Acta Dermatovener (Stockholm) 60: 57–62, 1980

RANKING OF GLUCOCORTICOID CREAMS AND OINTMENTS

J. Poulsen and H. Rorsman

Department of Dermatology, University of Lund, Lund, Sweden

Abstract. 20 corticosteroid ointments and 19 corticosteroid creams available on the Swedish market in January 1977 were tested for their blanching effect. Three ointments and three creams showing pronounced blanching were tested only without occlusion. Hydrocortisone preparations were tested only with occlusion. Other preparations were tested with and without occlusion. All ointments and creams were tested at four randomized sites on the flexor aspect of the forearm in each of 11 or 12 subjects. When used occlusion was applied for 6 hours. Repeated readings were made, using scores 0, 1, 2, and 3. The readings at the time when most preparations showed blanching were analysed statistically. The scores for blanching showed a Poisson distribution when the mean score was ≤ 1. Classification of preparations according to blanching was facilitated by the fact that statistical methods for Poisson distribution could be used. A ranking of corticosteroids based on vasoconstriction was obtained, and four different groups for ointments and four for creams emerged. The arbitrary nature of any ranking and grouping of steroids is evident from the data presented.

There are many glucocorticoids intended for topical application in dermatological practice, and they are available in different vehicles. The tremendous variety of preparations can make the choice of steroid and mode of administration difficult in the individual case. The glucocorticoids have therefore been classified according to efficacy. One such classification is that of Hagerman (3), who distinguished three groups of which I is the mildest and III the most potent. Hydrocortisone is placed in Group I, fluorinated glucocorticoids such as triamcinolone acetonide in Group II, and fluocinonide acetonide and betamethasone valerate preparations with potent anti-inflammatory effect, which appeared in the early 1960's, in Group III. This classification has been used in Sweden when comparing the clinical properties of different steroids. Side-effects have also been related to these groups. Classification of steroids with regard to potency has also been taken up in other countries. Several new classifications have been proposed since the development of new, highly potent steroid preparations, and some new preparations have been placed in a fourth group, Group IV comprising extra-potent preparations with good clinical effects but involving a high risk of undesirable glucocorticoid side effects (1, 5, 8, 9, 11). The great advantage of classification has been that clinicians have acquired appropriate respect for the side-effects of the most potent of the preparations, but it has probably also contributed to a false feeling of exactness with regard to the relative value and risks of different preparations.

Even though no general correlation has been shown between clinical effect of topical steroids and vasoconstriction, in the absence of comprehensive scientific, comparative clinical investigations there is good reason to base the classification of these drugs on vasoconstriction studies (7). Stoughton (10) reports five different studies in which two steroid preparations were compared with regard to vasoconstriction and clinical effect in psoriasis, with close correlation in all.

Maibach & Stoughton (5), both of whom have great experience of tests of vasoconstriction and clinical trials, use the vasoconstrictory effect when classifying steroid preparations with regard to potency. They maintain that owing to the time and work required of highly qualified experts to make a thorough clinical comparison there is no alternative but to follow vasoconstriction assay in order to obtain a classification, according to potency.

The object of this investigation was to rank the glucocorticoid ointments and creams for dermatological use registered in Sweden on 1 January 1977 according to their skin-blanching effect.

It has been shown that with few exceptions the addition of antimicrobial agents does not affect the vasoconstrictory action of glucocorticoids, (2), and we therefore did not include any such compound preparations. Nor did we test preparations containing pharmacologically active substances other than steroids.

