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EFFECT OF PHENYLEPHRINE HYDROCHLORIDE ON BETAMETHASONE SIDE EFFECT IN RELATION TO VISCOSITY OF OPHTHALMIC PREPARATIONS
II - GEL-STATE

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ABSTRACT

Combination preparations of betamethasone and phenylephrine hydrochloride were prepared in the form of ophthalmic gels based on polyethylene glycols, PEG, a carboxyvinyl polymer (carbomer 934)or methylcellulose. The intraocular pressure, IOP, was followed after the application of these gels to the rabbit eye. Three parameters have been utilized to assess the performance of combination preparations of the two drugs. These are the area under the curve, AUC, the maximum response, MR, and the duration of side effect (increased the IOP). It was found that the inclusion of phenylephrine hydrochloride in the gel reduces, to marked extent, viz. 80-90%, the AUC compared to the corresponding gel devoid of phenylephrine hydrochloride, and that ~ 60% reduction in the duration of betamethasone side effect with regard to the IOP. The most effective gel system appeared to be methylcellulose based gel.

INTRODUCTION

A rise in the ocular tension is marked with the antiinflammatory drug betamethasone.[1] α-Sympathomimetic drug (such as phenylephrine hydrochloride was used to lower the intraocular pressure (IOP)[2,3].

A study[4] attributed the increased response to homatropine in presence of methylcellulose,1%,to the increased contact time with the eye implied by the viscous nature of the vehicle.

Another study[5] came to a general conclusion that with both methylcellulose and PVA, the optimum viscosity of the solution would be in the range of 12-15 cp. Further increase in viscosity above this level did not appear to give proportional increase in drug levels. It was also proved[6,7] that the addition of suitable polymers to liquid collyria prolongs the contact time of the drug (pilocarpine) and hence increase drug bioavailability.

Other authors[8] demonstrated, in the eye of rabbit, that adrenaline bitartrate produced greater mydriasis and lowering of IOP in a hydrogel base (carbopol 934 or poloxamer 407) when compared to a similarly dosed simple aqueous solutions of the drug.

The aim of this work was to complete the study concerning the effect of viscolizers on the action of phenylephrine

hydrochloride on counteracting the side effect of betamethasone (elevation in the IOP). This part dealt with the effect of the gel state. The gels were based on methylcellulose, MC, carboxyvinyl polymer (carbomer 934) and polyethylene glycol (PEG I and PEG II). Measurements of viscosity of the preparations and IOP of the rabbit's eye were carried out. General discussion of the influence of viscolizers on the counter effect of phenylephrine hydrochloride in both solutions and gels was carried out.

EXPERIMENTAL

Materials

Betamethasone (Schering), phenylephrine hydrochloride (Siegfried), carboxyvinyl polymer (carbomer, 934, B.F. Goodrich Chemical Co.), methylcellulose 450 (BDH), polyethylene glycols 300, 400, 600, 1500 , 2000 and 4000. All of pharmaceutical grade.

Methods

Preparation of ophthalmic gels, measurement of IOP, investigation of rheology: all were carried out as previously described[9].

The gels were based on 5% w/v methylcellulose, MC, 2% w/v carbomer 934 and polyethylene glycols (PEGI and PEG II).

The composition of PEG I was : PEG 300, PEG 1500 and isotonic phosphate buffer in the ratio 9:9:2.

The composition of PEG II was : PEG 400 (52,11% , PEG 600 (18.54%), PEG 1500 (9%), PEG 2000(6.66%) and PEG 4000 (3.69%)[10]. The concentration of betamethasone was 0.05% w/w while that of phenylephrine hydrochloride was 2.5% w/w.

RESULTS

Three parameters have been utilized to assess the performance of combination preparations of betamethasone and phenylephrine hydrochloride. These are AUC, MR and duration of side effect, DA . The above mentioned parameters are those-found in the light of the foregowing investigations most indicative of drug effect for the individual drug. The combination preparations contained the two drugs in the same concentrations as those used for the individual drugs.

