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Comparison of the blanching activities of Dermovate, Betnovate and Eumovate creams and ointments

E. Meyer, A.D. Magnus, J.M. Haigh and I. Kanfer

School of Pharmaceutical Sciences, Rhodes University, Grahamstown (South Africa)

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Summary

The human skin blanching assay was used to determine the blanching activities of Dermovate, Betnovate and Eumovate creams and ointments. Dermovate was found to elicit a superior blanching response to Betnovate which in turn elicited a superior blanching response to Eumovate, except in the comparison of Betnovate and Eumovate ointments under occlusion. The importance of employing the correct methodology of the blanching assay is emphasized and the good correlation between the results of this study and clinical trials is indicated.

Introduction

The human skin blanching assay has been used since 1962 (McKenzie and Stoughton) as a reliable method of assessing topical corticosteroid activity. The aim of this study was to investigate the blanching activities of 6 commercially available formulations and to compare their blanching activities to the results of reported clinical trials. The corticosteroid preparations used were Dermovate cream and ointment (0.05% clobetasol 17-propionate), Betnovate cream and ointment (0.1% betamethasone 17-valerate) and Eumovate cream and ointment (0.05% clobetasone 17-butyrate), manufactured by Glaxo (Pty.) Ltd., South Africa. These corticosteroids have been shown to be effective anti-inflammatory agents (Corbett, 1976; Allenby and Sparkes, 1981) and to elicit a blanching response in human skin (Barry and Woodford, 1974; Gibson et al., 1983). Dermovate, Betnovate and Eumovate formulations have been classified in the United Kingdom Monthly Index of Medical Specialities as very potent, potent and moderately potent, respectively.

Materials and Methods

Two trials were mounted for this study, one for the creams and one for the ointments. All the formulations were purchased shortly before use from a local pharmacy. A total of 12 healthy male and female subjects were selected for each trial from a panel of volunteers known to show a skin blanching response to a standard preparation (Betnovate cream). The volunteers had not received topical or systemic corticosteroids for at least 6 weeks prior to the investigation. The formulations were applied to the forearms of the volunteers as

Correspondence: J.M. Haigh, School of Pharmaceutical Sciences, Rhodes University, Grahamstown, 6140 South Africa.

previously reported (Haigh and Kanfer, 1984). One arm of each volunteer was occluded with non-porous plastic tape while the sites on the other arm were left unoccluded. The formulations were removed from both forearms after 6 h. Assessment of the blanching response was made independently by three experienced observers at 7, 8, 9, 10, 12, 14, 16, 18, 28, 32, 52 and 56 h after application using a 0–4 scale where 0 = normal skin and 4 = intense blanching (Meyer et al., 1981). The percentage of the total possible score (%TPS) was calculated (Haigh and Kanfer, 1984) and plotted against time in h after application to produce blanching profiles. The trapezoidal rule was used to calculate the area under the blanching curve (AUC) values. Analyses (χ^2) were performed on the graded responses of the formulations being compared and on direct comparisons between application sites (Poulsen et al., 1974). Statistical analyses were performed at the 95% level of significance.

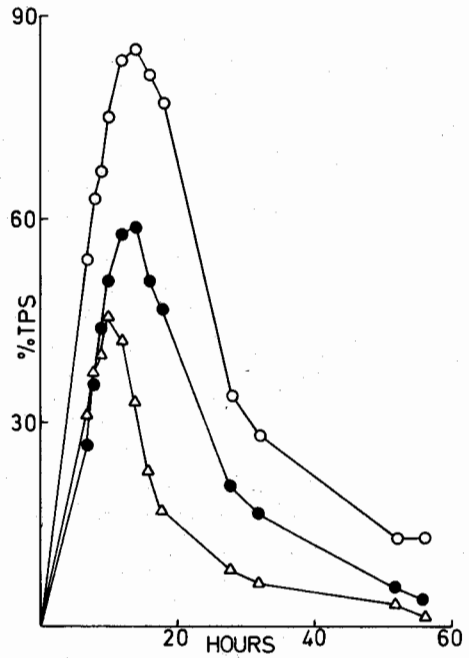

Fig. 1. Blanching profiles of occluded ointments. ○, Dermovate; ●, Betnovate; △, Eumovate.