Table I. *Ointments tested for blanching effect*

Trade name	Generic name	Concentration %
Apolar	Desonide	0.1
Betnovat	Betamethasone valerate	0.1
Celestona valerat	Betamethasone valerate	0.1
Cortiment	Hydrocortisone	0.25
Dermovat	Clobetasol propionate	0.05
Diproderm	Betamethasone dipropionate	0.05
Drocort	Fluandrenolone	0.05
Ficortril 1%	Hydrocortisone	1
Ficortril 2.5%	Hydrocortisone	2.5
Hydrocortison 1% ACO	Hydrocortisone	1
Hydrocortison acetat 1% ACO	Hydrocortisone acetate	1
Kenacort-T	Triamcinolone acetonide	0.1
Ledercort acetonid	Triamcinolone acetonide	0.1
Locacorten	Flumethasone pivalate	0.02
Metosyn	Fluocinonide	0.05
Synalar 0.01%	Fluocinolone acetonide	0.01
Synalar 0.025%	Fluocinolone acetonide	0.025
Topilar	Fluclorolone acetonide	0.25
Ultralanum	Fluocortolone	0.25
	Fluocortolone caproate	0.25
Ultralanum (fatty)	Fluocortolone	0.25
	Fluocortolone caproate	0.25

MATERIAL

Preparations. Packs of 20 commercially available ointments (Table I) and 19 creams (Table II) were used. The first few grammes from each tube were discarded. Syringes of 1 ml were then flushed with the preparation and filled. We have used the name for the vehicle given by the manufacturer, although we are aware that differences between some bases called ointments and bases called creams may be infinitesimal.

Experimental subjects. 48 healthy volunteers, 26 women (age 20–54 years, mean 27.5) and 22 men (age 20–51 years, mean 27.0) who had not used glucocorticoids during the preceding 6 months took part in the investigation.

METHODS

A modification of the method described by Moore-Robinson & Christie (6) was used. Four rows of 8 round holes 7 mm in diameter were punched in strips of 72 mm-wide double-adhesive Blenderm® polyethylene tape (3M Medical Products Division, St Paul, Minnesota, USA) after which the one side was covered with polyethene film

Table II. *Creams tested for blanching effect*

Trade name	Generic name	Concentration %
Betnovat	Betamethasone valerate	0.1
Celestona valerat	Betamethasone valerate	0.1
Corticodern	Fluprednidene acetate	0.1
Dermovat	Clobetasol propionate	0.05
Diproderm	Betamethasone dipropionate	0.05
Drocort	Fluandrenolone	0.05
Halog	Halcinonine	0.1
Hydrocortison acetat 1% ACO	Hydrocortisone acetate	1
Ibaril	Desoxymethasone	0.25
Kenacort-T	Triamcinolone acetonide	0.1
Ledercort acetonid	Triamcinolone acetonide	0.1
Locacorten	Flumethasone pivalate	0.02
Medrone	Methylprednisolone acetate	0.25
Synalar 0.01%	Fluocinolone acetonide	0.01
Synalar 0.025%	Fluocinolone acetonide	0.025
Synalar 0.2%	Fluocinolone acetonide	0.2
Topilar	Fluclorolone acetonide	0.25
Ultralanum	Flucortolone caproate	0.25
	Flucortolone pivalate	0.25

Table III. *Poisson distribution of blanching scores*

Score	Observed	Expected
0	490	484.0
1	179	192.2
2	46	38.2
3	5 } 5	5.1 } 5.6
>3	- }	0.5 }
Total	720	720

$\chi^2=2.638$, df=2, $0.3>P>0.2$

(Glad Pack, Union Carbide Deutschland, GMBH). This templet was used to apply at random 2.7 mg±0.3 mg of each preparation on both ulnar and radial sides of the flexor surface of each forearm.

In experiments using occlusion the Blenderm templet was left intact for 6 hours after which it was removed and the remaining ointment or cream was dabbed with absorbent paper. In the experiments with no occlusion, coarse woven textile (5×5 mm) was used for protection of the applied preparations for the first 3 hours, after which any remaining ointment or cream was removed as described.

The degree of vasoconstriction was observed under standardized conditions in Wood's light (Philips, Holland HPW 125 W, type S7202E/10) in accordance with the following scale: 0, no blanching; 1, slight blanching in part of the patch; 2, blanching of the whole patch; 3, marked blanching of the whole patch.

In the experiments in which no occlusion was used, the reactions were read off after 3, 5, 7, 9, 12, 24, 32, 48, and 56 hours. In the 6-hour-occlusion experiments readings were made after 6, 7, 9, 11, 13, 24, 32, 48, 56, 72, etc. hours as long as blanching was discernible.

