Topical Treatment with Glucocorticoids 52

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52.1 Introduction

Cortisol, the physiologically occurring adrenal steroid, and its derivatives (here referred to as glucocorticoids) are the most widely used topical preparations in dermatology. According to Schäfer et al. there were times when 95% of all topically applied drugs for skin diseases contained glucocorticoids[69]. No other drug has changed the treatment of a wide range of dermatoses as successfully as topical glucocorticoids. In concordance with this, Howard Maibach has differentiated the history of dermatology into an era *before* and one *after* corticosteroid therapy.

More than 50 years ago, Hench (1896–1965) first reported the therapeutic benefit of a systemically administered adrenal cortical hormone (17-hydroxy-11-dehydrorcorticosterone, compound E) [32]. In 1950, Philip S. Hench, Eduard C. Kendall, and Tadeusz Reichstein (the latter two had discovered the natural cortisone of the adrenal gland in 1936) received the Nobel prize [35]. The introduction of topical hydrocortisone by Sulzberger and Witten in 1952 provided a major pharmacologic breakthrough for dermatotherapy [78]. However, it was the first halogenated substance – triamcinolone acetonide – that initiated the revolution of highly potent topical corticosteroids. In the development of potent corticosteroids through chemical modification of the cortisol molecule (11β,17α,21-Trihydroxy-4-pregnene-3,20-dione, Fig. 52.1), there have been four important steps: dehydrogenation, alkylation (e.g., methylation), halogenation, and esterification.

Dehydrogenation of the molecule was the first important development in the treatment of dermatoses and other diseases with corticosteroids. The introduction of a double bond in position C1-C2 (Δ^1-Δ^2) for example, led to a fivefold increase of the antiphlogistic

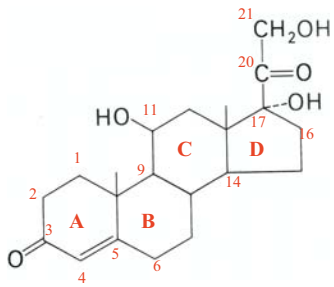

Fig. 52.1. Chemical structure of cortisol

effects of cortisol. Today, Δ^1-Δ^2-cortisol (prednisolone, first generation corticosteroid) is one of the best known and still most frequently used systemically administered corticosteroids. Methylation in ring B in 6β-position and in ring D in 16β- and 16α-position initiated a further significant increase of anti-inflammatory effects of prednisolone. Substitution with halogens (halogenation), e.g., through introduction of fluoride (F) in position 6α and/or 9α also significantly increased the efficiency of the molecule in comparison to cortisol. Topical corticosteroids of the so-called second generation are characterized by single fluoridation (e.g., triamcinolone acetonide and clobetasol), corticosteroids of the 3rd generation have a double fluoridation (e.g., diflucortolone and fluometason) [56]. However, third-generation corticosteroids are not necessarily more effective than second-generation ones.

Several organic acids, such as propionic or acetic acid, can be used to form esters (esterification) with hydroxyl groups of cortisol. A more recent trend to potentiate the efficacy of topically applied corticosteroid preparations is the formation of di-ester compounds of the molecule. The combination of different modifications in the cortisol molecule led – especially for topical treatment – to extremely effective preparations such as clobetasol-17-propionate.

Enthusiasm for highly effective corticosteroids such as fluorinated substances found its peak during the 1960s and 1970s. Together with the development of appropriate vehicles, corticosteroids rapidly became mainstay of topical therapy for various inflammatory dermatoses such as atopic eczema. However, the strong clinical efficacy of highly potent corticosteroids was also linked to more severe unwanted effects such as skin atrophy and suppression of the adrenal gland. The subsequent backlash of opinion and strong criticism against topical corticosteroids, in particular after 1984, has created confusion and misunderstanding among patients as well as physicians. In recent years, much care has been invested to re-establish a legitimate image of corticosteroids in the public opinion. Furthermore, strong efforts have been taken to improve the pharmacologic and clinical aspects of topical corticosteroids, resulting in the development of substances that exhibit a strong effectiveness, while being linked to less systemic and topical unwanted effects. This has been achieved by trying to separate the desired activity from unwanted properties of the molecule, which succeeded at least in part.

Among these newer substances with increased therapeutic index (benefit/risk ratio) there are several nonhalogenated corticosteroid double esters (e.g. fluocortinbutyl, hydrocortisone double esters and prednicarbate) and halogenated ones such as mometasone furoate [16, 38, 40, 42, 81]. The C_{21}-butyl-ester in fluocortinbutyl was the first corticosteroid strictly adhering to the concept of drug targeting. It is derived from the steroid C-21 acid by esterification with butanol leading to an inverse arrangement of the acid and alcohol components within the side chain. After absorption into the skin, fluocortinbutyl is inactivated by esterases preventing systemic effects; however, largely at the expense of potency. Prednicarbate (a prednisolone derivative esterified in positions 17 and 21) and the hydrocortisone double esters hydrocortisone aceponate and hydrocortisone buteprate, are nonhalogenated, mid-potency corticosteroids of the newest generation (fourth generation [56]) with a favorable benefit-risk ratio [22, 39, 43, 56, 70, 73, 81].

It has been shown *in vivo* that nonhalogenated corticosteroids influence fibroblast proliferation less markedly than fluorinated compounds, indicating a lower atrophogenic risk [31]. Mometasone furoate (MMF) is a synthetic, halogenated corticosteroid structurally related to adrenocorticoids and pharmacologically related to prednisolone. However, MMF has been shown to offer a superior therapeutic index with low risk of skin atrophy compared to conventional halogenated corticosteroids [40]. The steroid nucleus of MMF is the 16-alpha–methyl analog of beclomethasone [63]. MMF contains chlorine substitutes in 9-α- and 21-positions and a furoate moiety at position 17. Among all marketed corticosteroids, the 17(2')-furoate side chain is a structural modification unique to MMF [36].