Results and Discussion

The AUC values for the creams and ointments in both modes of application are shown in Table 1. Figs. 1 and 2 represent the blanching profiles of the ointments in the occluded and unoccluded modes, respectively. The shapes of the blanching profiles obtained for the creams were similar to those in Fig. 1 and are not reproduced here. In this study Dermovate was compared to Betnovate in all cases and Betnovate was compared to Eumovate in all cases. Dermovate was not compared to Eumovate.

It is clear from the AUC values and the blanching profiles depicted in Fig. 1 that for the creams in the occluded and unoccluded modes and for the ointments in the occluded mode, the expected blanching order is observed, i.e., Dermovate > Betnovate > Eumovate. χ^2-Analysis showed these differences to be statistically significant. In the case of the unoccluded ointments, however, a different situation obtains. Reference to Fig. 2 shows the unequivocal blanching superiority of Dermovate ointment over Betnovate and Eumovate ointments, but the comparison of Betnovate ointment with Eumovate ointment did not give the expected results. Statistical analysis indicated that Eumovate elicited a superior blanching response to Betnovate up until the 14-h reading. The blanching profiles intersected at 16 h after which time no statistically significant differences were observed. It therefore appears that Eumovate ointment should fall into the potent classification of the United Kingdom Monthly Index of Medical Specialities since the unoccluded mode of application is the most frequent application mode used in the clinical situation.

The expected increase in blanching response

TABLE 1

Area under the curve values

Preparation	Creams		Ointments	
	Occluded	Unoccluded	Occluded	Unoccluded
Dermovate	1766	1935	2173	2161
Betnovate	1157	778	1267	965
Eumovate	823	359	724	1024

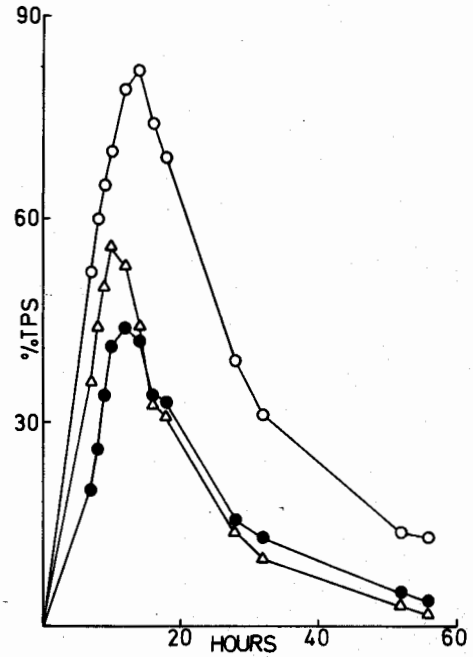

Fig. 2. Blanching profiles of unoccluded ointments. ○, Dermovate; ●, Betnovate; △, Eumovate.

due to occlusion (Meyer et al., 1981; Poulsen et al., 1974) was observed in all cases except Dermovate cream and Eumovate ointment. The AUC values for Dermovate cream in the occluded and unoccluded modes were 1766 and 1935 respectively. This could indicate a well-formulated vehicle which facilitates release of the corticosteroid without occlusion, although a good blanching response could be expected from all but poorly formulated bases containing a corticosteroid as potent as clobetasol propionate.

The unoccluded sites to which Eumovate ointment had been applied elicited an overall blanching response 40% greater than the occluded sites. This same increase in the blanching response of Eumovate ointment without occlusion has been observed in our laboratories previously with different volunteers, ointments from different batches and different observers having taken the readings in the different trials. A similar phenomenon has been reported (Barry and Woodford, 1974) for Topilar cream where it was found that no occlusion increased the AUC value by 35%, but no explanation was offered.

The reason for the anomalous blanching behaviour of Eumovate ointment in the occluded and unoccluded application modes is open to speculation. There is a possibility that the corticosteroid does not penetrate the hydrated stratum corneum to the same extent as the stratum corneum in its natural state. This is, however, an unlikely explanation as the expected increased blanching response was noted when Eumovate cream was applied under occlusion. It is possible that the steroid is not well released from the ointment base, but this should not result in the major difference observed between the occluded and unoccluded applications. Another possibility is that hydration of the stratum corneum affects the partitioning of the corticosteroid between the vehicle and the skin. Other possibilities which have been suggested (Woodford, personal communication) are (i) the act of occlusion may somehow alter the nature of the formulation so that some substance was expelled from the bulk of the ointment and formed a barrier on the skin surface; (ii) during occlusion an unknown substance from the vehicle penetrated the epidermis thus slowing down further passage of corticosteroid and (iii) some substance with vasodilating properties accompanied the corticosteroid into the dermis thus reducing the observed blanching. A combination of the above factors is also possible. It is worth noting that whilst the Company which manufactures these preparations is not prepared to divulge the formulation of the vehicles, we have been assured that the bases of Dermovate, Betnovate and Eumovate ointments are all different. If any of the possibilities discussed above are correct, they would appear to be specific for clobetasone butyrate incorporated into this particular ointment base.