In preliminary trials hydrocortisone, hydrocortisone acetate and fluprednidene preparations caused no vasoconstriction and Halog, Dermovat, Metosyn and Topilar caused vasoconstriction in 80% or more of the subjects tested without occlusion. Therefore the first preparations were investigated only with occlusion and the later only without occlusion, whereas the other preparations were tested both with and without occlusion.

RESULTS

Maximum vasoconstriction was seen after different intervals with the different preparations, but in most cases the effect was most marked after 9–12 hours. This was true of both creams and ointments, and both with and without occlusion. Different individuals showed maximum responses after different intervals, and this applied to all preparations.

We now report the results 11 hours after application with occlusion and 12 hours after application without occlusion. We have chosen these times because the number of reactions was greatest then.

The 15 different ointments applied without occlusion at four different sites in 12 subjects gave at most test sites no vasoconstriction. The reactions were assessed with regard to their possible fit to a Poisson distribution with $\mu=0.3972$ (E), and the results are shown in Table III. Our observations closely match a Poisson distribution, $\chi^2=2.638$, df=2, $0.3>P>0.2$.

All ointments gave scores matching a Poisson distribution (Table IV). Statistical analysis was therefore performed on the assumption that the scores were Poisson distributed.

It was now ascertained whether the scores for the different ointments belonged to the same population or whether they formed separate groups of Poisson distributions. Poisson heterogeneity testing excluded the former alternative.

Dermovat, Topilar, and Metosyn formed a group that differed from the rest ($p<0.01$). The other ointments did not seem to make up a single group, but were sub-grouped as shown in Table V.

The scores of the different ointments applied for 6 hours under occlusion and read after 11 hours, when the number of positive reactions was highest, are given in Table VI.

The five hydrocortisone ointments were applied at four sites in 12 subjects. The other ointments were applied at four sites in 11 subjects. Kenacort-T and ointments with lower scores were found to be Poisson distributed. Locacorten differed significantly from the hydrocortisone preparations with regard to score values ($p<0.01$, Table V).

No definite sub-groups emerged among the preparations giving scores higher than those for hydrocortisones, but groups II and III suggested by tests without occlusion were confirmed by the test results after occlusion.

Table IV. *Sums of blanching scores for ointments tested without occlusion*

Locacorten	2
Ledercort acetonid	5
Kenacort-T	5
Apolar	7
Celestona valerat	9
Synalar 0.01%	10
Betnovat	14
Diproderm	14
Ultralanum (fatty)	15
Drocort	19
Synalar 0.025%	20
Ultralanum	20
Topilar	41
Metosyn	46
Dermovat	59

Table V. *Corticosteroid ointments ranked according to blanching effect.*

	Cortiment
I	Hydrocortison 1% AC●
	Hydrocortison acetat 1% AC●
	Ficortril 2.5%
	Ficortril 1%
II	Locacorten
	Ledercort acetonid
	Kenacort-T
	Apolar
III	Celestona valerat
	Synalar 0.01%
	Betnovat
	Diproderm
	Ultralanum (fatty)
	Drocort
	Synalar 0.025%
	Ultralanum
IV	Topilar
	Metosyn
	Dermovat

Table VI. *Sums of blanching scores for ointments tested with occlusion*

Cortiment, Hydrocortison 1% ACO, Hydrocortison acetat 1% AC●, Ficortril 1%, and Ficortril 2.5% were applied to 48 test sites. The others were applied to 44 test sites

Cortiment	2
Hydrocortison 1% ACO	7
Hydrocortison acetate 1% ACO	10
Ficortril 2.5%	16
Ficortril 1%	28
Kenacort-T	38
Ledercort acetonid	49
Apolar	61
Locacorten	65
Synalar 0.025%	72
Synalar 0.01%	74
Betnovat	84
Diproderm	89
Ultralanum (fatty)	90
Celestona valerat	94
Drocort	95
Ultralanum	98

Creams

The scores of different cream preparations tested without occlusion are listed in Table VIII.

