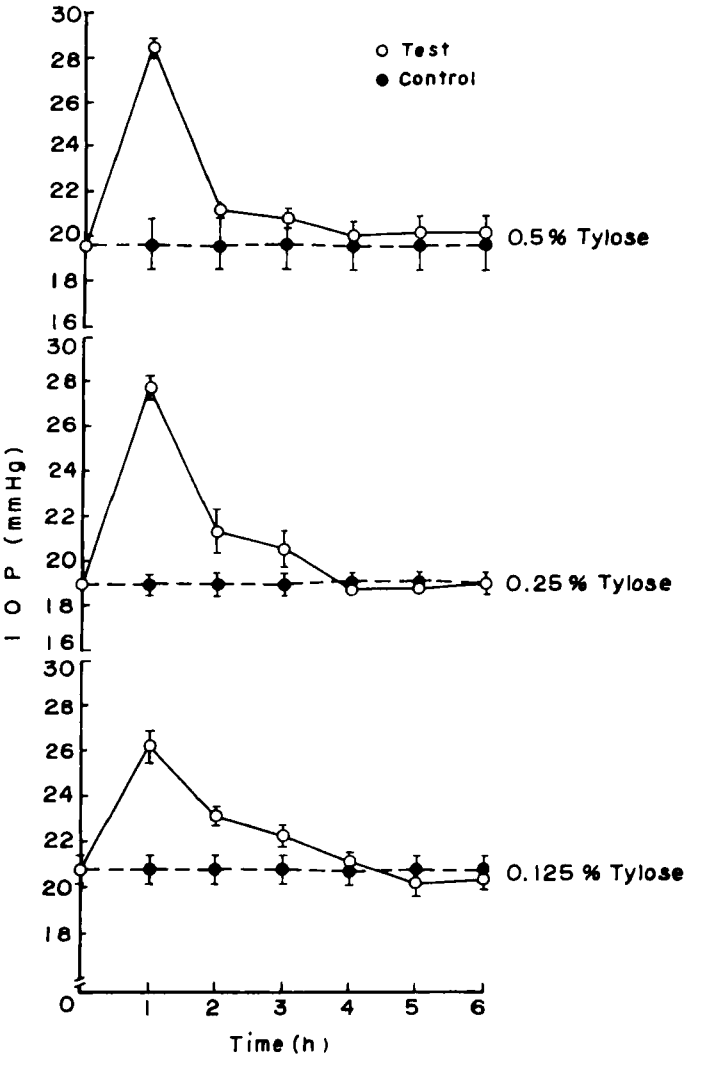


Fig.(3): Intraocular Pressure (in mmHg) of Rabbit's Eye Post-Instillation of Ophthalmic Solutions of Betamethasone and Phenylephrine Hydrochloride Containing Methylhydroxyethylcellulose (Tylose).

