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The clinical evaluation of a new topical corticosteroid, clobetasol propionate

AN INTERNATIONAL CONTROLLED TRIAL*

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SUMMARY

A new topically active corticosteroid, clobetasol propionate, has been investigated in the laboratory and in dermatological clinics to determine the best formulation for clinical use. Clinical trials involving 1150 patients were undertaken. In patients with bilateral psoriasis or eczema, clobetasol propionate, at a strength of 0·05%, was compared with betamethasone 17-valerate ointment and cream, fluclorolone acetonide ointment and cream and fluocinonide (FAPG). The new steroid was shown to be effective therapeutically, especially in psoriasis. Each comparison in the trial was analysed independently and the following statistically significant differences were demonstrated.

Psoriasis
Clobetasol propionate ointment > fluocinonide ($P<0·01$).
Clobetasol propionate ointment > fluclorolone acetonide ($P<0·05$).
Clobetasol propionate cream > fluocinonide ($P<0·05$).
Clobetasol propionate cream > fluclorolone acetonide ($P<0·05$).

Eczema
Clobetasol propionate ointment > fluclorolone acetonide ($P<0·01$).
Clobetasol propionate cream > fluclorolone acetonide ($P<0·05$).

A number of methods of screening corticosteroids for topical activity have been described. These include the fibroblast inhibition test (Berliner & Nabors, 1967), inhibition of the inflammatory response induced in rats' ears by the application of irritants (Dorfman, 1970), inhibition of mitosis (Fisher & Maibach, 1971; Marks, Pongsehirun & Saylan, 1973), and the vasoconstriction test (McKenzie & Stoughton, 1962). Of these, only the vasoconstriction test has stood the test of time, being both practical for screening large numbers of compounds and reliable, giving a reasonable prediction of therapeutic activity. That this was so, was first shown by McKenzie & Stoughton (1962)

* A list of the dermatologists who took part in the trials appears on page 202.

and has been confirmed by subsequent clinical experience (Williams *et al.*, 1964; Munro, Wilson & Rhodes, 1967).

Other screening tests have shown inconsistencies. For instance, inhibitory values obtained for some steroids in the Berliner test do not correlate with activity in the clinic; potency figures in the Berliner test for betamethasone valerate, triamcinolone acetonide and fluclorolone acetonide are 36, 156 and 320 respectively (Berliner *et al.*, 1970), yet it has not been demonstrated that these three compounds have such widely differing activity in normal use, or even that they are ranked in this order of efficacy (Rhodes *et al.*, 1972; Harman *et al.*, 1972; Wilson, 1973; Williams *et al.*, 1964).

In the past few years a large number of steroids have been synthesized and screened for possible topical activity using the McKenzie vasoconstriction test. Using this method, clobetasol propionate (21-chloro-21-desoxybetamethasone-17-propionate), a compound with a vasoconstriction index of 19 (cf. betamethasone valerate 3·6) was selected for further study in the laboratory and the clinic.

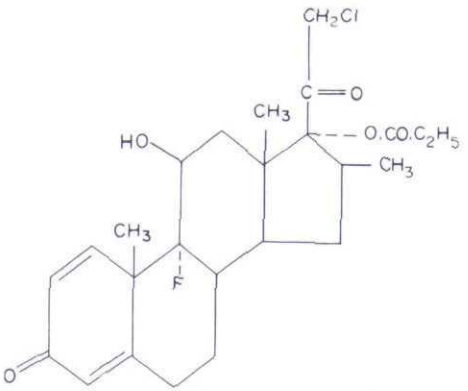

FIGURE 1. Clobetasol propionate.

Bio-availability of steroids from their vehicles is now recognized to be of great importance, thus in preliminary investigations clobetasol propionate was tested in various bases, in strengths up to 0·1%. These studies indicated that the optimal strength lay between 0·025% and 0·05%, and this paper reports the subsequent trials carried out.

METHODS

Patients were included if they had bilateral lesions of eczema or psoriasis which, at the start of the trial, were judged to show little or no difference in clinical severity between the two sides.

The preparations to be compared were allocated at random to left or right sides and the identical looking tubes were labelled accordingly. Neither the clinician nor the patient was aware of their distribution. Patients were asked to treat their lesions at least twice a day, but more frequently if the clinician so desired, either with or without polythene occlusion. Some patients were in hospital, but the majority were out-patients.

Assessment of the response to treatment was made at, or as near as possible to, 7 days after the start of the trial. The lesions were rated as healed, improved, static or worse; in addition, the clinician was asked to record whether the response had been better on one side or the other, or if the lesions were still indistinguishable. In some of the comparisons patients were asked if they experienced any sensation on application of the preparations.