The vasoconstriction scores of creams tested without occlusion were analysed for a possible Poisson distribution, and such was obtained only by excluding the three preparations with the highest scores. The observations for single preparations also showed Poisson distribution except for the three preparations with the highest scores. These three seemed to form a single group. The 13 other preparations could not be placed in a single group, however. A heterogeneity test showed that Locacorten and Topilar could not belong to the same group ($p<0.01$) (Table VII). Celestona valerate could equally well be placed in groups II or III (Table VII).

Tests with creams under occlusion for 6 hours and read at different times showed the highest number of blanching reactions at 11 hours for most preparations, and this time was therefore chosen for comparison. The score sums at 11 hours are shown in Table IX. Only the scores of the three least potent preparations were Poisson distributed. A significant difference was found between Corticoderm and Hydrokortisonacetat ACO 1% ($p<0.01$).

DISCUSSION

It would hardly be possible to make a clinical comparison of all glucocorticoid preparations available on the Swedish market. A comparison based on the blanching effects of steroids cannot give the same information as a clinical study, but supplies information about one of the pharmacological properties of glucocorticoid formulations, and this is probably closely correlated to the anti-inflammatory effects of the drug.

Table VII. *Corticosteroid creams ranked according to blanching effect*

I	Hydrocortison acetat 1% ACO
II	Corticoderm
	Medrone
	Ledercort acetonid
	Ultralanum
	Locacorten
	Celestona valerat
III	Betnovat
	Ibaril
	Diproderm
	Synalar 0.01%
	Synalar 0.025%
	Kenacort-T
	Drocort
	Topilar
IV	Dermovat
	Synalar 0.2%
	Halog

Table VIII. *Sums of blanching scores for creams tested without occlusion*

Medrone	9
Ledercort acetonid	9
Ultralanum	11
Locacorten	17
Celestona valerat	21
Betnovat	27
Ibaril	32
Diproderm	34
Synalar 0.01%	34
Synalar 0.025%	35
Kenacort-T	38
Drocort	44
Topilar	52
Dermovat	72
Synalar 0.2%	76
Halog	91

Table IX. *Sums of blanching scores for creams tested with occlusion*

Hydrocortison acetat 1% ACO	14
Corticoderm	39
Medrone	63
Locacorten	63
Ultralanum	72
Ledercort acetonid	76
Synalar 0.025%	93
Kenacort-T	95
Celestona valerat	98
Synalar 0.01%	99
Ibaril	99
Diproderm	101
Betnovat	108
Drocort	109
Synalar 0.2%	114

We studied all glucocorticoid creams and ointments available in Sweden in January 1977. Preparations containing pharmacologically active compounds over and above glucocorticoids were not included. Preparations with very pronounced blanching effects were only without occlusion, but all others were also applied under occlusion for 6 hours.

Since occlusion can modify the properties of a steroid preparation, and since most steroids are used without occlusion, a comparison of pharmacological effects should if possible be based on non-occlusive tests. We were guided mainly by blanching effects without occlusion when we attempted to rank the different creams and ointments with respect to their blanching activity.

We did not exclude subjects with poor blanching reactions, but on the contrary found it useful to include all types of reactors.

Effects of new glucocorticoids can easily be judged by testing a limited number of persons with known reactivity to standard corticosteroid preparations. Blanching is considered to parallel the clinical effect of glucocorticoids, although this may not apply to all preparations. One preparation may give good blanching, and this response may be correlated to the anti-inflammatory activity of the drug. The base, however, may not always be suitable for a particular condition, and this could influence the clinical effect. In fact, we suspect that certain vehicles may even damage the skin, and any anti-inflammatory effect (correlated to blanching) is counteracted by irritation, which becomes apparent later than the maximum blanching reaction. High concentrations of propylene glycol may have such an effect (4).

Different steroid preparation produce maximum blanching at different times after application, making comparison of the effects difficult. By arbitrarily selecting the time when most blanching responses appear, the fast-acting and slow-acting preparations show up to disadvantage on comparison. A rapid effect may be of clinical value, whereas a slowly developing effect is apparently of doubtful importance. A long-lasting effect may be clinically desirable, but this is not disclosed by comparison on a single occasion.