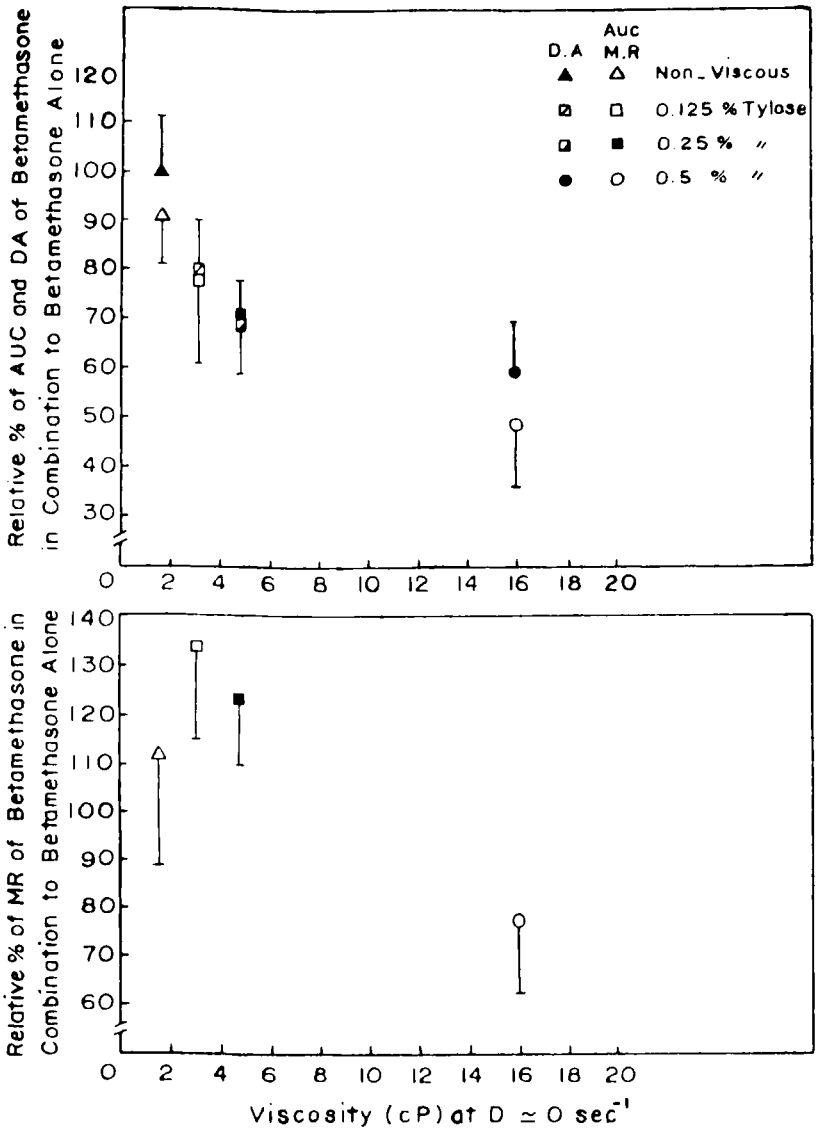


Fig.(4): Influence of Viscosity of Ophthalmic Solutions Containing Methylhydroxy-ethylcellulose (Tylose) on the Counter Effect of Phenylephrine-HCl with Regard to the Relative % of AUC, DA and MR.

Table (3) : Correlation of AUC, DA and MR to Viscosity of Ophthalmic Solutions of Betamethasone and Phenylephrine Hydrochloride Containing Methylhydroxyethylcellulose (Tylose).

Concentration	Viscosity at $D=0\ sec.^{-1}$ (cP)	Parameters of Activity		
		AUC (mmHg.h)	DA (h)	MR (mmHg)
0 %	1.67	90.50 (9) *	100 (11.2) *	112.4 (23.5) *
0.125%	3.24	78.13(17.8)	79.37 (9.9)	133.6 (18.6)
0.25 %	4.81	70.65(12.9)	69.25 (8)	123.6 (13.7)
0.5 %	15.87	48.71(12.7)	59.41 (10.2)	77.4 (14.7)

Statistical analysis of differences between the combination preparations, on one hand, and the corresponding betamethasone preparations, on the other hand, reveals that these differences are of no statistical significance for the non viscous preparations or the preparations of a viscosity less than 4 cP. If the viscosity of the preparations exceeds 4 cP, however, the differences become significant to highly significant (table 4).

Comparison of the values of the area parameter for solutions of different viscosities reveals that statistically significant differences are observed only for solutions of viscosities of ~ 2 and ~ 16 cP (table 4).

Table (4): Significance Level (Value of P) of Differences in the Parameters of Activity for Ophthalmic Solutions of Betamethasone and Phenylephrine Hydrochloride Containing Methylhydroxyethyl-cellulose (Tylose).