Combination preparations of betamethasone and phenylephrine hydrochloride were prepared in the form of ophthalmic gels based on PEG, a carboxyvinyl polymer (Carbomer 934) or methylcellulose.

The intraocular pressure was followed after the application of these gels to the rabbit eye. The time-course of the IOP is presented in figure (1)

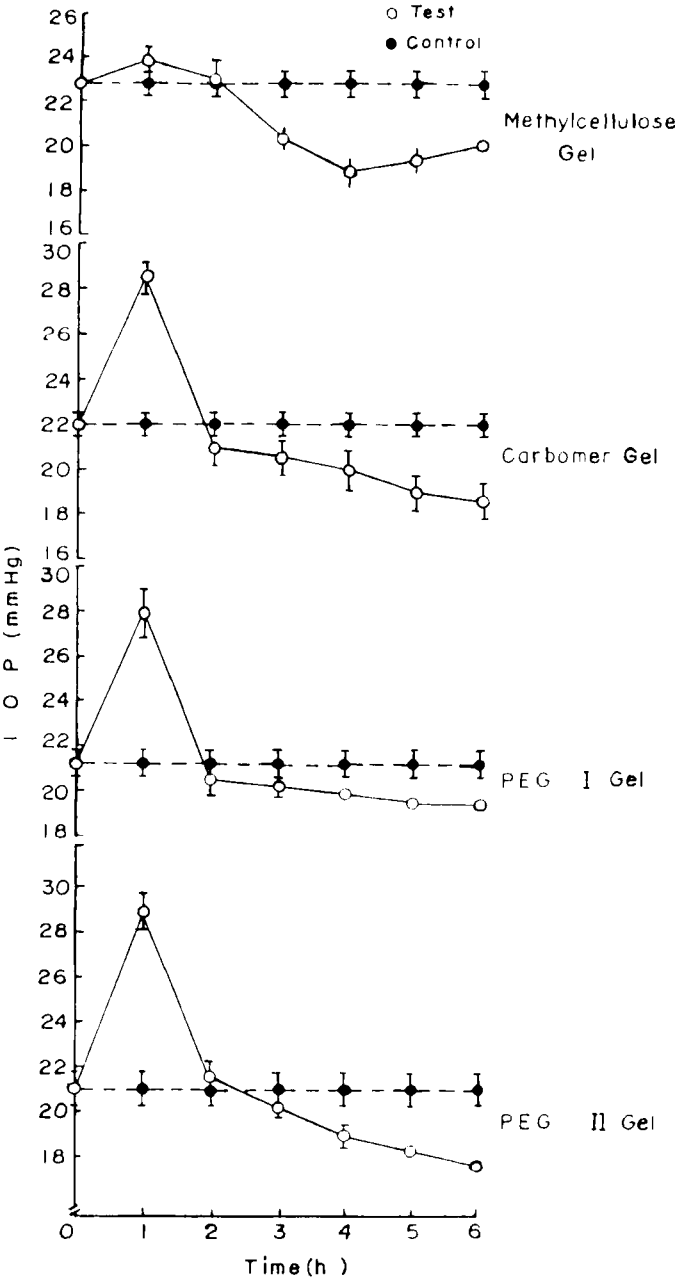

Fig. (1): Intraocular Pressure (in mmHg) Post-Installation of Ophthalmic Gels of Betamethasone and Phenylephrine Hydrochloride.

It is obvious that all gels investigated influence, to a great extent, the IOP time profile.

AUC

Figure (2) and table (1) present the area under the IOP time curve for the four gels investigated in percent of that for the corresponding gels containing betamethasone only.

It is obvious that the inclusion of phenylephrine hydrochloride in the gel reduces, to a marked extent, viz. 80 - 90%, the AUC compared to the corresponding gel devoid of phenylephrine hydrochloride. The AUC parameter is almost independent on the viscosity of the ophthalmic gel over a very wide range extending from ~ 10 - 180 P (D ≈ 0 sec^{-1}.).