Conclusions

With respect to blanching abilities, the overall conclusions which can be drawn from this study are that: (a) Dermovate cream > Betnovate cream > Eumovate cream in both the occluded and unoccluded modes of application. (b) Dermovate

ointment > Betnovate ointment > Eumovate ointment in the occluded mode. (c) Dermovate ointment > Eumovate ointment > Betnovate ointment in the unoccluded mode.

Two important general observations are also worth noting. Firstly, the much debated (Haigh et al., 1985; Gibson, 1985; McKenzie, 1986) importance of an extended observation period and of using more than one criterion to draw conclusions from the blanching elicited by topical corticosteroids is well illustrated in this study. This is especially evident in the comparison of Eumovate ointment and Betnovate ointment in the occluded mode of application where a single reading of blanching taken between 7 and 10 h after application would indicate equivalent preparations, but extended observations produce AUC values of 724 and 1267, respectively.

Secondly, the well-documented (Burdick, 1972; Cornell and Stoughton, 1985) correlation between the observed degree of blanching elicited by topical corticosteroids and their clinical anti-inflammatory action was noted in all comparisons in this study, with the exception of the anomalous result obtained for Eumovate and Betnovate ointments in the unoccluded mode of application. This further verifies the usefulness of this convenient and reproducible bioassay, if properly performed, as a means of predicting the clinical efficacy of topical corticosteroids.

Acknowledgements

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References

Allenby, C.F. and Sparkes, C.G., Halogenation and topical corticosteroids: a comparison between the 17-butyrate esters of hydrocortisone and clobetasone in ointment bases. *Br. J. Dermatol.*, 104 (1981) 179–183.

Barry, B.W. and Woodford, R., Comparative bio-availability of proprietary topical corticosteroid preparations; vasoconstrictor assays on thirty creams and gels. *Br. J. Dermatol.*, 91 (1974) 323–338.

Burdick, K.H., Corticosteroid bioavailability assays: correlation with a clinical study. *Acta Derm. Venereol.*, 52, Suppl. 67 (1972) 19–23.

Corbett, M.F., The response of psoriasis to betamethasone valerate and clobetasone propionate. *Br. J. Dermatol.*, 94, Suppl. 12 (1976) 89–93.

Cornell, R.C. and Stoughton, R.B., Correlation of the vasoconstriction assay and clinical activity in psoriasis. *Arch. Dermatol.*, 121 (1985) 63–67.

Gibson, J.R., Kirsch, J., Darley, C.R. and Burke, C.A., An attempt to evaluate the relative clinical potencies of various diluted and undiluted proprietary corticosteroid preparations. *Clin. Exp. Dermatol.*, 8 (1983) 489–493.

Gibson, J.R., Correlation of the vasoconstrictor assay and clinical activity in psoriasis. *Arch. Dermatol.*, 121 (1985) 1105.

Haigh, J.M. and Kanfer, I., Assessment of topical corticosteroid preparations: the human skin blanching assay. *Int. J. Pharm.*, 19 (1984) 245–262.

Haigh, J.M., Kanfer, I., Meyer, E. and Smith, E., Relative potencies of topical corticosteroid formulations. *Br. J. Dermatol.*, 113 (1985) 502–503.

McKenzie, A.W. and Stoughton, R.B., Method for comparing percutaneous absorption of steroids. *Arch. Dermatol.*, 86 (1962) 608–610.

McKenzie, A.W., First blast of the trumpet against the monstrous regiment of scientists (with apologies to John Knox). *Br. J. Dermatol.*, 115 (1986) 637.

Meyer, E., Kanfer, I. and Haigh, J.M., Comparative blanching activities of some topical corticosteroid containing lotions. *S. Afr. Pharm. J.*, 48 (1981) 551–552.

Poulsen, B.J., Burdick, K. and Bessler, S., Paired comparison vasoconstrictor assays: a comparison of methods for the determination of relative vasoconstrictor potency of topically applied corticosteroids. *Arch. Dermatol.*, 109 (1974) 367–371.