52.2 Mechanism of Action

Glucocorticoids influence the inflammatory or immunologic process at different points. Concerning the molecular mechanism of action within the cell, not all details have been revealed yet. However, the mechanisms of corticosteroids can be divided into genomic (via nucleus and DNA) and nongenomic effects [85]. While genomic effects take at least 1 – 2 h to occur, nongenomic ones occur within minutes[35].

Corticosteroids exhibit three main effects: vasoconstriction, anti-inflammatory effects, and antiproliferative effects [9]. After topical application of corticosteroid preparations, the constriction of blood vessels leads to blanching of the skin. There is a correlation between the intensity of the pharmacodynamic effect of a corticosteroid formulation and the degree of skin blanching [68, 69, 86]. Using the vasoconstriction test, it is possible to predict the therapeutic effect of a corticosteroid preparation. The vasoconstriction test was first introduced in dermatology by McKenzie and Stoughton as early as 1962 [53]. Later, it was modified in various ways [50, 69, 87]. At present, the vasoconstrictor assay is still the most widely used topical steroid ranking system [33]. One problem, however, is the well-known development of tachyphylaxis of corticosteroid preparations. Tachyphylaxis describes a reduction (and finally abolishment) of corticosteroid effects (including vasoconstriction) after repeated applications [14]. The exact mechanism of action of corticosteroid-induced vasoconstriction is not known yet. Increased sensitivity against norepinephrine inhibition of histamine-induced vasodilatation or a direct action have been discussed [9].

Concerning anti-inflammatory effects, corticosteroids exhibit a variety of effects on different cells such as granulocytes, lymphocytes, and mast cells. All of

these cells modulate the inflammatory reaction in a number of ways and the influence of corticosteroids results in an overall inhibition of inflammation. Corticosteroids are, for example, known to reduce the number of lymphocytes, in particular T cells, in the peripheral blood. They also impair the phagocytic activity of macrophages and inhibit expression and release of mediators such as IL-1 and IL-2 from macrophages and T-cells. Corticosteroids inhibit cellular reactions to a greater extent than humoral ones [57].

Concerning the molecular basis of their anti-inflammatory actions, it is known that corticosteroids interact with specific receptor proteins in the target cell (intracellular glucocorticoid receptors [23]). They thereby regulate the expression of corticosteroid-responsive genes and subsequently the level and array of proteins synthesized by the cell [27]. This main intracellular mechanism of action is of clinical significance, as most beneficial effects of corticosteroid are not immediate, but take some time to become apparent. Corticosteroids predominantly *increase* the transcription of genes, but there are also examples in which they may decrease expression of certain target genes (e.g., the proopiomelanocortin gene POMC) [27]. In addition to the genomic effects, corticosteroids are also known to induce some immediate effects mediated by membrane-bound receptors [27].

The glucocorticoid receptor mediating genomic effects is present in every cell (in varying numbers of 1,000 – 100,000) and is composed of 777 amino acids and three functional domains [35]. It resides predominantly in the cytoplasm in an inactive form (as complex with other proteins such as heat shock proteins, e.g., HSP-90) until it binds the corticosteroid ligand, which enters the cytoplasm through passive diffusion. The ligand binding leads to receptor activation, dissociation from its associated proteins and translocation to the nucleus [27]. In the nucleus, it interacts with specific DNA sequences (glucocorticoid-responsive elements) and activates (or negatively regulates) the transcription of target genes. Via transcription of mRNA, an increased de novo synthesis of certain proteins takes place. Corticosteroid receptors are structurally related to receptors for other small hydrophobic ligands such as thyroid hormones, vitamin D and retinoids [27].

The genes encoding proteins, which are directly induced by corticosteroids, include lipocortin and vasocortin (Fig. 52.2). Lipocortin-1 inhibits phospholipases such as phospholipase A_2, which reduces the release of arachidonic acid and the synthesis of pro-inflammatory mediators such as prostaglandins, leukotrienes and platelet activating factor [57]. Vasocortin inhibits histamine release and thereby exerts anti-allergic effects.

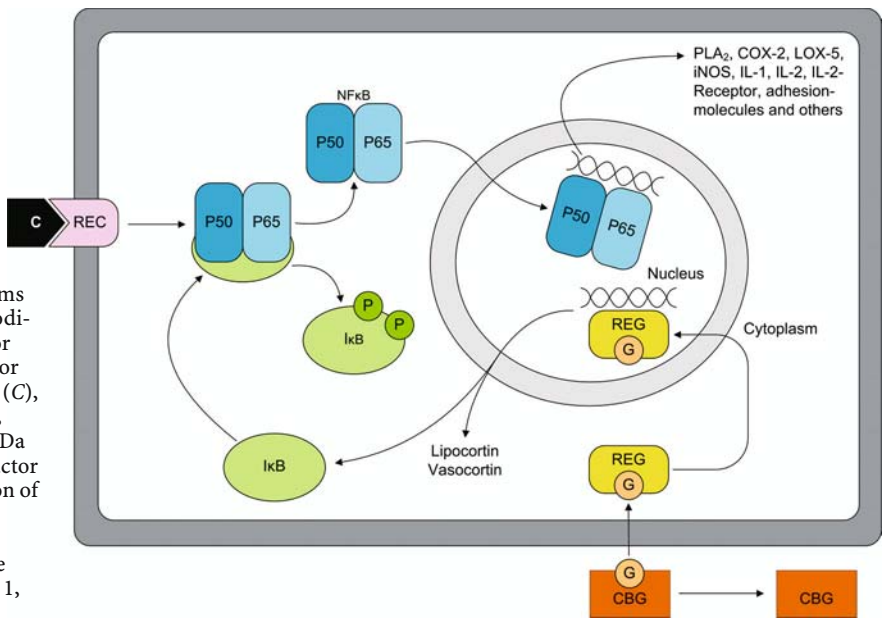

Fig. 52.2. Intracellular mechanisms of action of glucocorticoids (modified from [57]). *REG* receptor for glucocorticoids (*G*), *REC* receptor for pro-inflammatory cytokines (*C*), *CBG* corticoid binding globulin, *IκB* Inhibitor kappa B, *P50* 50-kDa subdivision of NFκB (nuclear factor kappa B), *P65* 65-kDa subdivision of NFκB, *PLA*$_2$ phospholipase A_2, *COX-2* cyclooxygenase 2, *LOX-5* 5-lipooxygenase, *iNOS* inducible NO synthetase, *IL-1* Interleukin 1, *IL-2* Interleukin 2

