CLINICAL INVESTIGATION OF CORTICOSTEROIDS INTENDED FOR USE ON THE SKIN

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CONTENTS

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1. INTRODUCTION

The following guidelines on clinical testing hold good in principle for all topical corticosteroids which are intended to be used on the skin. The effects including local adverse reactions are, in principle, the same for all corticosteroids, due to common properties, i.e. anti-inflammatory and mitosis-reducing action and inhibition of collagen synthesis. Apparent differences between substances in fact reflect differences in strength, concentration and rates of absorption and elimination.

This note for guidance should be read in the light of the annex to Directive 75/318/EEC as amended and is intended solely to assist applicants in the interpretation of the latter with respect to specific problems presented by topical forms of corticosteroids. The document deals with:

– general characteristics of topical corticosteroids (see 2),

– specific points which should be investigated in man for each new product containing a corticosteroid as active substance (see 3).

The document does not specifically apply to studies on fixed combinations; nevertheless for such products, the general principles drawn up in the note for guidance on *Fixed Combination Medicinal Product*s are fully applicable; in particular, the advantages of such combinations and the significant contributions of each of their active substances to the clinical activity should be demonstrated.

2. GENERAL CHARACTERISTICS OF TOPICAL CORTICOSTEROIDS

2.1 Penetration and local activity

To be locally effective, corticosteroids must penetrate the skin. The extent of absorption and therefore the clinical activity, as well as most of the adverse reactions, have been demonstrated to depend, both on the substance itself and, for a given corticosteroid, on several factors:

a) Concentration of the substance

however, above a certain concentration in a given vehicle, a further increase in concentration does not result in a proportionately greater effect but does increase the occurrence of adverse reactions;

b) Pharmaceutical formulation

the penetration of the active substance depends on the physico-chemical properties of the base. The presence of other components or excipients can modify the penetration through the stratum corneum and/or the effect (e.g. salicylic acid, urea, propylene glycol, antibiotics and antiseptics, tar);

c) Site of application

a thick stratum corneum is responsible for the weak penetration in areas such as soles and palms. Due to opposite conditions, a very rapid and important absorption may occur, for example, through mucosa, the scrotal skin, eyelids, and to a somewhat lesser extent, the skin of the forehead and the hair zone of the head;

d) Skin condition

penetration is increased in damaged skin (e.g. abrasion or pathological situations like parakeratosis). Damaged stratum corneum, however, often recovers within a few days of treatment;

e) Conditions of application

occlusion promotes the penetration: it may be unintentionally produced by napkins in babies or may result from application in intertriginous areas or flexures.

The influence of these different factors should be taken into account during the clinical trials.

2.2 Levels of activity and indications

The activity of a product is controlled by the extent of cutaneous penetration (see 2.1), the intrinsic activity of the compound and the rate of its elimination. Among the known corticosteroids, it is customary to distinguish, depending on the substance and the concentration, four levels of activity ranging from mild via moderately strong and strong to very strong. The data in Table 1 annexed are adapted from J.A. Miller and D.D. Munro (Drugs, 1980, 19, 119-34).

This is a rough guide, as no direct comparison has been made between all these preparations. The borderline between the classes, in particular between the intermediate classes 'moderately strong' and 'strong' is not easy to define. Some corticosteroids are available in different concentrations, which may qualify them for inclusion in a different category of clinical activity. In addition, the influence of the vehicle can result in a shift to an adjacent level of activity (see 2.1, subparagraph (b)). In view of these variables it would in principle be desirable to have available an objective comparison of all existing proprietary products of this type using a method the validity of which is universally acknowledged. However, in view of the large number of proprietary products and methodological uncertainties this is not yet feasible.

It is generally accepted that some indications of corticosensitive dermatosis are directly linked to the level of activity of the preparation as reported in Tables I and II annexed: this list is only for guidance and may be adapted to national practices.

2.3 Adverse effects

With the majority of corticosteroids, under normal conditions of use, it is not the possible systemic adverse effects due to percutaneous resorption which are the first concern, but the often irreversible local adverse reactions on the skin, such as dermatrophia.