Statistical analysis of the data (table 2) reveals that the differences between gels containing the two drugs and the corresponding ones containing only betamethasone are very highly significant.

Differences between the gels containing the two drugs are found to be statisttically insignificant except for methylcellulose and polyethylene glycol gels.

Duration of Side Effect .

Figure (2) demonstrates the duration of betamethasone side effect for the gels containing the two drugs, expressed

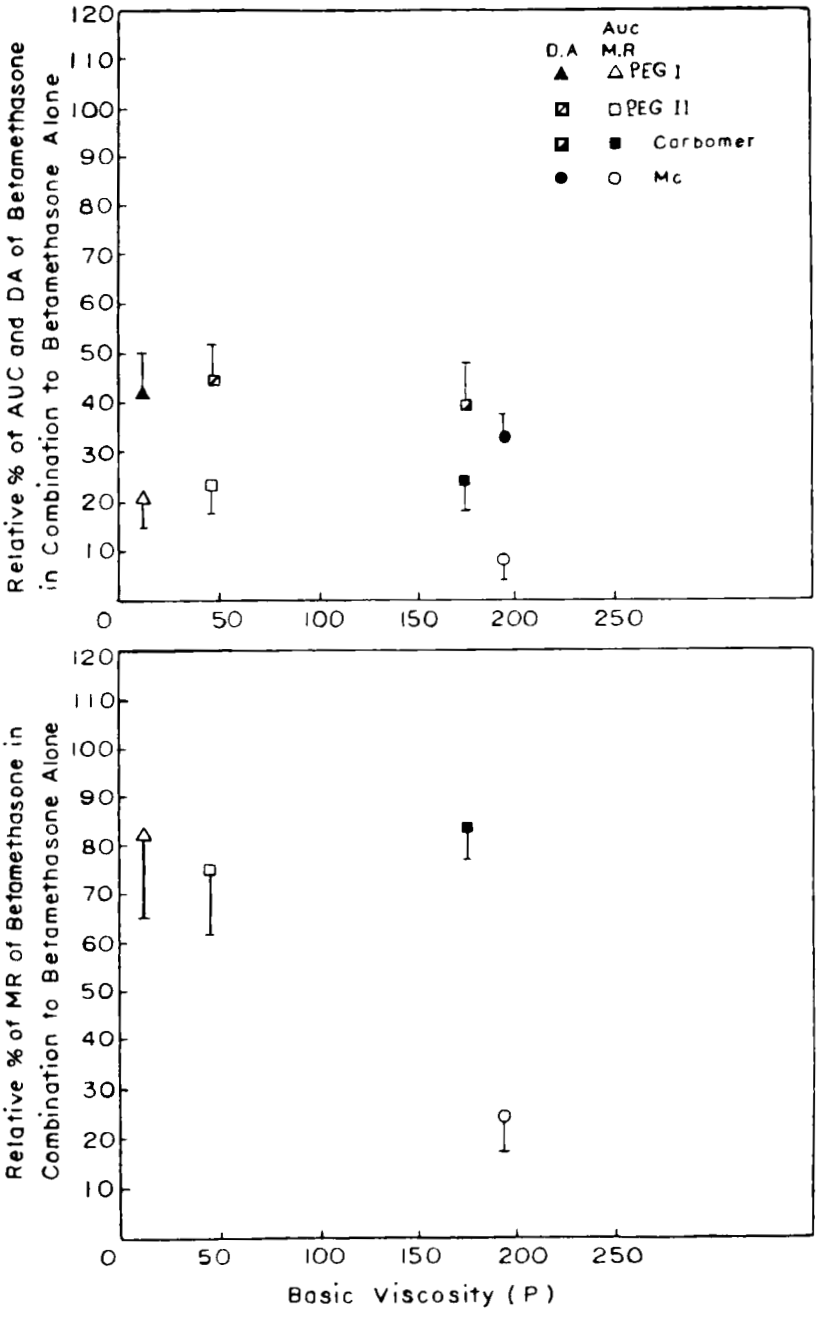

Fig. (2): Influence of Viscosity of Ophthalmic Gels on the Counter Effect of Phenylephrine HCL with Regard to the Relative % of AUC, DA, and MR.