However, there are also indirect effects via inhibition of transcription factors such as AP-1 and NFκB. NFκB is a heterodimer (subunits p50 and p65), which generally forms a complex with its inhibitor IκB (Fig. 52.2). This binding prevents translocation of NFκB to the nucleus and subsequent transcription of genes encoding pro-inflammatory proteins such as cyclooxygenase, lipoxygenase, phospholipase A_2, inducible NO synthetase, certain cytokines (e.g., TNF-α and interleukins), and adhesion molecules (e.g., ICAM-1, ELAM-1). Corticosteroids influence the transcriptional activity of NFκB by increasing IκB, which binds and inactivates NFκB [72] . Phospholipase A_2 is an important pro-inflammatory mediator, influencing various membrane-mediated reactions in the cell, e.g., within the arachidonic acid metabolism.

In addition, there are also inhibitory protein–protein interactions of the corticosteroid receptor with the p65 subunit of NFκB and with AP-1. This mechanism inhibits the transcription of various NFκB- and AP-1-regulated genes such as IL-2 and collagenase [57].

Nongenomic effects of corticosteroids, which do not require the nucleus (and therefore also occur in cells without a nucleus such as erythrocytes), are thought to occur mainly (but not exclusively) after high-dose systemic steroid administration. They include effects on the cell membrane such as reduction of the membrane permeability for kations and protection against post-traumatic membrane lipid peroxidation [35]. Furthermore, corticosteroids have a nongenomic influence on cellular energy metabolism (e.g., reduction of ATP production [35]).

The antiproliferative effects of corticosteroids refer to an inhibition of mitosis in the basal cell layer of the epidermis and dermal fibroblasts. This obligatory antiproliferative effect of potent corticosteroids is desired in certain hyperproliferative dermatoses such as psoriasis. However, in most other corticosteroid-treated skin diseases, including atopic eczema, it an unwanted effect and may lead to atrophy of the dermis and the epidermis, one of the most feared side effects of topical corticosteroid application.

52.3 Corticosteroid Classification

There is a wide variety of topical corticosteroid preparations containing various active ingredients and base preparations on the market, which can be ranked following their strength of effect. However, potency rankings in the international literature are not always consistent and classification systems vary. The most commonly employed corticosteroid classification in Germany consists of four classes: 1) mild, 2) medium, 3) potent and 4) very potent. Table 52.1 gives an overview of some commonly used topical corticosteroids and their ranking following this German classification. It should be noted that there are age restrictions for certain products.

Class	Generic name	Brand name (examples)	Formulation	Concentration
1. Mild	Hydrocortisone	Hydrogalen	C, O, S, L	1.0 %
		Hydro-Wolff	C	1.0 %
		Hydro-Wolff	C, L	0.5 %
		Hydrocutan mild	O	0.1 %
		Systral Hydrocort	L	0.25 %
	Hydrocortisone acetate	Ebenol 0.25 %	O	0.25 %
		Ebenol 1 %	O	1.0 %
		Ficortril	O (Eye)	0.5 %
		Veluopural OPT	O	0.5 %
	Prednisolone	Prednisolon LAW	C, O	0.25 %
		Linola-H N	C (O/W)	0.4 %
		Linola-H Fett N	C (W/O)	0.4 %
		Prednisolon Augensalbe Jenapharm	O (Eye)	2.5 %
	Triamcinolone – acetonide	Volonimat	C, O	0.025 %
	Dexamethasone	Dexamethason LAW	C, O	0.05 %

Table 52.1. Potency ranking of some frequently used topical steroids (only products without additional active ingredients; no claim of completeness; modified from [35, 66])

C cream, *O* ointment, *G* gel; *L* lotion, *S* solution, *FC* fatty cream, *FO* fatty ointment, *Cresa* cream ointment, *Crelo* cream lotion, *P* paste

Table 52.1. (*contin.*)

Class	Generic name	Brand name (examples)	Formulation	Concentration
2. Medium	Prednicarbate	Dermatop	C, O, FO, S	0.25 %
	Hydrocortisone buteprate	Pandel	C, O, Cresa	0.1 %
	Triamcinolone acetonide	Delphicort	C, O	0.1 %
		Volon A	C, O	0.1 %
		Volon A Haftsalbe	O (Mouth)	0.1 %
		Volon A Tinktur N	L	0.1 %
	Clobetasone butyrate	Emovate	C, O	0.05 %
	Dexamethasone	Cortidexason	O, FO	0.1 %
	Alclometasone dipropionate	Delonal	C, O	0.05 %
	Flumethasone pivalate	Locacorten	C	0.02 %
		Cerson	C, O, S	0.02 %
		Cerson liquidum	S	0.02 %
	Fluprednidene acetate	Decoderm	C, O, P	0.1 %
	Hydrocortisone butyrate	Alfason	C, O, S, Cresa, Crelo	0.1 %
		Laticort	C, O	0.1 %
	Methylprednisolone aceponate	Advantan	C, O, FO, S, L	0.1 %
	Fluocinolone acetonide	Jellisoft	C	0.01 %
3. Potent	Mometasone furoate	Ecural	FC, O, S	0.1 %
	Fluocortolone pivalate and fluocortolone hexanoate	Ultralan	C, O, FO, L	0.25 % (each)
	Betamethasone valerate	Cordes Beta	C, O	1.22 %
		Betnesol V crinale	S	0.112 %[1]
		Betnesol V	C, O, L	0.112 %[1]
		Celastan V	C, O	0.112 %[1]
		Betagalen	C, O, L, S	0.122 %[1]
	Betamethasone dipropionate	Diprosone	C, O, S	0.064 %[2]
		Diprosis	O, G	0.064 %[2]
	Fluticasone propinate	Fluivate	C, O	0.005 %
	Halometasone	Sicorten	C, O	0.05 %
	Fluocinolone acetonide	Jellin	C, O	0.025 %
	Desoximetasone	Topisolon	O, FO, L	0.25 %
	Diflucortolone pentanoate	Nerisona	C, O, FO	0.1 %
	Fluocinonide	Topsym	C, O, S	0.05 %
	Amcinonide	Amciderm	C, O, FO, L	0.1 %
4. Very potent	Clobetasol propionate	Dermoxinale	L	0.05 %
		Dermoxin	C, O	0.05 %
		Clobegalen	C, O, L, S	0.05 %
		Karison	C, O, FO	0.05 %
		Karison crinale	S	0.05 %