2.3.1 Local adverse reactions

The stronger the preparations, the greater the chance of development of adverse effects, such as:

a) skin atrophy which becomes often irreversible producing clinical thinning of the skin, tele-angiectasia, purpura, striae;

b) rosacea-like and perioral dermatitis with or without skin atrophy;

c) rebound which may lead to steroid 'dependence';

d) impairment of healing;

e) effects on the eye: increased risk of glaucoma, cataract, exacerbation of mycosis and of herpes simplex;

f) miscellaneous: depigmentation, hypertrichosis, etc.

The chance of development of dermal toxicity also increases with duration of treatments and when application is performed under occlusion or on particular sites such as the face (see 2.1, subparagraph c).

Due to the substances of the base, or to a substance incorporated in the preparation, and rarely to the corticosteroid itself, contact allergy may also occur. Due to the suppression of immune defence, masking and/or worsening of infection may be observed in case of erroneous use of corticosteroid preparations in fungal, viral or bacterial cutaneous diseases.

2.3.2 Systemic effects

In adults, as a result of hypothalamo-pituitary-adrenal (HPA) axis suppression, a fall in plasma cortisol levels can generally be observed within the first days of treatment. Those systemic effects occur rarely. They occur more readily in children (e.g. acute adrenal insufficiency at the discontinuation of the substance, hypercorticism, arrest of growth, intracranial hypertension) because of the high surface/weight ratio and unintentional occlusion by napkins.

The systemic effects are due to the high penetration of a strong compound (or of its active metabolite(s)); this occurs because one or more of the factors promoting penetration (see 2.1) apply. This risk of systemic effects increases with applications over large areas, use of large amounts of material, and prolonged administration.

Local and systemic adverse effects can be generally avoided with well-studied and well-defined products, when the strength of the preparation and the nature of the pharmaceutical form are adequately chosen with regard to the type of dermatosis, the site of application, the period of treatment and the patient's age and when products are applied according to appropriate conditions of use as validated by clinical trials.

3. GUIDE FOR CLINICAL TESTING

In view of the characteristics listed under paragraph 2, it is necessary that a new product of this type be examined in such a way that the place of the corticosteroid in question (used in the concentration and base specified in the application) in the spectrum of corticosteroid products can be determined and conditions of use defined.

3.1 Pharmacodynamic studies

The place of a new product in the spectrum of corticosteroid preparations and the optimal concentrations for clinical use can to a large extent be predicted on the basis of the results of a number of pharmacological tests (anti-inflammatory effect, mitosis inhibition) in animals or in vitro.

Corticosteroid induced vasoconstriction in man may provide a preliminary rough but useful guide to topical anti-inflammatory activity. Vasoconstriction tests derived from McKenzie and Stoughton (Archives of Dermatology, 1962, 86, 608-10), using the new substance incorporated in its base should therefore be compared with the effects of established corticosteroid preparations, not only with those of approximately equal activity, but also with stronger and weaker preparations.

Other methods can also be used or are currently under development. It is not considered desirable to specify particular methods of investigation as obligatory; regulatory agencies will be prepared to consider new methods provided the clinical relevance of these methods is demonstrated. The level of activity estimated in the light of these tests will always have to be confirmed by clinical investigation (see 3.2.1).

3.2 Clinical investigation

3.2.1 Efficacy

The level of activity, as estimated in the tests listed under 3.1, will have to be confirmed clinically.

a) A product should be studied in randomised double-blind investigations; single-blind investigation should only be permitted if it is virtually impossible to perform double-blind tests. Parallel groups are probably superior in most instances, but there have been conflicting opinions expressed about whether parallel groups are preferable to intra subject half-side studies (left-right comparisons). If studies of the latter type are used, however, attention should be paid to possible interactions of the treatments due to systemic transfer from one side to the other, especially when the comparisons is being made between products of different activities applied on large areas. A product should be studied in principle against its base but also against known products of different activity. Where the product can be regarded as a minor modification of an existing one, it will often be possible to rely on a comparison with this latter product used as a reference, at least through an adequate vasoconstriction test.