The blanching responses are scored 0, 1, 2, and 3. In the statistical evaluation it was found that most score series for non-occlusion tests formed a Poisson distribution, exceptions being preparations with potent blanching effect. Many preparations tested with occlusion gave score series that were not Poisson distributed. The finding that scores might be Poisson distributed facilitated the statistical evaluation of the results, and made it possible to group the steroids in different blanching classes. The number of subjects in our series is small and the results should be interpreted with caution. The model seems to be well suited for this type of comparative investigation, however.

The different steroid preparations, both creams and ointments, fell naturally into four classes on the basis of the statistical analysis. A distinct borderline could sometimes but not always be established. It should also be noted that the ranking within groups is unreliable owing to the limited number of subjects.

It is evident that one and the same steroid, e.g. triamcinolone acetonide, may have different blanching effects depending on the vehicle. No direct comparison can be made between creams and ointments of the same steroids. They were tested on different occasions in different subjects. Ranking and grouping are made within creams and within ointments and this study does not permit any conclusion with regard to the relative blanching effect of creams and ointments.

The results may provide guidelines for the selection of preparations for clinical comparison. We would suggest that investigations be supplemented by simultaneous observations on blanching effects, to give a wider idea of the correlation between blanching and clinical efficacy of corticosteroids. We do not believe a strict correlation exists—certain vehicles may be superior in the treatment of a particular state, and this may obscure even a strong correlation between blanching and clinical anti-inflammatory and/or antimitotic effects of the corticosteroids tested.

Studies along the proposed lines may be helpful in selecting the most appropriate vehicles and in avoiding the irritant ones. It is possible that too much attention has been paid to the efficacy of the corticosteroid and too little to the acceptability of the base.

ACKNOWLEDGEMENTS

This investigation was supported by grants from the Walter, Ellen, and Lennart Hesselman Foundation for Scientific Research.

REFERENCES

1. Agrup, G., Lassus, A., Lidén, S., Osmundsen, P.-E., Rajka, G. & Søndergaard, J.: Hur starka är kortisonsalvorna? Läkartidningen (Stockholm) 75: 1924, 1978.
2. Barry, B. W., & Woodford, R. W.: Comparative bioavailability and activity of proprietary topical corticosteroid preparations: Vasoconstrictor assays on thirty-one ointments. Br J Dermatol *93*: 563, 1975.
3. Hagerman, G.: Dermatologisk lokalbehandling. Allmänna principer. Läkartidningen (Stockholm) *68*, Suppl. 4, 65, 1971.
4. Hannuksela, M., Pirilä, V. & Salo, O. P.: Skin reactions to propylenglucol. Contact Dermatitis *1*: 112, 1975.
5. Maibach, H. I. & Stoughton, R. B.: Topical corticosteroids. *In* Steroid Therapy, p. 174, W. B. Saunders Co., Philadelphia, London, Toronto, 1975.
6. Moore-Robinson, M. & Christie, G.: Vasoconstrictor activity of topical corticosteroids—methodology and results. Br J Dermatol *82*:, Suppl. 6, 86, 1970.
7. Place, V. A., Valasquez, I. G. & Burdick, K. H.: Precise evaluation of topically applied corticosteroid potency. Arch Dermatol *101*: 531, 1970.
8. Skog, E.: Synpunkter på lokalbehandling med kortikosteroider. *In* Cortison och Hudsjukdomar—ett Glaxo symposium, p. 99. Glaxo Läkemedel, Göteborg, 1976.
9. Sneddon, I.: Clinical use of topical corticosteroids. Drugs *11*: 193, 1976.
10. Stoughton, R. B.: Penetration of drugs through the skin. Dermatologica *152*, Suppl. 1: 27, 1976.
11. Swanbeck, G.: Steroidernas plats i psoriasisbehandlingen. *In* Cortison och Hudsjukdomar—ett Glaxo symposium, p. 99. Glaxo läkemedel, Göteborg, 1976.

Received June 8, 1979

H. Rorsman, M.D.
Department of Dermatology
University of Lund
S-221 85 Lund
Sweden