C cream, *O* ointment, *G* gel; *L* lotion, *S* solution, *FC* fatty cream, *FO* fatty ointment, *Cresa* cream ointment, *Crelo* cream lotion, *P* paste,
[1] = 0.1 % Betamethasone,
[2] = 0.05 % Betamethasone

52.4 Local and Systemic Unwanted Effects of Topical Glucocorticoids

After the initial enthusiasm for topical corticosteroid ointments (see "Introduction"), they were often applied over prolonged periods of time without critical assessment of unwanted effects, especially as long-term data was still missing. In the following decades, many of the undesired effects of corticosteroids –most often referred to as side effects – became increasingly evident and gradually well known to the general public. The consequence of the somewhat overestimated role of unwanted effects in the public opinion was that today many patients completely reject corticosteroid treatment in any form. However, in particular with the newest, fourth-generation of topical corticosteroids such as prednisolone, hydrocortisone buteprate, or mometasone furoate, unwanted effects of corticosteroid preparations can be avoided in the majority of cases (if employed sensibly and with ground knowledge of possible undesired effects).

The range of unwanted effects or side effects of topical corticosteroid application differ depending on the duration of administration. Short-term application is in general less often associated with severe unwanted effects, while they are more likely to develop in long-term use.

Overall, most of the side effects of corticosteroid applications are local problems, including various types of skin damage (epidermal and dermal atrophy), striae distensae, purpura, impaired wound healing, and telangiectasia (see Table 52.2 for details) [37]. One of the most dangerous effects during treatment with corticosteroids is an increased susceptibility to infections of the skin. This does not only occur after long-term use, but can also potentially be observed already after short-term application. Infections caused by fungi, bacteria, viruses, or others are more frequent in patients with atopic eczema compared to most other skin diseases or healthy individuals (e.g., tinea, pyoderma, or herpes) or can be worsened by topical application of corticosteroids (e.g., scabies). Today nearly all of these infections can be treated easily with appropriate topical or in severe cases systemic drugs (e.g., fungicidal azoles in tinea, antibiotics in pyoderma and acyclovir in herpes). With very few exceptions, there is usually no need for directly adding antibiotic or antimycotic agents to corticosteroid preparations.

Table 52.2. Potential unwanted effects of topically applied glucocorticoids

Suppression of proliferation
Atrophy of the epithelium
Disturbances of pigmentation
Striae distensae
Telangiectasia
Purpura and ecchymosis
Impaired wound healing
Pseudo-anetoderma
Cutis linearis punctata colli
Rubeosis faciei
Milia
Atrophy of the subcutaneous fat tissue (in particular after intralesional injection of crystalline corticosteroid formulations)
Embolia medicamentosa cutis or embolia arteriae centralis retinae (after injection of crystalline corticosteroid formulations)
Distal phalangeal atrophy
Interactions with skin appendages
Acne (steroid acne)
Rosacea
Hair loss
Hypertrichosis
Immunosuppression
Pyoderma
Folliculitis
Tinea (e.g. *Candida intertrigo*)
Herpes simplex
Aggravation of scabies
Allergic reactions
Allergic contact dermatitis
Photoallergic contact dermatitis
Miscellaneous
Granuloma gluteale infantum
Perioral dermatitis, aggravation of perioral dermatitis
Increased light sensitivity
Suppression of the physiological adrenal function

In 1989, Akers summarized the risk of unoccluded treatment of corticosteroid-containing preparations (betamethasone-benzoate, -dipropionate, -valerate, fluocinolone, halcinonide, hydrocortisone, and triamcinolone acetonide) in an overview of 2,849 patients [1]. In his 14-paired comparison, he used the above-mentioned seven steroid preparations in six corticosteroid-sensitive skin disorders including atopic dermatitis. In summary, after 5,698 treatments, 248 adverse reactions were demonstrated corresponding to a total frequency of 4.4%. In detail, he reported irritation (1.39%), itching (0.95%), burning (0.81%), dryness (0.46%), scaling (0.30%), and vesicle formation (0.16%).

Relatively rare unwanted effects of corticosteroid administration that have been published more recently are, for example, milia (especially on the neck and the supraclavicular region)[80], distal phalangeal atrophy [10] and photocontact dermatitis [75].

Systemic effects are not very common after topical application of corticosteroids. However, in rare cases of significant systemic absorption, it is possible that corticosteroid levels higher than the Cushing dose (i.e., >7.5 mg prednisolone equivalent per day in adults) occur. This may lead to adrenal insufficiency or hypercorticism (Cushing syndrome) [9, 76]. Carruthers et al. have shown that, for example, topical application of 45–90 g (weekly) 0.05% clobetasol propionate cream or ointment suppressed the hypothalamic-pituitary-adrenal axis in both normal individuals and patients with diseased skin [7].