   For new corticosteroids the optimal concentration for clinical use will have to be confirmed by comparative investigation of various concentrations. This is important because of the possibility of increase in the occurrence of adverse effects above a certain concentration (see 2.1, subparagraph a) without notable improvement of therapeutic efficacy. Reports should give a clear picture of the frequency of application, especially in the initial period of treatment. When frequencies differ from those usually recommended (i.e. once or at most twice daily), it is desirable that this should be justified by the applicant. Reports should also clearly state the sites of application, the areas which have been treated and the amounts of product used per week.

   If the preparation is intended to be used under occlusion, the influence of this on the effect in clinical studies should be examined.

b) Valid comparisons can only be made between treatments given for the same condition. A product should be tested in a series of conditions, each requiring different degrees of intensity of treatment.

Dermatoses advisable for clinical trials are listed in the left column of Table III. They are presented in two groups: one requiring preparations of very strong and strong activity and the other where moderately strong and mild products can be used, with psoriasis and atopic dermatitis, respectively, being the most suitable conditions for testing. From the efficacy observed in the different clinical forms of these dermatoses, the indications can be defined and the place of the new product in the spectrum of corticosteroid preparations definitively established (see classes of Table II). Provided they require treatment with products from the same class, extrapolation of the results is possible for skin conditions listed in the right column of Table III. Clinical trials may also be performed in the skin conditions listed in the right column, but they do not allow extrapolation to other skin diseases. Indications other than those listed can also be suggested, provided that positive results have been obtained in specific clinical studies conducted with an adequate methodology.

As a general principle it is not satisfactory to assume that a substance active at a certain level of dose will be equally suitable at other levels for more-severe or less-severe disease. However, it is recognised that under conditions of normal practice, a failure of treatment with a given product might lead to the use of a stronger preparation for only a few days, followed by the use of a weaker product for maintenance treatments. This mode of use should be mentioned in data sheets.

c) Short term studies over one or two weeks may not be the only relevant investigation for the clinical comparison of two topical steroids. In practice, these are sometimes applied over long periods of time and differences in clinical efficacy and safety may only become apparent after treatment for several weeks or months. For this reason, depending on the novelty of the product and the indications claimed, certain studies of efficacy as well as of safety in long-term use (e.g. over a period of three months) will sometimes be necessary.

3.2.2 Safety

Since the importance of adverse effects may not inevitably run parallel with clinical activity, the possibility of their occurrence should be studied during clinical investigation.

Where a product is claimed to produce less frequent or severe adverse effects than a well-established substance of the same degree of activity, this should be justified by controlled studies.

a) Local adverse effects

– Atrophogenic activity

The degree of atrophy induced by the product will have to be determined, after application of the product. The mode of use including the sites of application should be specified. The changes due to thinning of the epidermis and alteration of the dermis can be detected by different methods, such as measurement of the thickness of the skin (radiographical techniques, ultrasonography), histology, measurement of collagen fibrils, stereomicroscopy. They cannot be detected until a topical treatment has been given under normal conditions of use for four

weeks. Nevertheless, in experimental conditions where application is performed with occlusion, the exposure can be shorter.

– In any study, tolerance will have to be determined (drying of skin, irritation, sensitisation) both for the product as a whole and for the base. After conclusion of the trial, patch tests should be performed with the pharmaceutical formulation and the base.

b) Systemic actions

Interesting and practicable is the direct assessment of the effect on the HPA axis. In this respect, plasma cortisol determinations give more information than studies of cortisol metabolites in urine. When performing plasma cortisol determinations account must be taken of the diurnal rhythm exhibited by plasma cortisol levels and of factors which influence these levels, such as stress, sex, seasonal influences, use of oral contraceptives etc. Since healing of damaged stratum corneum, which often occurs within eight days of treatment, produces a decrease in the systemic passage, it is necessary to make repeated determinations during the exposure period. It is also customary to determine plasma cortisol levels under normal and extreme conditions of application, the latter predisposing to maximum absorption. Therefore, it is desirable to determine plasma cortisol levels under such conditions as:

– at the fifth and at the 20th day of treatment without occlusion and at the fifth day with occlusion on the normal and diseased skin,

– several times, in a number of patients treated for long periods.