Pairs of Comparison	Parameters of Activity		
	AUC (mm Hg.h)	DA (h)	MR (mm.Hg)
0 % with 0.125 %	0.1	0.1	0.1
0 % with 0.25 %	0.1	0.05	0.1
0 % with 0.5 %	0.05	0.05	0.1
0.125% with 0.25 %	0.1	0.1	0.1
0.125% with 0.5 %	0.1	0.1	0.05
0.25 % with 0.5 %	0.1	0.1	0.05
0 % with 0 %	0.1	0.1	0.1
0.125% with 0.125 %	0.1	0.1	0.1
0.25 % with 0.25 %	0.05	0.01	0.1
0.5 % with 0.5 %	0.01	0.01	0.1

These findings demonstrate that the side effect of betamethasone, measured by the area under the IOP/time curve may be alleviated by incorporation of phenylephrine hydrochloride in a solution containing Tylose as viscolizer and that the alleviation increases with solution viscosity.

In a non viscous solution or in a solution of a viscosity less than 4 cP, on the other hand, the

influences of phenylephrine hydrochloride is not only much less pronounced but is also statistically insignificant.

Duration of Side Effect.

The duration of side effect for the combination preparation in percent of that for the corresponding (of same viscosity) betamethasone preparation is presented in figure (4).

The figure depicts a relation of the duration parameter to viscosity very similar to that of the area parameter The duration parameter decreases with increasing viscosity of the ophthalmic solution. While phenylephrine hydrochloride does not influence the duration of side effect in an aqueous (non viscous) solution, it reduces the duration of the side effect by 30% in a solution of a viscosity of $\sim$ 5 cP and by 40% if the viscosity increases to $\sim$ 15 cP.

Statistical analysis of the data (table 4) reveals that phenylephrine hydrochloride does not reduce betamethasone side effect unless the viscosity of the ophthalmic solution exceeds $\sim$ 4cP ($D \simeq 0$ sec.$^{-1}$).

Statistical analysis of differences between the duration parameter for different viscosities reveals that these differences are significant only for the comparison between the non-viscous solution, on one hand,

and the solutions of viscosities greater than ~ 4 cP ($D \simeq 0$ sec.$^{-1}$), on the other hand (table 4).

The above mentioned findings demonstrate, thus, the incapability of phenylephrine hydrochloride to reduce the duration of betamethasone side effect in a non viscous vehicle or in a vehicle of a viscosity less than 4 cP. A prerequisite for the endorsement of the effect of phenylephrine hydrochloride on the duration of the side effect seems to be increasing the viscosity of the ophthalmic solution beyond a critical value (here ~ 4 cP).

Maximum Response

Figure (4) shows the maximum response for the combination preparations expressed as percent of the response of the corresponding (of same viscosity) betamethasone preparations.

It is obvious that the maximum response parameter tends to decreases with increasing viscosity of the ophthalmic solution after an initial increase in the viscosity range 2-4 cP. This decrease, however, seems to be less pronounced than that observed for the area or duration parameter. The maximum response parameter does not decrease more than 25% at a viscosity of ~ 16 cP.

Statistical analysis of the data (table 4) reveals that the differences between the combination preparations,

on one hand, and the corresponding (of same viscosity) betamethasone preparations, on the other hand, are consistently statistically insignificant. From this point of view, methylhydroxyethylcellulose would occupy a lower rank order compared to methylcellulose since the latter influences beneficially all of the three parameters considered.

The dependency of the maximum response parameter on the viscosity of the ophthalmic solution is found to be statistically significant ($P = 0.05$) only over the viscosity ranges $\sim 3 - 16$ and $\sim 5 - 16$ cP.

The findings presented above demonstrate thus that incorporation of phenylephrine hydrochloride into ophthalmic solutions of betamethasone does not reduce the side effect of the latter unless a viscolizer is added. In presence of methylhydroxyethylcellulose , suppression of the side effect takes place to a significant extent as soon as the viscosity of the solution exceeds ~ 4 cP($D \simeq 0$ sec.$^{-1}$).

Viscosities exceeding 4 cP do not only favour less side effects but also in the mean time more betamethasone anti-inflammatory effect.

Effect of Polyvinyl Alcohol.