Table (I) : Correlation of AUC, DA and MR to the Viscosity of Ophthalmic Gels of Betamethasone and Phenylephrine Hydrochloride.

Gel Type	Viscosity at D≈0 sec.$^{-1}$ (P)	Parameters of Activity		
		AUC (mm Hg.h)	DA (h)	MR (mm Hg)
Methylcellulose(MC)	193.80	8.19 (3.18)*	33.00 (3.65)*	23.08 (7.45)*
Carbomer	175.40	24.24 (5.94)	38.80 (8.92)	83.01 (6.39)
PEG Base (I)	14.04	21.20 (6.18)	42.00 (7.56)	82.43 (17.2)
PEG Base (II)	40.32	23.10 (5.43)	44.33 (6.36)	74.62 (12.9)

in percent of the duration of side effect for the corresponding gel containing betamethasone.

It is evident that the dependency of the duration of side effect on gel viscosity is the same as that observed for the AUC parameter. Here also the duration of side effect for the combination preparation - in percent of that for the corresponding betamethasone preparation - is independent on gel viscosity over the range of ~10 -~ 180 P.

It is also obvious that incorporation of phenylephrine hydrochloride with betamethasone in a gel system reduces effectively (~ 60%) the duration of betamethasond side effect with regard to the intraocular pressure.

Statistical analysis of the data (table 2) reveals that incorporation of phenylephrine hydrochloride into the gel brings about a very highly significant difference. Differences between the individual gels containing both drugs are statistically insignificant.

Maximum Response.

The maximum response to the combination preparation- expressed in percent of that for the corresponding beta-methasone preparation - is presented for the different gels in figure (2).

Also here, the maximum response parameter is independent on the viscosity of the gel over the range ~10 - ~ 180 P.

The duration in the MR to betamethasone in a gel system as a result of incorporation of phenylephrine hydrochloride seems to be rather limited (~ 20%) except for methylcellulose gel where the reduction approaches ~ 75%.

Statistical analysis of the data (table 2) reveals that the effect of phenylephrine hydrochloride is significant (P = 0.001) only in methylcellulose gel.

Comparison between the different gels containing the two drugs reveals that methylcellulose gel is the only one which shows significant (P = 0.01 - 0.001) differences to the other gels.

Table ([2]): Significance Level (Value of P) of Differences Between Ophthalmic Gels of Betamethasone and Phenylephrine Hydrochloride.

Pairs of Comparison	Parameters of Activity		
	AUC (mm Hg.h)	DA (h)	MR (mm Hg)
MC with Carbomer	0.05	0.1	0.001
MC with PEG (I)	0.1	0.1	0.01
MC with PEG(II)	0.05	0.1	0.01
Carbomer with PEG(I)	0.1	0.1	0.1
Carbomer with PEG (II)	0.1	0.1	0.1
PEG (I) with PEG (II)	0.1	0.1	0.1
MC with MC	0.001	0.001	0.001
Carbomer with Carbomer	0.001	0.001	0.1
PEG (I) with PEG (I)	0.001	0.001	0.1
PEG (II) with PEG (II)	0.001	0.001	0.1

* The figures between parenthesis represent the standard error.

The findings reported above would point to that gel systems favour, to a marked extent, the suppression of the side effect of betamethasone by phenylephrine hydrochloride. The effect of the gel seems to be almost independent on gel-viscosity over a rather wide range (~ 10 - ~ 180 P ; D ≈ 0 sec^{-1}). The most effective gel system appears to be methylcellulose based gel of a viscosity around 200 P (D ≈ 0 sec^{-1}).

On the basis of data presented in the tables and figures it would be obvious that the gel systems markedly reduce

the side effect and enhance the effect itself to a less marked extent. This may present a point of difference between the investigated gels and the ophthalmic solutions containing a viscolizer. In the latter systems it was possible to come to situations involving reduction of side effect and in the mean time enhancement of drug effect to different extents depending on viscosity of ophthalmic solution and type of polymer used. This would provide an effective means in the proper design of ophthalmic preparations addressing not only drug effect but also drug side effect.