The penetration and percutaneous absorption of the corticosteroid is primarily dependent on the molecule structure, the type of vehicle, addition of potential penetration enhancers and the anatomical region treated (Fig. 52.3). The risk of systemic effects of topically applied corticosteroids is also higher in very young children and in patients with significantly impaired barrier function of the skin. Naturally, the larger the body area treated and thus the more corticosteroid preparation is applied onto the skin, the higher the risk of systemic side effects. Percutaneous absorption is also increased in certain body areas such as the face and the anogenital region and under occlusive conditions. In addition, significant interindividual absorption differences (up to factor >10) of identical topical corticosteroid preparations in the same anatomical region have been observed [49].

However, a reduction of plasma cortisol levels or a disturbance of the circadian cortisol rhythm do not necessarily mean hypocorticism. It has been shown, for example, that systemic corticosteroid treatment beyond the Cushing level may reduce plasma cortisol levels without a disturbance of the regulation of the pituitary-adrenal axis and without an actual consequence for adrenal function. Therefore, a small reduction of cortisol plasma level or shift of circadian cortisol peaks in the peripheral blood do not necessarily indicate a pronounced disturbance of adrenal function. However, the fact remains that it is certainly important to avoid any influence on adrenal function and its regulation via pituitary hormones, even though it is not very probable that this will happen with topical, nonocclusive corticosteroid therapy, especially in adults. Table 52.2 summarizes some of the most common unwanted effects of topical corticosteroid use.

One potential adverse reaction of topical corticosteroid application that should not be forgotten, as it is probably more frequent than generally expected, is the development of allergic reactions to the corticosteroid compound. Most commonly, allergic reactions against the steroid molecule in external preparations are type

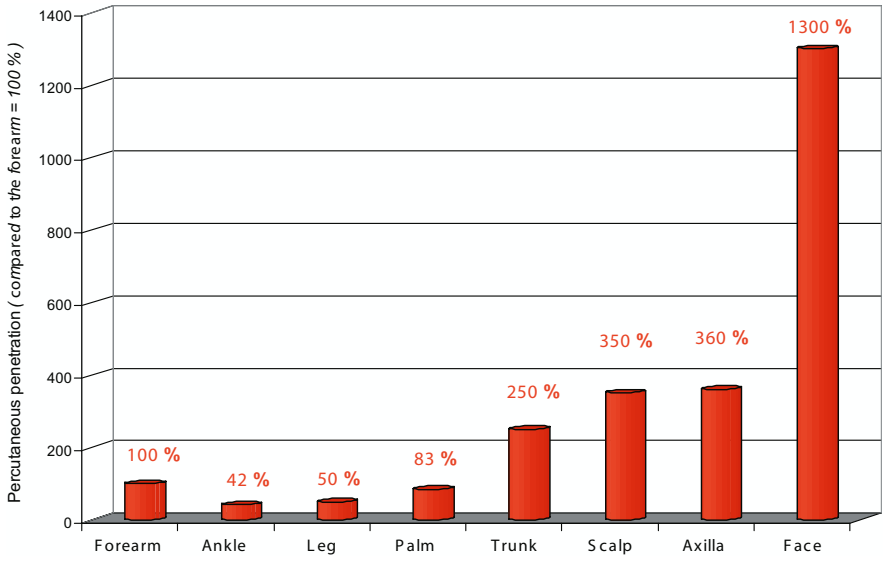

Fig. 52.3. Percutaneous penetration of topical corticosteroids in different body regions compared to the volar aspect of the forearm (modified from [17, 24])

IV reactions such as allergic contact dermatitis. Apart from the development of allergic contact dermatitis, there have also been reports of contact urticaria caused by ingredients of topical preparations [49, 59, 64].

Since the first reports on allergic contact dermatitis to corticosteroid compounds by Burckhardt, Kooij, Church, Sönnichen, O'Hara, and Bandmann et al., more than 100 patients with such allergic reactions have been described [3, 5, 8, 41, 58, 64, 74]. Dooms-Goossens assumed for Belgium that allergic skin reactions induced by corticosteroids might be as frequent as allergic reactions against PABA (ϱ-aminobenzoic acid) and its esters [12]. Since corticosteroids suppress allergic contact dermatitis, the patch test reaction is often difficult to interpret. Overall however, especially considering the frequency of corticosteroid applications, allergic reactions to corticosteroid-containing preparations are still comparably rare. This is remarkable since the cortisol molecule has been modified extensively in the past 40 years such that only the ring structure of the mother substance remained. The exclusively topically applied corticosteroid derivative tixocortol pivalate (pregn-4-ene-3,20-dione-21-thiol-11β, 17α-dihydoxy-21-pivalte), however, seems to be an exception in this context. Hausen and Foussereau demonstrated that tixocortol pivalate is a potent allergen in guinea pigs [30]. It is interesting that allergic patch test reactions were found to be positive even in patients who had never been treated with tixocortol pivalate. The reason for this might be a cross-reactivity of tixocortol pivalate and hydrocortisone [44]. In fact, most corticosteroid-allergic patients react to several corticosteroids because of cross-reactions [44]. Four groups of cross-reactions have been proposed [44]. However, reactions to budesonide are correlated with reactions to both the acetonide group (group B) and the ester group (group D) [44].

Apart from anti-inflammatory glucocorticoids, modifications of the steroid structure cyclopentanoperhydrophenanthrene (e.g., in androgens, cardiaca [digitalis glycosides] and vitamin D) are used for numerous other indications in medicine. Most frequently, allergic reaction to this substance group are seen after topical application. However, cyclopentanoperhydrophenanthrene itself is a weak allergen. Only exceptionally do allergic reactions occur after systemic administration, e.g., progesterone urticaria or drug eruption after digitalis glycosides have been described [4, 89].

Which corticosteroid molecule, which concentration, and which vehicle should be used for patch tests is discussed controversially in the literature [11–13, 29, 64]. One protocol, for example, implies the use of tixocortol pivalate, hydrocortisone-21-acetate, and budesonide in petrolatum in addition to the preparation suspected to be the cause of the patient's contact dermatitis.