The effect of PVA 14000 or PVA 72000 on the time-course of the intraocular pressure following the ophthalmic

application of combination preparations is presented in figures (5 and 6).

It is obvious that the time-course of the I O P is highly dependent on the presence or absence of PVA, on PVA concentration as well as on the molecular weight of PVA.

AUC.

The AUC for the combination preparations expressed in percent of the area for the corresponding (of same viscosity) betamethasone preparations is presented in Fig. 7 & 8 and table (5) as a function of the viscosity of the ophthalmic solution.

It is evident that the area parameter is highly dependent on the viscosity of the ophthalmic solution. It decreases to a marked extent with increasing viscosity. The effect is very pronounced at relatively low viscosities, viz. around 4 cP. At such a viscosity the AUC is reduced to reach values ~ 35% and ~ 15% that for the corresponding betamethasone preparations, in the case of PVA 14000 and PVA72000, respectively.

In the case of the aqueous solution, containing no viscolizer, the AUC for the combination preparations is reduced to a minimal extent to reach values ~ 90% that for the corresponding betamethasone solution.

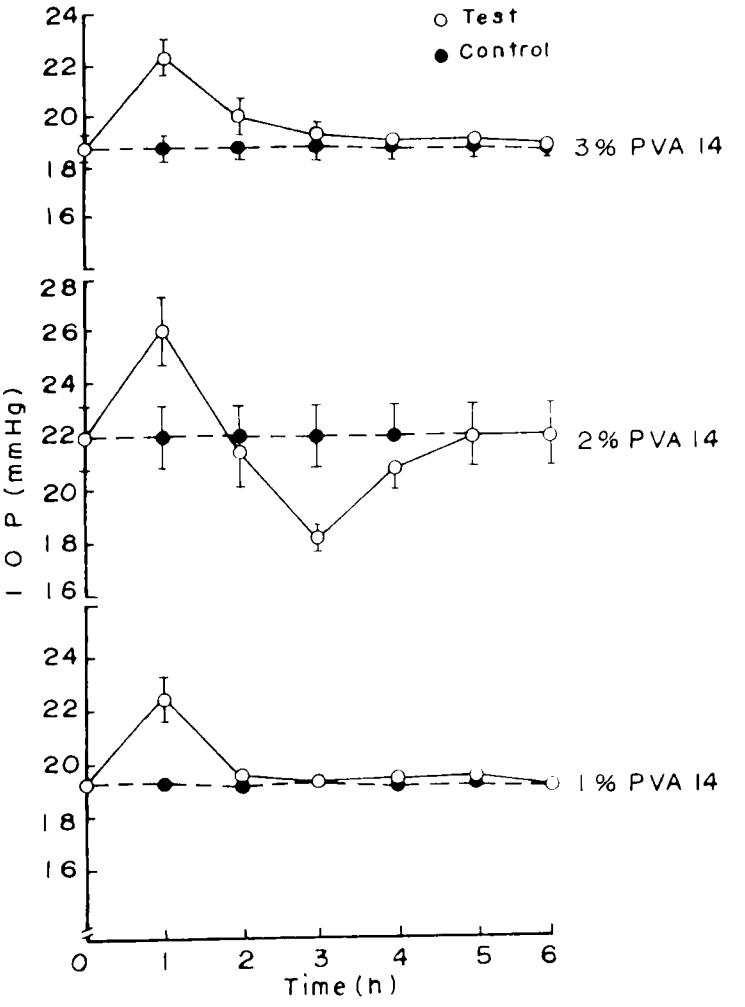


Fig.(5): Intraocular Pressure (in mmHg) Post-Instillation of Ophthalmic Solutions of Betamethasone and Phenylephrine Hydrochloride Containing Polyvinyl Alcohol 14000 (PVA14).

Statistical analysis of the data, reveal that the differences between the combination preparations and the corresponding (of same viscosity) betamethasone preparations are statistically significant only if the viscosity of the ophthalmic solution exceeds 3 cP.