The data obtained with the gel systems are also in line with the hypothesis-advanced under the ophthalmic solution - that a low release rate constant is essential for phenylephrine hydrochloride to counteract the side effect of betamethasone. The gel state represents a situation very similar to ophthalmic solutions with viscosities higher than 4 cP with regard to the values of the release rate constants of the two drugs[11], both values being in their low level.

DISCUSSION OF INFLUENCE OF VISCOLIZERS ON THE COUNTER EFFECT OF PHENYLEPHRINE HYDROCHLORIDE.

AUC for the Side Effect in Relation to Viscosity.

Figure (3) depicts the dependency of the influence of phenylephrine hydrochloride on the AUC for combination

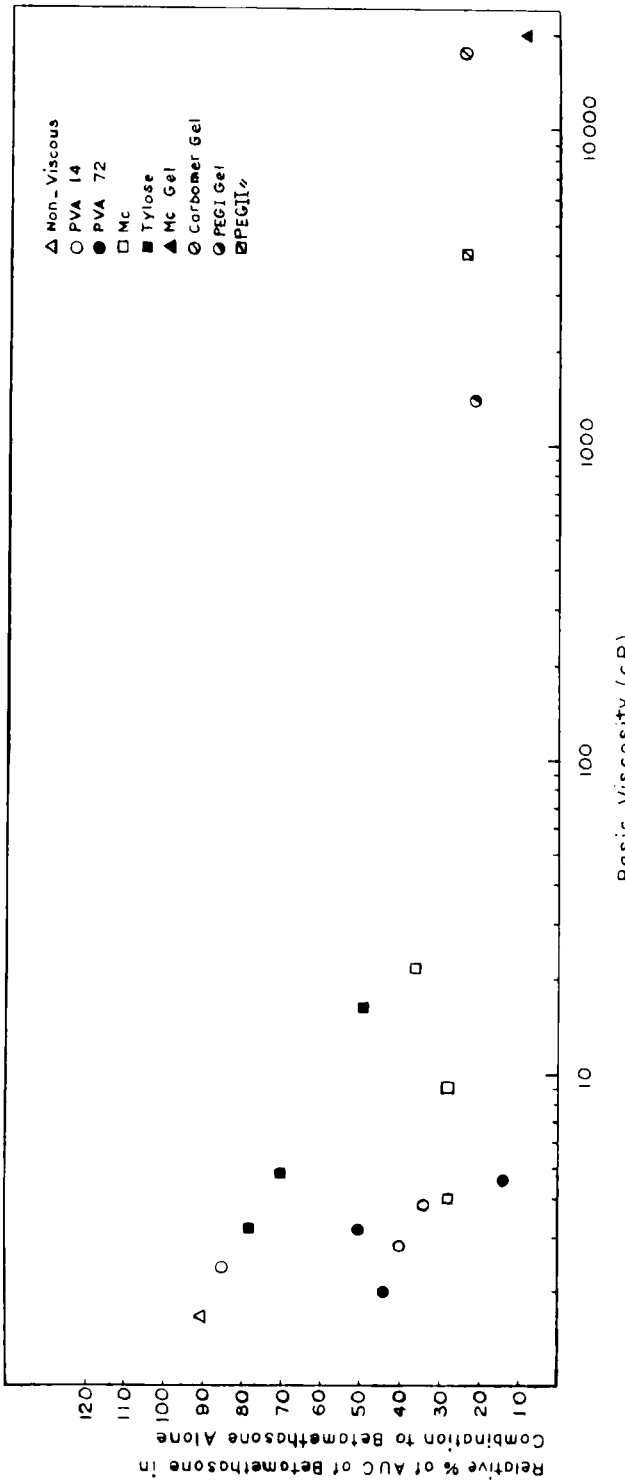

FIG. 3: Influence of Viscosity of Ophthalmic Preparations on the Counter Effect of Phenylephrine-HCL in Combination Preparations with Regard to the AUC.

preparations - expressed in percent of that for the corresponding betamethasone preparation - on the viscosity of the preparations. The figure, thus, integrates not only different polymers but also different ophthalmic preparations viz. liquids and gels.