The trial code was held by a trial co-ordinator. As each patient completed the trial the clinician

returned the completed record card to the trial centre. Here the card was scrutinized by one co-ordinator, who was not in possession of the code, to ensure that it is was correctly completed and that a clear choice was recorded by the clinician. If there was any doubt about any detail the report was either returned for clarification or excluded from the trial.

The card was then decoded by a second co-ordinator. In each case both objective (by clinician) and subjective (by patient) assessments were made. Differences between these two assessments were extremely rare, so that all analysis of data that follows is based only upon the clinicians' choice. As each card was decoded the result was plotted on a sequential analysis design, as described by Armitage (1960); a choice for one or other treatment being termed a preference, and an equal response (or lack of response) a tied pair. If the preference line met a boundary assigned to one or other treatment it indicated a statistically significant difference in favour of that treatment. Boundary lines were set at two places, such as to indicate a significance of $P<0{\cdot}05$ and $P<0{\cdot}01$. Results were plotted sequentially as they were decoded, and this allowed the trial to be stopped after treating the minimum number of patients. This method analyses preferences only; further data are presented as histograms (Figs. 2 and 3), where the number of choices may be larger than appears in the graphs, as they include a number of patients already under study when the decision was made to stop.

Clobetasol propionate was formulated in both cream and ointment bases. In both bases propylene glycol was used as the solvent to provide optimum conditions for the release of the steroid. Formulations of clobetasol propionate were compared with fluclorolone acetonide, fluocinonide and betamethasone valerate. All three control steroids were used in their marketed formulations (Topilar, Metosyn and Betnovate respectively). Two of these (fluclorolone acetonide and betamethasone valerate) are available in both cream and ointment bases. In these cases, clobetasol propionate ointment was compared with the control ointment and clobetasol propionate cream with the control cream. However, fluocinonide is only available in one base (FAPG), which has been said to have the properties of both a cream and an ointment (Portnoy & Sarkany, 1972). Consequently, this preparation was compared with both clobetasol propionate ointment and cream. In view of the nature of the FAPG base it was considered possible, though unlikely, that there might be a residue of cream, ointment or FAPG left on the skin at the time of assessment and that this might give the clinician a clue as to the identity of the materials, thus introducing a bias into the trial. In order to eliminate this possibility all patients in all sections of the trial were asked not to use the preparations on the day they returned to their doctor for assessment. A card supplied to each patient gave this instruction and also asked them to wash their hands after using the first preparation, before applying the second.

RESULTS

Preliminary investigations

Preliminary investigations were carried out to confirm the laboratory predictions of the ideal bases for release of the steroid and to establish the optimal concentration of clobetasol propionate.

Bases. The topical vasoconstrictor activity of clobetasol propionate formulations was measured using a modification of the McKenzie assay described by Busse *et al.* (1969).

For the ointments, it was found that maximum vasoconstriction was obtained with preparations containing only sufficient propylene glycol to dissolve the steroid. For the creams, it was found that a nearly saturated solution of clobetasol propionate in the aqueous phase (i.e. propylene glycol in water) was required to give optimum release.

Clinical results confirmed these laboratory tests, showing that the amount of propylene glycol in each preparation was critical. In patients with psoriasis there were significantly more preferences for clobetasol propionate 0·05% formulated in a cream base containing 47% propylene glycol than in a base containing 25% ($P<0{\cdot}05$).

Steroid concentration. Early double-blind clinical studies in psoriasis treated without occlusive dressings, showed that, although the number of preferences for a cream containing 0·025% clobetasol propionate exceeded the number for either betamethasone valerate or fluocinonide, the difference did not reach statistical significance. The further clinical investigations were, therefore, carried out using an 0·05% clobetasol propionate cream and ointment.

Comparative clinical evaluation of clobetasol propionate 0·05%

Psoriasis. In patients with psoriasis, there were more preferences for clobetasol propionate than for each of the control steroids, regardless of the base employed or the use or not of polythene occlusion