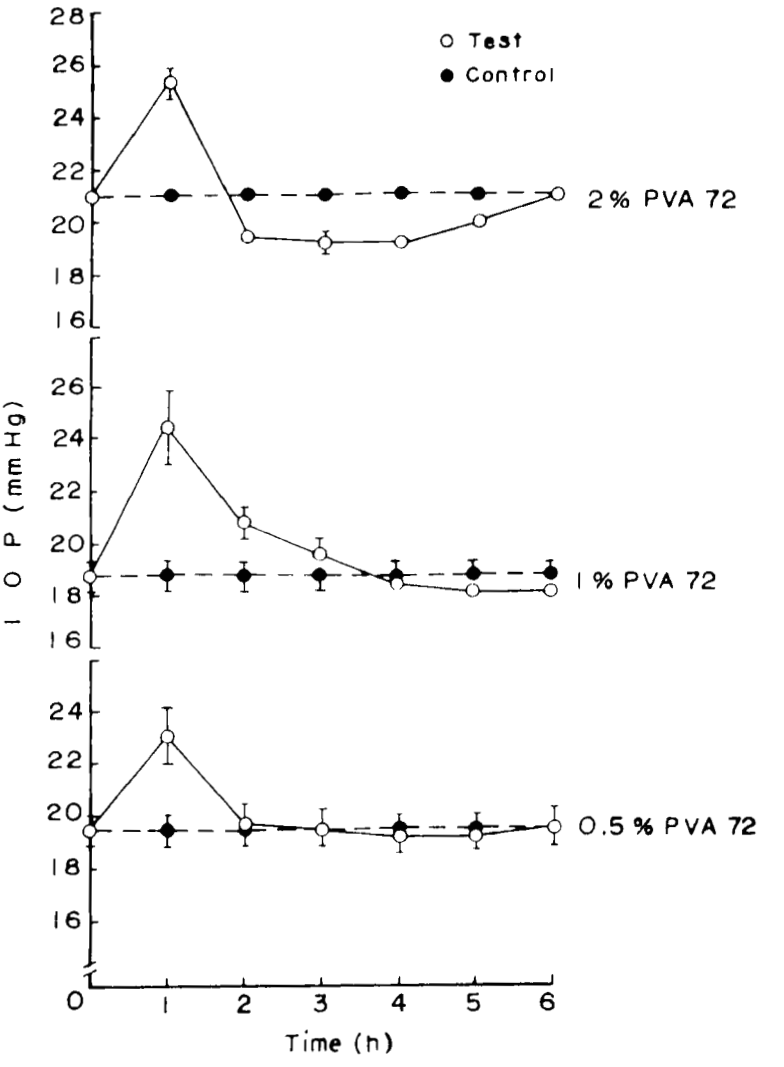