The following phenomena may be deduced from the figure :

a) 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.

b) The benificial effect of increasing the viscosity with regard to minimization 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 ($D \simeq 0\ sec^{-1}$.).

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

d) Extreme increase in the viscosity of the ophthalmic solutions to reach a gel state do not bring about any marked advantage with regard to minimization of betamethasone side effect or, in other words, maximization of phenylephrine hydrochloride counter effect.

Gels of viscosities in the order of 10^3- 10^4 cP do not greatly differ from solutions of viscosities around 10 cP. This shows that a 1000-10000-fold increase in viscosity do not bring about any further advantage.

e) In the gel state, the counter effect of phenylephrine hydrochloride seems to be almost independent on the viscosity.

Duration of Side Effect in Relation to Viscosity.

Figure (4) demonstrates the dependency of the duration of side effect for combination preparations - expressed in percent of that for the corresponding betamethasone preparations on viscosity. The figure integrates different polymers as well as liquid preparations and gels.

The similarity between this figure and the previous one is rather striking. Both figures demonstrate the great potential of "adjusted" viscosity in enhancing the counter effect of phenylephrine hydrohcloride with regard to the side effect of betamethasone.

The following conclusions may be derived from the figure :

a) While the counter effect of phenylephrine hydrochloride is negligible in a purely aqueous solution of phenylephrine hydrochloride and betamethasone, it