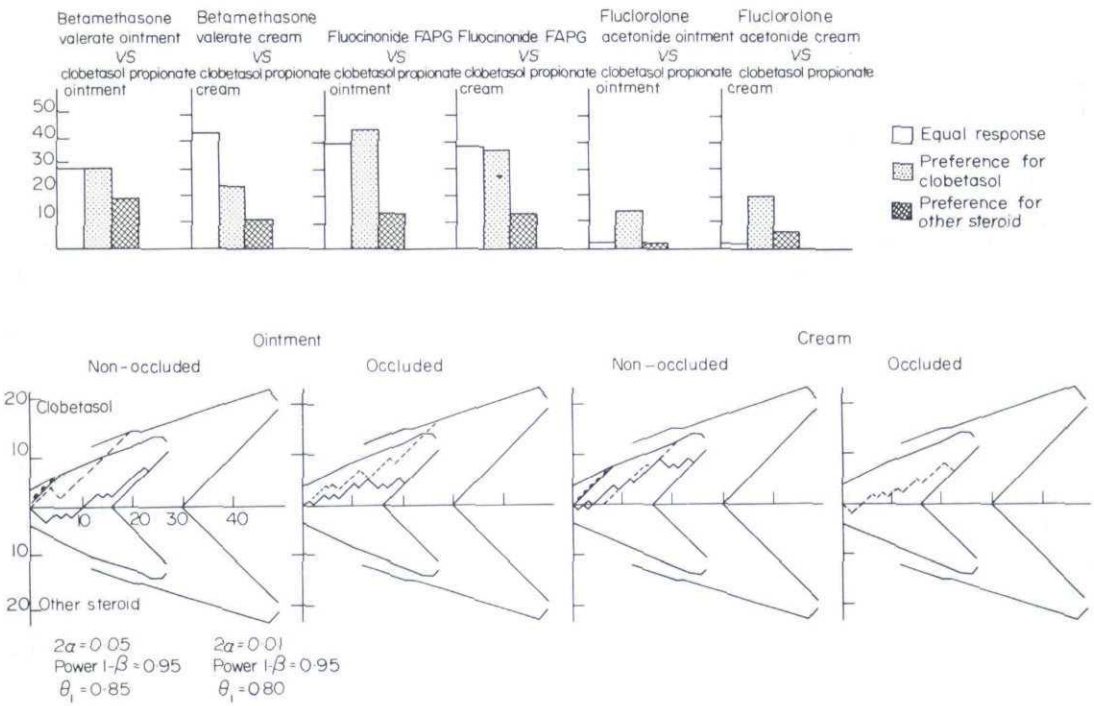

FIGURE 2. Psoriasis—all cases. ——, *clobetasol vs betamethasone;* – – –, *clobetasol vs fluocinonide;* ••••, clobetasol vs fluclorolone.

(Fig. 2). Fig. 2 also illustrates the individual comparisons. Preferences for clobetasol propionate ointment when used without polythene occlusion were significant when compared with fluocinonide ($P<0·01$) and fluclorolone acetonide ($P<0·05$), but not with betamethasone valerate. When polythene occlusion was employed clobetasol propionate was significantly better than fluocinonide ($P<0·01$), but was not significantly different from betamethasone valerate.

Clobetasol propionate cream used without polythene occlusion was superior to fluocinonide and fluclorolone acetonide ($P<0·05$). However, there was no significant difference between the new steroid cream and betamethasone valerate cream.

Eczema. Similarly, in patients with eczema, there were more preferences for the new steroid than there were for the controls (Fig. 3). However, in this disease category differences were not so marked. Preferences for clobetasol propionate were significantly greater in comparison with fluclorolone ace-

tonide ointment ($P<0{\cdot}01$) and fluclorolone acetonide cream ($P<0{\cdot}05$), but not in the other comparisons.

Side effects. Only one of the 1150 patients was not able to complete the treatment because of deterioration equally on the test and the control steroid treated lesions, and he was withdrawn from the trial.

303 patients were asked if they experienced any stinging on application of the cream or ointment.