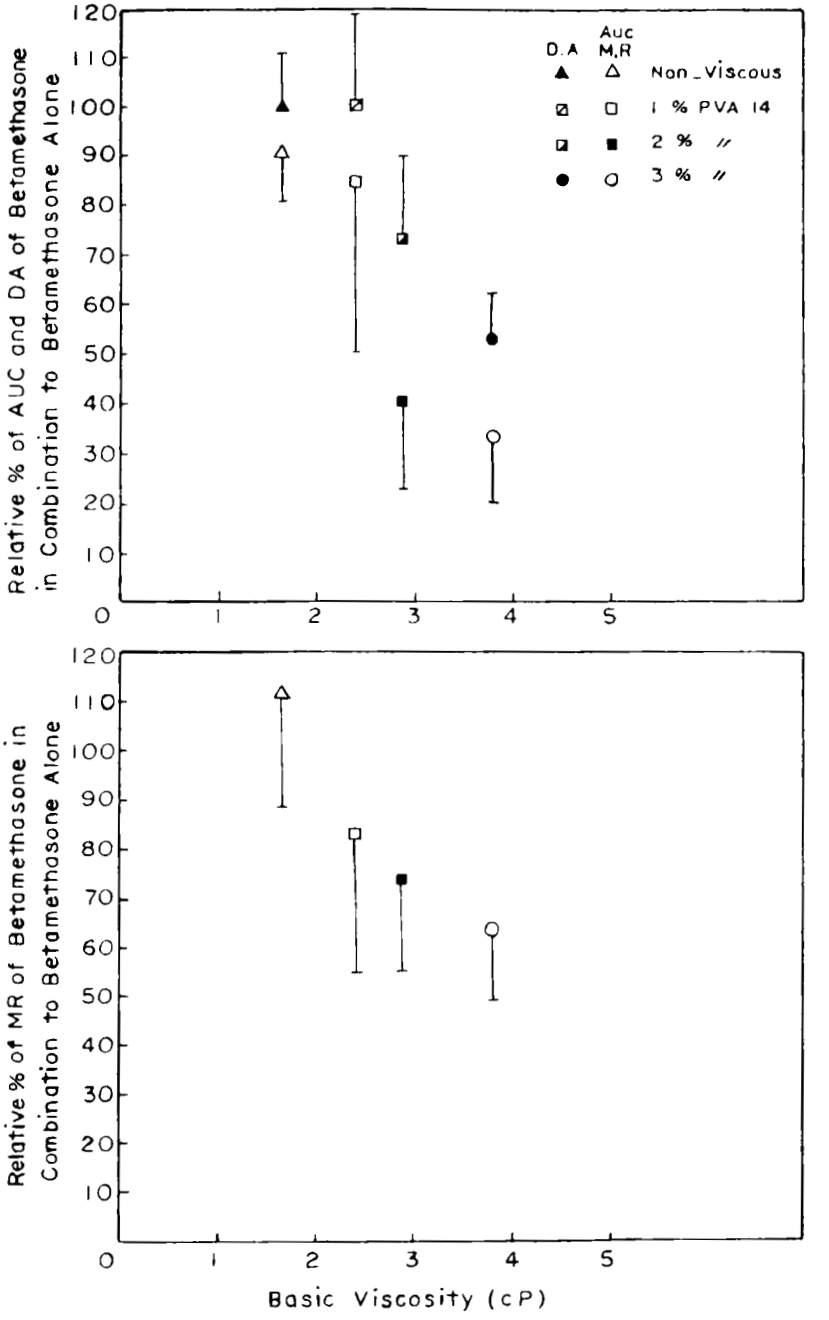