However, an allergic contact dermatitis to a corticosteroid-containing formulation does not necessarily have to be caused by the steroid molecule itself. Many of the constituents of the vehicle (e.g., emulgator, antioxidant, or stabilizer) or additional active ingredients of the product (e.g., antibiotics, antimycotics, antiseptics) can cause allergic contact reactions.

52.5 Influence of the Vehicle on the Effect of Topical Corticosteroid Preparations

It has been shown by Stoughton and co-workers that the same steroid preparation offered by different companies can potentially exert very different therapeutic effects [77]. This is due to the complex influences of various factors of the formulation on clinical effects of the product. The affinity between the corticosteroid molecule and its vehicle, for example, is an important factor determining the penetration into the skin (if the barrier function of the horny layer is intact) and clinical efficacy [46–48, 62, 69]. The higher the degree of corticosteroid saturation in a vehicle, the greater its therapeutic effect. However, this is only correct if the drug is in solution (solution-type ointment). If on the other hand the corticosteroid is suspended in the base preparation – suspension-type ointment – (under the prerequisites that (a) the corticosteroid concentration is sufficient to guarantee a constant flux and (b) there is a fast corticosteroid liberation without changes of the skin barrier), its maximum effect is independent of the base preparation [34, 46, 47, 50, 51, 60].

Malzfeldt and co-workers demonstrated that a betamethasone-17-benzoate solution-type ointment (e.g., neutral oil gel) was less effective compared to an identically concentrated (5.6 mg per 100 g ointment) suspension-type ointment (e.g., paraffin gel) in the treatment of atopic eczema and allergic contact dermatitis [50]. This is in accordance with findings showing that corticosteroid liberation and skin blanching are stronger

after topical application of betamethasone-17-benzoate in suspension-type ointment (paraffin gel) than in solution-type ointment (neutral oil gel) of the same concentration [46–48, 51]. Without knowledge of the degree of saturation, the solubility, and liberation of the corticosteroid from the base preparation into the skin, the therapeutic effect of the applied product cannot be precisely predicted.

It is also possible that a dilution of the corticosteroid in certain ointment bases does not reduce its potency equivalently [19, 51], and may as a consequence cause unexpected side effects. Gibson et al. could not confirm significant differences in blanching activity of clobetasol after a tenfold dilution [19]. This finding can only be understood by assuming that a solution-type ointment was used as vehicle [51]. Furthermore, the results of Watson and Findlay revealing nearly identical liberation of clobetasol from a propylene glycol and a paraffin ointment can be interpreted insomuch that clobetasol was most likely suspended in the concentration used [84]. In these experiments, it was also demonstrated that a very high amount (90 %) of the drug was found in the gauze which covered the skin after application of the ointment [84].

While W/O emulsions have been shown to improve the stratum corneum barrier, many O/W emulsions (e.g., nonionic hydrophilic cream DAB, hydrophilic skin emulsion base NRF and base cream DAC) may themselves compromise the epidermal barrier function [21]. This might lead to enhanced drug penetration, as has been shown for hydrocortisone in a study by Gloor et al. [21]. Additional ingredients such as moisturizers or other drugs (e.g., salicylic acid, urea, polyethylene glycol) are also able to influence the penetration of corticosteroids and thereby alter the effects of the product in a manner that is difficult to predict [7, 25, 56]. In summary, free formulations with unknown liberation and penetration characteristics of the active ingredient should be used with caution, as the entire formulation has an important influence on the efficacy and safety of the product.

52.6 Additional Active Ingredients in Topical Corticosteroid Preparations

It is known today that *Staphylococcus aureus* plays an important role in the pathogenesis of atopic dermatitis and a reduction of *S. aureus* on the skin surface may improve clearing of the disease [2, 18, 45]. Furthermore, atopic dermatitis is frequently associated with skin infections, especially those caused by bacteria (e.g., impetiginized atopic dermatitis). Therefore, antiseptics or antibiotics are often added to corticosteroid products for atopic dermatitis. It has been shown, for example, that a preparation containing betamethasone valerate and gentamycin was more effective than either compound alone [82]. However, one should be very careful with the use of combination products and the addition of topical antibiotics should be avoided. The reason for this is the risk of allergic reactions to the antibiotic and the development of resistance against topically applied antibiotics.

Neomycin is frequently used as a topical antibiotic, since it is not administered systemically. However, an allergy against neomycin can be associated with allergic cross-reactions against other aminoglycoside antibiotics such as gentamycin, a very important systemic drug. Mupirocin is an antibiotic preparation developed exclusively for topical use. As no other drug with a comparable chemical structure is used in human medicine, the danger of antibiotic cross-reactions with potent systemic drugs is comparably low for this molecule. Therefore mupirocin can be used safely in impetiginized atopic dermatitis. However, it is preferable to apply mupirocin ointment on its own for a couple of hours followed by a conventional corticosteroid preparation. Alternatively, a combination of an antiseptic substance (e.g., Triclosan) and a corticosteroid or a corticoid ointment underneath wet wraps with aqueous antiseptic solutions (e.g., chinosol solution) can be used. If a more severe bacterial infection or superinfection such as strong pyoderma occurs, systemic administration of an antibiotic is warranted. This can be performed either according to an antibiogram or using a broad spectrum antibiotic against those bacteria most frequently found in infectious skin disorders (e.g., penicillin derivatives, erythromycin or gyrase inhibitor).

Many additional active ingredients such as tar derivates, salicylic acid, antihistamines (H_1-receptor blockers), or fungicides have been incorporated into corticosteroid preparations, especially in products for atopic eczema. However, the clinical effect of these preparations is in most cases largely caused by the efficacy and potency of the corticosteroid itself.

Since unpredictable interactions between the corticosteroid and additives are possible, caution must be

exerted, especially when the prescription is composed individually without being thoroughly evaluated.