The ability of the HPA axis to respond to a stimulation can also be usefully assessed by determination of plasma cortisol after stimulation (i.e. adrenocorticotrophic hormone).
Comparative data with one or several reference products used under the same conditions would in principle be necessary to assess fully the extent of systemic absorption.
Because the passage into the circulation depends on various factors (see 2.3.2), the precise conditions (i.e. sites and percentage of body surface treated, weight of product used) and mode of use should be specified for each subject treated. In the case of products for which the manufacturer wishes to claim the treatment of chronic conditions in an area of high absorption, an investigation of absorption will have to be performed after application to this area. If the product is to be recommended for use in young children, systemic effects should also be recorded in this age group, but particular attention should be given to the ethical aspects of such an investigation.

TABLE I

Levels of Activity of Known Corticosteroids

(Adopted from J.A. Miller and D.D. Munro, Drugs, 1980, 19, 119-34)

Corticosteroid	very strong	strong	moderately strong	mild
Beclomethasone dipropionate	0,5%	0,025%	–	–
Betamethasone benzoate	–	0,025%	–	–
Betamethasone dipropionate	–	0,05%	–	–
Betamethasone valerate	–	0,1%	–	–
Clobetasol propionate	0,05%	–	–	
Clobetasone butyrate	–	–	0,05%	–
Desonide	–	0,05%	–	–
Desoxymethasone	–	0,25%	–	–
Dexamethasone	–	–	–	0,01%
Diflorasone diacetate	–	0,05%	–	–
Diflucortolone valerate	0,3%	0,1%	–	–
Fluclorolone acetonide	–	0,025%	–	–
Fludroxycortide (flurandrenolone)	–	0,05%	0,0125 to 0,025%	–
Flumethasone pivalate	–	–	0,02%	–
Fluocinolone acetonide	0,2%	0,025%	0,01%	–
Fluocinonide	–	0,05%	–	–
Fluocortin butylester	–	–	0,25%	–
Fluocortolone	–	0,5%	0,2%	
Fluoprednidene acetate	–	0,1%	–	–
Halcinonide	–	0,1%	–	–
Hydrocortisone	–	–	–	0,1 to 1%
Hydrocortisone butyrate	–	0,1%	–	–
Methylprednisolone	–	–	–	0,25%
Triamcinolone acetonide	–	0,1%	–	–

TABLE II

Indications for Topical Corticosteroids in Relationship to Their Level of Activity

VERY STRONG ACTIVITY	Localised and resistant plaques of: – psoriasis – lichenification – discoid lupus erythematosus – lichen hypertrophic Hypertrophic scars
STRONG ACTIVITY	Psoriasis Lichenifications Lichen planus Lichen sclerosus and atrophicus Granuloma annulare Discoid lupus erythematosus Pustulosis palmaris and plantaris Mycosis fungoides
MODERATELY STRONG ACTIVITY	Atopic dermatitis Irritant and/or allergic contact dermatitis Nummular dermatitis Pompholyx ('dyshidrosis')
MILD ACTIVITY	Seborrhoeic dermatitis Stasis dermatitis Ano-genital pruritus

TABLE III

Skin Conditions Advisable for Clinical Investigation of Topical Corticosteroids

Advisable	Non-advisable
VERY STRONG AND STRONG CORTICOSTEROIDS	
– Psoriasis	– Granuloma annulare
– Lichen planus	– Discoid lupus erythematosus
– Lichen sclerosus and atrophicus (genital)	– Mycosis fungoides
– Pustolosis palmaris and plantaris	
– Localised lichenifications	
MODERATELY STRONG AND MILD CORTICOSTEROIDS	
– Atopic dermatitis	– Irritant and/or allergic contact dermatitis
– Seborrhoeic dermatitis	– Stasis dermatitis
– Nummular dermatitis	– Pompholyx ('dyshidrosis')
	– Ano-genital pruritus