Fig.(6): Intraocular Pressure (in mmHg) Post-Instillation of Ophthalmic Solutions of Betamethasone and Phenylephrine Hydrochloride Containing Polyvinyl Alcohol(PVA 72).

Below this value the combination preparations do not differ from the corresponding betamethasone preparations to any significant extent.

Statistical analysis of differences between the values of the area parameter for different viscosities



Fig(7): Influence of Viscosity of Ophthalmic Solutions Containing Polyvinyl Alcohol 14000 (PVA14) on the Counter Effect of Phenyleprhine-HCl with Regard to the Relative % of AUC, DA and MR.

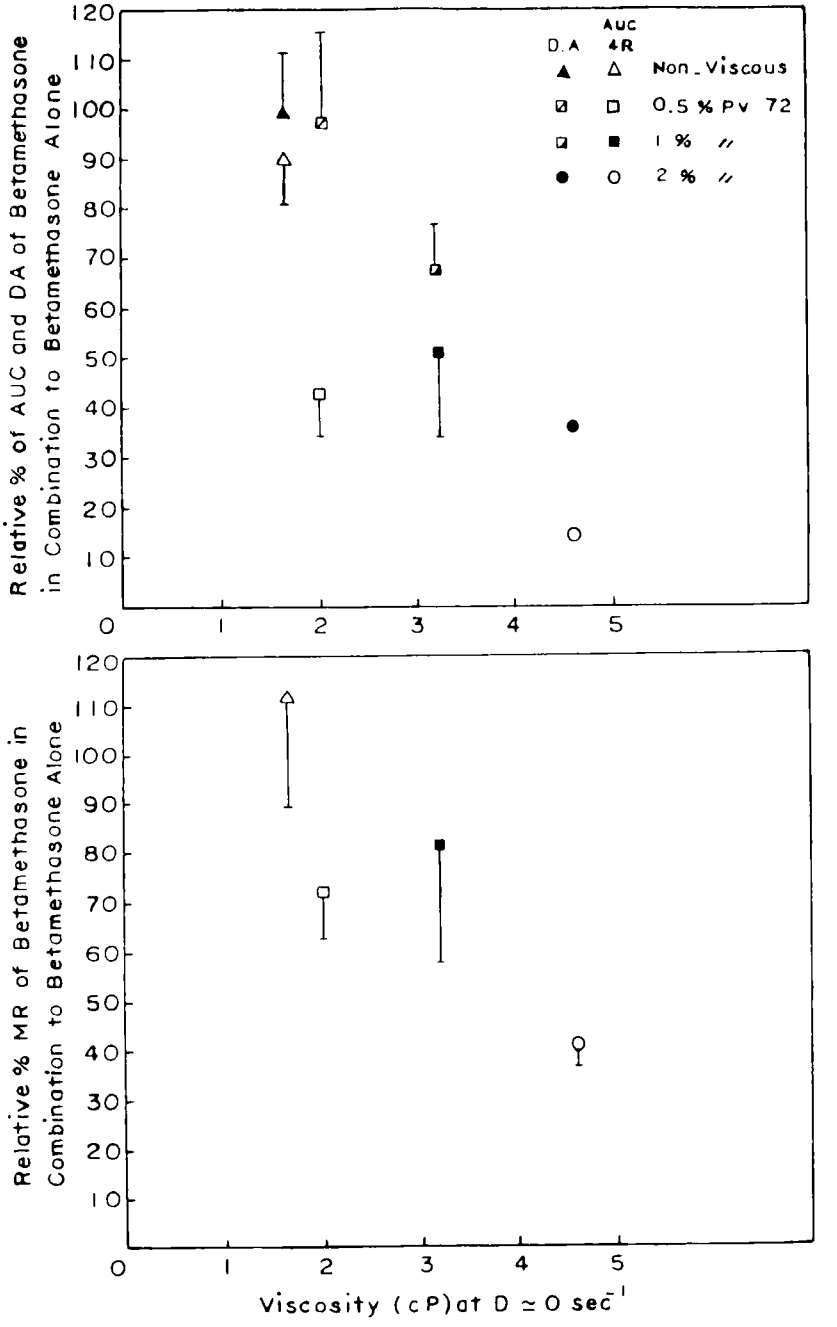


Fig.(8): Influence of Viscosity of Ophthalmic Solutions Containing PVA72 on the Counter Effect of Phenylephrine-HCl with Regard to the Relative to of AUC, DA and MR.

Table (5): Correlation of AUC, DA and MR to Viscosity of Ophthalmic Solutions of Betamethasone and Phenylephrine Hydrochloride Containing Polyvinyl Alcohol 14000 and 72000

Concentration	Viscosity (cP)	Parameters of Activity		
		AUC (mm Hg.h)	DA (h)	MR (mm Hg)
PVA 14000				
0%	1.67	90.5 (9)*	100 (11.2)*	112.4 (23.5)*
1%	2.39	84.92(34.8)	100 (18.2)	82.91(29)
2%	2.86	39.93(17.2)	73.5 (16.95)	74.18(19.1)
3%	3.82	33.49(13.06)	52.83 (10)	63.49(14.3)
PVA72000				
0%	1.67	90.5 (9)	100 (11.2)	112.4 (23.5)
0.5%	2.00	43.76(9.07)	97.67 (18.18)	72.24 (9.39)
1 %	3.20	50.34(16.8)	67.49 (9.6)	81.23 (23.17)
2 %	4.62	14.16(1.49)	35.78 (1.09)	40.93 (3.98)

reveals, in the case of PVA 72000, that the observed differences are significant (P = 0.05 - 0.01) throughout the viscosity range investigated with the exception of the range ~ 2-3 cP.