52.7 Acceptance of the Use of Topical Corticosteroids

The first topical application of a corticosteroid preparation was given as treatment for atopic eczema [78]. Since then, the treatment of atopic eczema with topical corticosteroids has been mainstream therapy and until very recently the only powerful topical alternative for active flare-ups of the disease. Only a few years ago, the therapeutic armamentarium of topical agents for atopic dermatitis was enriched by another group of potent, anti-inflammatory substances, the calcineurin inhibitors.

Calnan stated nearly 30 years ago that the value of a drug or of a topically applied substance can be measured by three main requisites: (a) efficacy, (b) harmlessness, and (c) acceptance [6]. This statement is still valid today. It is still the case that there are few topical drugs in the treatment of atopic eczema that are as effective as corticosteroids. However, we have to be cautious concerning the judgment of their harmlessness and potential side effects. The acceptance of corticosteroids in the general population is certainly still not at its best. The acceptance history of treatment of atopic eczema with topical corticosteroids can be divided into two main periods. At first it was assumed enthusiastically that topical corticosteroid therapy could be given without *any* side effects. In comparison to other topical alternatives for atopic dermatitis such as coal tar preparations, they also offered the advantage of being cosmetically highly acceptable. However, when the undesired influences of topical steroids on the skin and potentially the entire organism became gradually better known, a period of major antipathy toward corticosteroid therapy started. Today, despite major efforts to inform patients about the realistic risk of unwanted effects and, on the other hand, great benefits of intermittent corticosteroid treatment, there is still a considerable amount of unjustified "cortico-phobia" among patients and parents of children with atopic dermatitis.

This empiric observation has been confirmed in many studies. In 1993, Haggenmüller, for example, described that among 200 questioned mothers, 70 % stated that they had apprehensive reservations against a corticosteroid therapy for their child [26]. Most of these patients also felt they were not well enough informed by their physician concerning this matter and more than 50 % had acquired their "knowledge" from the public press. Among 1,409 Swiss patients, who visited their physician for different health reasons, 79 % stated they would have doubts about whether to accept a corticosteroid therapy [88]. It is interesting that even patients who had never received corticosteroid therapy had reservations against these substances, while patients who already had been treated with corticosteroids were generally less anxious. In comparison to these high numbers, only 10 % of 66 patients with asthma stated they were anxious of corticosteroids [61].

There are even significant numbers of physicians, in particular physicians with an interest in alternative healing methods, who are against any form of treatment with topical corticosteroids in atopic eczema as well as other corticosteroid-responsive skin diseases. However, one has to accept that potent treatment modalities, which are highly effective, usually do not come without *any* potential unwanted effects. But with the newer generations of corticosteroids and when used sensibly, these can usually be avoided completely.

The treatment of atopic dermatitis with corticosteroid preparations is complicated by the fact that after systemic administration of the drug, a dosage reduction and final conclusion of therapy may induce a relapse, which is often stronger than the previous one (rebound phenomenon), is harder to treat, and requires higher doses of corticosteroids to ameliorate the symptoms. The same phenomenon is well known in the treatment of other chronic, steroid-responsive disorders such as psoriasis. Therefore, oral or parenteral corticosteroid administration is only indicated in atopic dermatitis if severe complications are present. In contrast to the undesired effects after systemic corticosteroid treatment, topical application is only exceptionally accompanied by significant systemic resorption and a rebound phenomenon can be avoided in most cases by gradual withdrawal of the corticosteroid.

52.8 Principles of Topical Treatment with Corticosteroids in Atopic Eczema

The choice of a topical corticosteroid preparation has to be adjusted to several factors such as acuity of the disease, body location, and skin condition. The acuity of dermatitis determines the choice of the corticosteroid as well as the vehicle. In an acute phase, a light corticosteroid preparation (e.g., water-rich O/W cream) should be used, while lipid-rich formulations and occlusive ointments should be avoided. Usually the corticosteroid for acute phases should be potent (e.g., 0.1 % mometasone furoate or 0.05 % clobetasol-17-propionate). However, in some patients a medium-strength preparation (e.g. 0.25 % prednicarbate) is preferable (dependent on body location, age of the patient, etc.) in order to prevent unwanted effects. If a potent or very potent corticosteroid (class III or IV) is administered to a large body area, it makes sense to adjust the application time to the physiological circadian cortisol rhythm (i.e., apply the preparation early in the morning before 8:00 a.m.) in order to avoid adrenal suppression. In atopic eczema, this also makes sense, as the physiological maximum of mitotic activity takes place in the early morning hours [56].

The initial application of a medium to potent corticosteroid is preferable to (prolonged) administration of a weaker substance. Schalla discussed the possibility of initially applying a weak steroid, because a disturbed epidermal barrier function in the acute inflammatory phase of atopic dermatitis may increase percutaneous absorption and thus the risk of side effects [71]. However, findings of Malzfeldt et al. have shown that differences in epidermal barrier function in the acute inflammatory phase of atopic dermatitis do not influence the efficacy of a corticosteroid preparation [51]. In addition, tachyphylaxis, which means that the preparation becomes significantly less effective after repeated applications, has to be taken into account [14, 49]. Therefore, it is reasonable to start therapy with a rather potent corticosteroid in order to induce a quick remission; usually, once daily application is sufficient, as the corticosteroid will form a reservoir within the stratum corneum [56]. In some cases, application twice daily will be preferred. The exact frequency and duration of corticosteroid therapy have to be adjusted individually. In most cases, however, remission is achieved after 1 – 4 days of treatment with a potent corticosteroid. In children potent corticosteroid preparations should be avoided in the face, anogenital, and intertriginous areas.