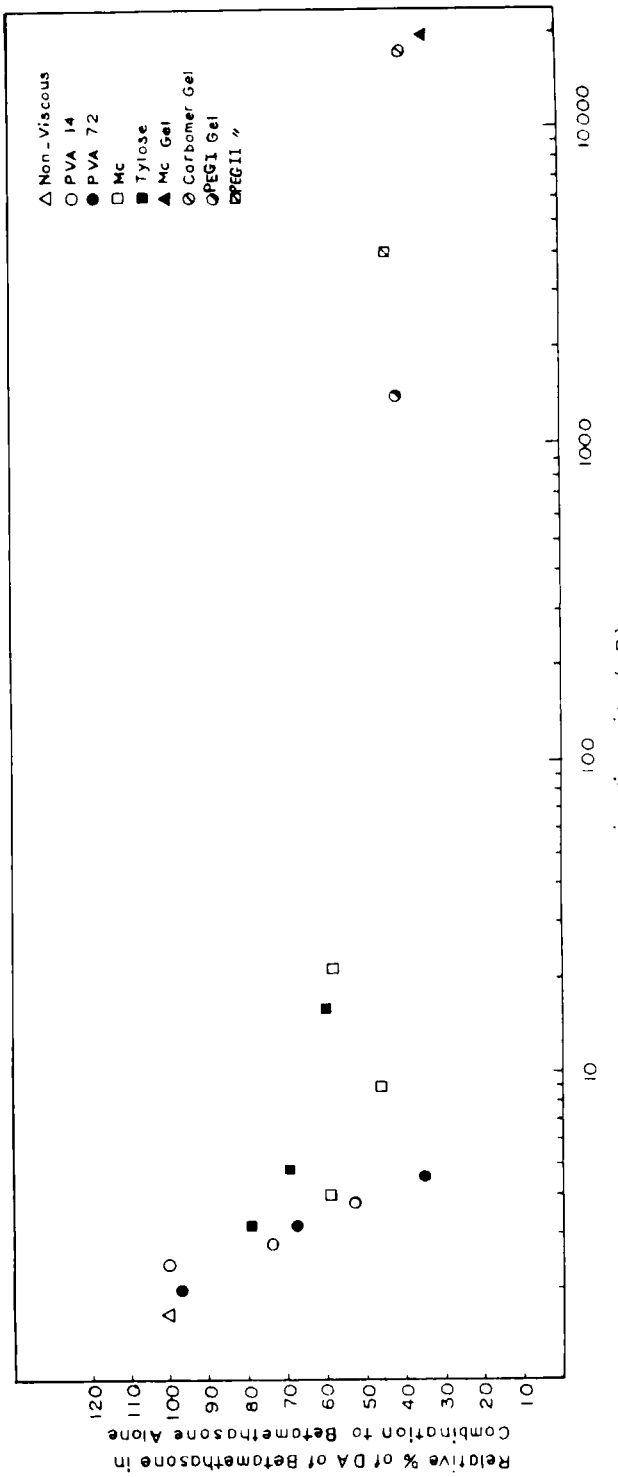

FIG. 4: Influence of Viscosity of Ophthalmic Preparations on the Counter Effect of Phenylephrine-HCL in Combination Preparations with Regard to the DM.

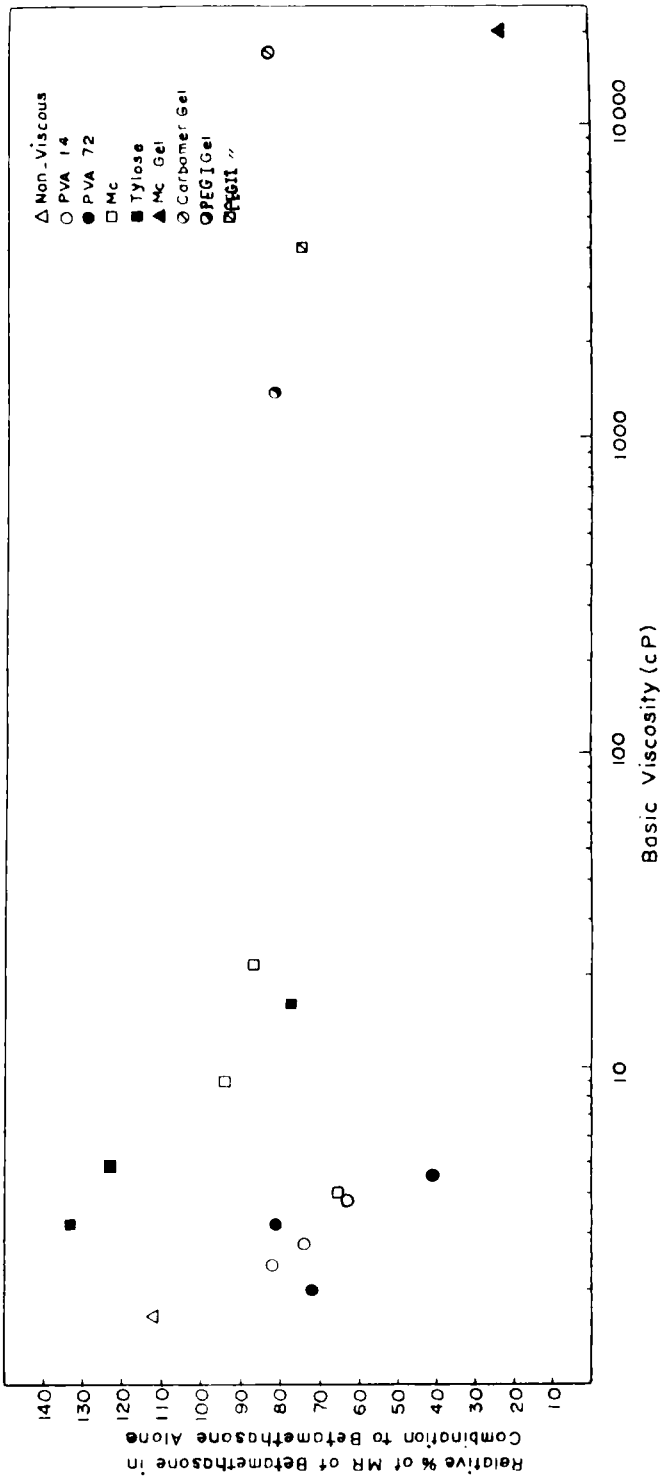

FIG. 5: Influence of Viscosity of Ophthalmic Preparations on the Counter Effect of Phenylephrine-HCL in Combination Preparations with Regard to the MR.