In the case of PVA 14000, however, the differences observed are statistically significant only throughout the viscosity range ~ 1.5 - 3 and ~ 1.5 - 5 cP.

The above mentioned findings, thus, demonstrate the capability of PVA, specially the higher molecular weight

grade, in effectively reducing the area under the intraocular pressure/time curve for combination preparations of phenylephrine hydrochloride and betamethasone. This effect reveals itself already at viscosities as low as ~4 cP.

Duration of Side Effect.

Figures (7 & 8) reveal that the duration of side effect for the combination preparation-expressed in percent of that for the corresponding betamethasone preparation - is highly dependent on the viscosity of the ophthalmic solution. Increased viscosity is found to favour minimization of the duration of the side effect of betamethasone. This is evident both for PVA 14000 and PVA72000, the phenomenon being more marked for the latter polymer.

At viscosities around 4 cP the duration of side effect for the combination preparation reaches ~ 55 and ~35% that of the corresponding betamethasone preparations in presence of PVA 14000 and PVA 72000, respectively .

Statistical analysis of the data, reveals that the differences between the combination preparations , on one hand, and the corresponding (of same viscosity) betamethasone preparations, on the other hand,

are very highly to highly significant as soon as the viscosity reaches values around 4 cP, both for PVA14000 and PVA 72000.

The dependency of the duration parameter on solution viscosity seems to be more statistically significant in the case of PVA 72000 compared to the lower molecular weight polymer (PVA 14000).

The above mentioned findings demonstrate that PVA is a viscolizer which can effectively reduce the duration of betamethasone side effect in its combination preparation with phenylephrine hydrochloride.

Maximum Response

Figures (7 & 8) depict the dependency of the maximum response to the combination preparation-expressed in percent of that for the corresponding betamethasone preparation on the viscosity of the ophthalmic solution.

For both PVA 14000 and PVA 72000 there is a trend of lowering of MR parameter with increased viscosity. This phenomenon is more pronounced for solutions containing PVA 72000. At a viscosity of around 4 cP, this polymer reduces the maximum response for the combination preparation to a value about 40% that for the corresponding betamethasone preparation.

Statistical analysis of the data, reveals that all the differences observed for solutions con-

taining PVA 14000 are insignificant. For PVA 72000, on the other hand, the differences between the combination preparation and the corresponding betamethasone preparation are significant ($P = 0.001$) only if the viscosity reaches values around 4 cP.

For PVA 72000, the dependency of the MR parameter on the solution viscosity is statistically significant only throughout the ranges ~ 1.5 - 4.5 and ~ 2-4.5 cP.

The results presented above point to that PVA is a viscolizer which is very effective in reducing the side effect of betamethasone in its combination preparation with phenylephrine hydrochloride. The effect of PVA is optical at a viscosity around 4 cP. and seems to be more pronounced and significant for PVA 72000. These conditions are not only opitmal from the view point of minimizing the side effect of betamethasone but also from the view point of potentiating its effect.

From the results obtained it can be concluded that: Increasing the viscosity of the system seems to enhance the counter effect of phenylephrine hydrochloride. This effect is so marked to the extent that one may reduce the side effect of betamethasone, by about 70% , simply by the proper "adjustment" of viscosity.

The benificial effect of increasing the viscosity with regard to minimzation of betamethasone side effect - in terms of AUC - seems to be limited to a very narrow and low viscosity range, viz up to about 10 cP at maximum ($D \simeq 0\ sec^{-1}$).

Polymer specificity or polymer to polymer variability seems to overlap with the effect to viscosity.

These findings agree with those reported by Kassem et al.[12], Adler et al.[13] and Saettone et al.[8] who reported the superiority of PVA to hydroxypropylcellulose and PVP.

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