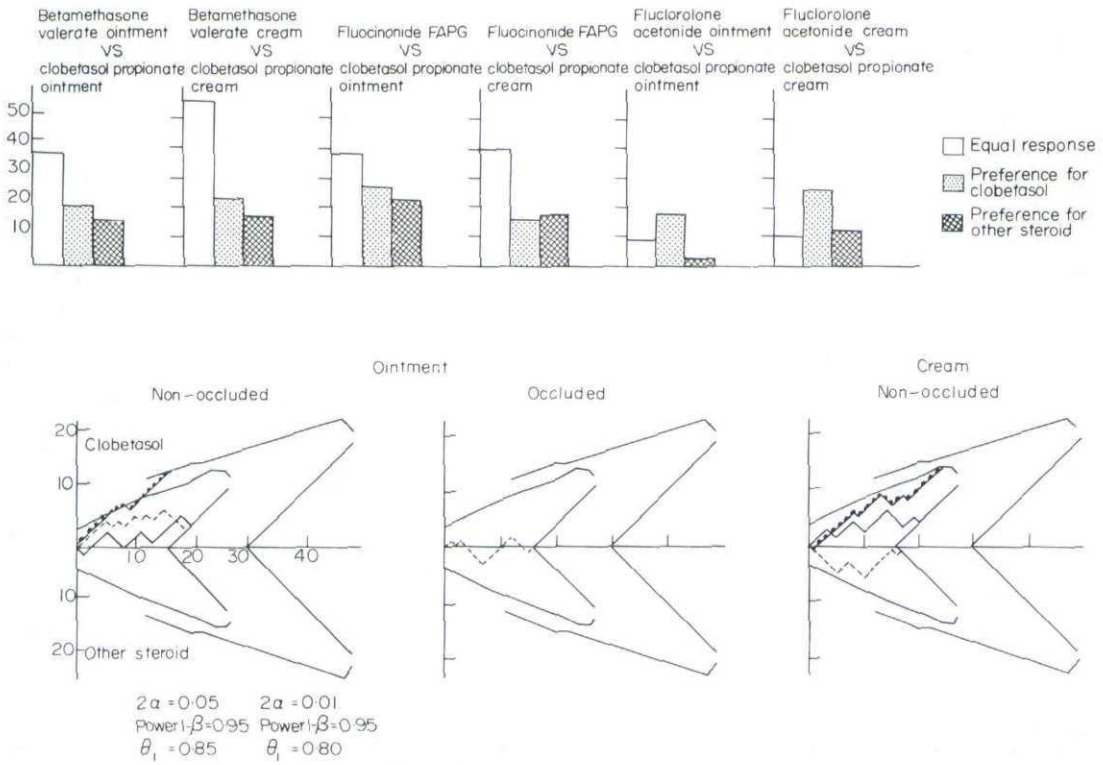

FIGURE 3. Eczema—all cases. ——, clobetasol vs betamethasone; – – –, clobetasol vs fluocinonide; ••••, clobetasol vs fluclorolone.

Of these, twenty-seven experienced some sensation with the clobetasol propionate preparations and forty-six with the control preparations. However the effect was usually slight, experienced only on the first application, and in no case did it necessitate interrupting the prescribed regimen.

DISCUSSION

It is recognized that the interpretation of this type of trial has limitations and that it is only after longer term use that the full value of a new topical steroid will emerge. However, short-term assessments have frequently been used in the past and they give a good indication of the relative therapeutic value of compounds (Williams *et al.*, 1964; Munro *et al.*, 1967). Further trials are in progress to assess the response to clobetasol propionate in more detail and in other specific lesions.

Psoriasis is a difficult disease to treat and consequently any differences in potent topical applications show up more clearly in this than in less stubborn diseases. This has been noted by Nicholls (1972) and

is apparent in this study, especially when psoriasis was treated without the use of polythene occlusion. Where occlusion was used the differences were not so apparent. Patients are reluctant to use polythene unless it is obvious that their lesions are not going to clear without it; because of this, and its tendency to mask the differences between steroids, we did not study as many occluded as non-occluded cases.

Eczema tends to be less resistant than psoriasis to treatment, so that differences between highly active preparations are not so marked. The majority of preferences were for clobetasol propionate, but statistically significant differences between preparations were not so evident. This was so despite the fact that all the eczema patients had been referred to hospital consultants because of the stubborn nature of their lesions. Patients with eczema were a clinically heterogeneous group ranging from simple acute contact eczemas to chronic lichenified conditions. In a multi-centre study such as this it is difficult, if not impossible, to agree criteria which would enable a more specific categorization of eczema to be undertaken. Were this feasible it is possible that in the more intractable eczemas, more marked differences between the preparations may have emerged.

In this trial no attempt was made to assess the possible side effects of clobetasol propionate. When patients with more than 60% of their body surface affected by disease are treated with topical steroids under total body occlusion, according to the method of James, Munro & Feiwel (1967), all potent steroids cause transient depression of pituitary–adrenal function: clobetasol propionate is not an exception (Munro, personal communication). However, this is no guide to what happens in normal use. Wilson, Williams & Marsh (1973) have shown that betamethasone valerate in out-patient use in reasonable quantities is unlikely to affect pituitary–adrenal function: and this has been confirmed by Munro & Clift (1973). It is not expected that clobetasol propionate will behave differently. The more clinically important steroid side effects of skin atrophy and telangiectasia are not likely to be seen in any trial, since they are the consequence of prolonged misuse of steroids; however, there is no reason to believe that, should this steroid be misused, its propensity to cause such effects would differ from that of any other steroid preparation.

CLINICIANS WHO TOOK PART IN THE TRIAL

United Kingdom

C. F. Allenby	Hitchin
D. A. Birkett	Middlesbrough
A. Bowyer	Torquay
I. W. Caldwell	Southampton
E. S. Emslie	Rhyl
M. Hewitt	Truro
A. R. Kurwa	Birmingham
R. A. Main	Aberdeen
R. Marks	London
J. Overton	Leicester
N. R. Rowell	Leeds
P. D. Samman	London
R. W. B. Scutt	Gosport
D. E. Sharvill	Canterbury
J. R. Simpson	Exeter
C. J. Stevenson	Newcastle
R. S. Wells	London

Sweden

A. Björnberg	Göteborg
J. Bleeker	Lidköping
C. H. Flöden	Karlstad
L. Gip	Sundsvall
L. Hellgren	Göteborg
L. Juhlin	Uppsala
B. Magnusson	Malmö

Finland

A. Lassus	Helsinki

Belgium

J. Van der Meersch	St Niklaas

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