becomes increasingly marked if the viscosity is increased by small increments. Under appropriate conditions, the duration of side effect may be reduced by about 60%.

b) The dependency of the duration of side effect is pronounced in the viscosity range up to ~ 5cP ($D \simeq 0$ sec^{-1})

c) In the viscosity range up to ~ 5 cP, the viscosity of the system dictates its performance. In other words the overlap of polymer specificity with solution viscosity is much less pronounced than that observed for the area parameter.

d) Beyond the viscosity range up to ~ 5 cP and reaching to values as high as 10^3 or 10^4 cP, the duration of side effect is almost independent on the viscosity of the system. Gels do not differ to any makred extent from ophthalmic solutions of low viscosities.

e) The counter effect of phenylephrine hydrochloride with regard to betamethasone side effect seems to be independent on the viscosity of the system in the gel state.

Intensity of Side Effect in Relation to Viscosity.

Figure (5) integrates different polymers and different ophthalmic systems (liquids and gels) with regard to the effect of viscosity on the intensity of

side effect for a combination of betamethasone and phenylephrine hydrochloride (expressed in percent of that for the corresponding preparation containing only betamethasone).

It is evident that the intensity of betamethasone side effect is not alleviated by phenylephrine hydrochloride unless a viscolizer is added. The intensity of the side effect decreases with increasing viscosity; it may be reduced by about 40% if the viscosity is properly adjusted. This dependency is pronounced only in the viscosity range up to ~ 5 or 10 cP. Beyond this range the dependency on viscosity is minimal to the extent that gels of viscosities of 10^3 - 10^4 cP do not greatly differ from solutions of a viscosity of ~ 5 or 10 cP.

The overlap of viscosity and polymer specificity is, however, here very apparent.

The vinyl alcohol based polymers seem to be distinguished by their efficacy in maximizing the counter effect of phenylephrine hydrochloride. This observation is also valid for the other two parameters; viz. the AUC and the duration of side effect.

Summarizing, one may conclude the following :

a) The present results provide evidence that the viscosity of the ophthalmic preparations is a tangible factor which influences therapeutic drug/drug interactions.

b) The viscosity of the ophthalmic preparations seems to be a factor of great potential in minimizing the side effect of a drug by another one.

c) The specific examples investigated demonstrate that this factor is displayed only throughout a very narrow and low viscosity range extending up to about 5 or 10 cP ($D \doteq 0$ $sec.^{-1}$). Further increase of viscosity over up to 4 orders of magnitude to reach the gel-state is of minimal effect.

d) Polymer specificity seems to overlap with the viscosity factor for some parameters, viz. AUC and maximum response. For other parameters, viz. duration of side effect, there is almost no overlap.

e) Of the polymers investigated, polyvinyl alchol (72000 & 14000) seems to be the most powerful one in controlling the side effect of betamethasone.

f) The counter effect of a drug on the side effect of another one incorporated in the same ophthalmic preparation seems to be highly dependent on the viscosity of the preparation. In the combination of phenylephrine hydrochloride and betamethasone it was possible to reduce the side effect of betamethasone with regard to the intraocular pressure in terms of AUC by about 70%, in terms of duration of side effect by about 60% and

in terms of intensity of side effect by about 40%. This was effected by simple "adjustment" of the viscosity of the ophthalmic preparation.

g) Gels do not offer any advantage over liquid preparations of viscosities around 5 or 10 cP with regard to potentiation of the counter effect of phenylephrine hydrochloride. Hence, the use of gels to meet situations where a counter effect is indicated seems to be unjustified.

h) The data presented spot light a new dimension for the role that the viscosity of an ophthalmic preparation may play with regard to controlling drug side effect by drug combination. This new dimension worths further exploration on other drug examples, so that one may be able to come to general conclusions.

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