After disappearance of acute inflammatory signs, the skin will become dry and scaly, and a formulation containing more lipophilic and less hydrophilic constituents (e.g., a lipid-rich W/O cream or ointment) should be applied. At this stage, the potent corticosteroid should be changed to a less potent one. In the following 1 – 4 days, the treatment should stabilize the skin condition, which results in a corticosteroid treatment phase of 2 – 8 days in total. A placebo-controlled study has shown that intermittent continuation of the corticosteroid (2 days per week) is advantageous concerning stabilization of the remission. Intermittent application also reduces the risk of potential local and systemic unwanted effects [20]. Whether continued daily application of a weaker corticosteroid instead of intermittent application of a stronger one would have the same benefit in terms of delay of relapses is doubted [20]. Controlled studies comparing different corticosteroid application schemes at the end of therapy, i.e., intermittent application vs tapering (step therapy), are needed.

Alternatively, it is possible to introduce the topical application of a calcineurin inhibitor such as pimecrolimus or tacrolimus after the initial strong anti-inflammatory action of a potent corticosteroid. In our experience, this scheme optimizes clinical efficacy with rapid clearing of the disease, minimizes the risk of rebound phenomenon after cessation of the corticosteroid and therefore increases patient compliance. The latter scheme has proven to be of high value in practice.

Treatment of atopic dermatitis should never exclusively consist of topical corticosteroid application, but should be embedded in various additional measures. Other topical principles such as anti-pruritic drugs (e.g., polidocanol or urea), salicylic acid, tannic acid, tar preparations, bathing with various additives such as salt and long-term application of emollients can be added. The purpose of initial anti-inflammatory treatment with corticosteroids is to reduce pathological inflammation, while the following skin care regimen is aimed at delaying acute relapses. In addition, systemic antihistamines can be of value in order to disrupt the vicious cycle of scratching and inflammation. Table 52.3 summarizes recommended guidelines for topical corticosteroid therapy in order to avoid unwanted effects and complications of therapy. Systemic treatment with glucocorticoids is discussed elsewhere in this book.

Table 52.3. Guidelines for topical corticosteroid therapy in order to avoid unwanted effects

"As short as possible, as long as necessary"
Short-term application of potent steroids is preferable to long-term application of weaker preparations
Frequent re-evaluation and cessation of corticosteroid therapy, if possible after a maximum of 2 – 3 weeks
Combination with other topical measures
In children only mild or medium-strength corticosteroids
No potent preparations in the face, in intertriginous areas or anogenital region
The treated body surface should be kept as small as possible
The prescribed amount of corticosteroid-containing preparation should be adjusted to the treated body surface (Fig. 52.4)
The patient has to be informed that the prescribed formulation contains a corticosteroid
Application of the corticosteroid in atopic dermatitis preferably early in the morning
In children and intertriginous areas, no therapy under occlusion
Adjustment of base preparation to skin condition, acuity of disease, and body location
Preferably no combination with topical antibiotics
Enhanced percutaneous absorption by certain additives (e.g., salicylic acid and urea)
At the end of therapy intermittent continuation (e.g., 2 days per week) or slow tapering

52.9 Topical Corticosteroids Versus Topical Inhibitors of Calcineurin

Topical corticosteroids have significantly influenced dermatological therapy of atopic dermatitis for the past five decades. Before the venue of topical corticosteroids, therapy for atopic eczema was extremely difficult and often frustrating. Due to the proven efficacy in inflammatory skin diseases, the use of topical corticosteroids quickly became a first-line treatment for many dermatoses including atopic eczema.

After the development of highly potent topical corticosteroids in the decades after Hench's first therapeutic use of an adrenal cortical hormone[32], overzealous application of these without basic knowledge of the side effects led to uncontrolled use and induction of the well-known undesired effects in thousands of patients. This resulted in the aforementioned period of fear toward topical corticosteroid treatment. Due to the newest generation of topical corticosteroids with improved benefit-risk ratio and a more cautious application strategy by physicians, most of the side effects are no longer seen in daily practice. Today, it is a very rare event to encounter epidermal or dermal atrophy, disturbances of pigmentation, striae distensae, pyoderma, and folliculitis, purpura and ecchymosis, hy-

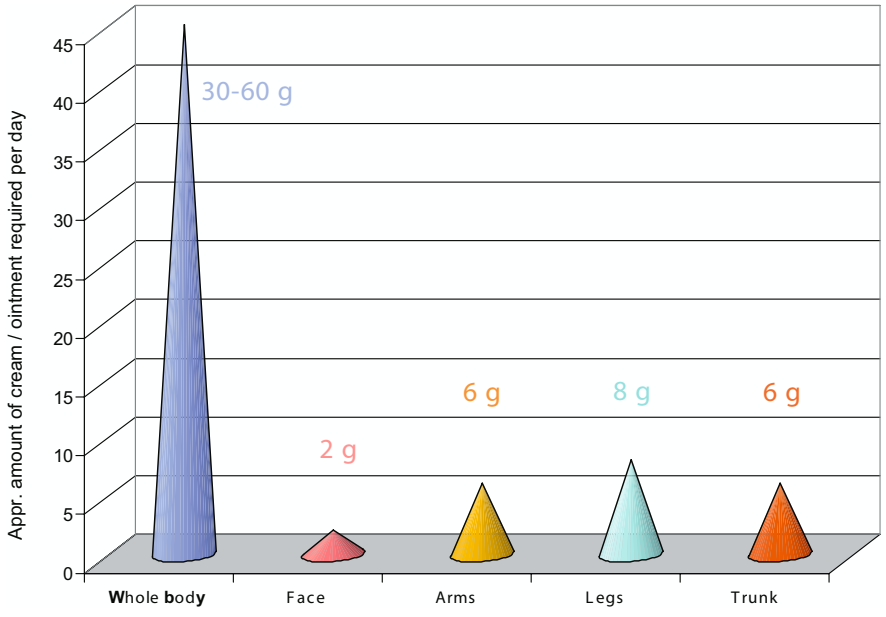

Fig. 52.4. Required amounts of cream/ointment for topical therapy of certain areas of the body per day (once daily application)

pertrichosis, or granuloma gluteale infantum following the correct application of topical corticosteroids. The only clinically significant side effect that may interfere with topical corticosteroids therapy is steroid-induced rosacea and steroid-induced perioral dermatitis. In this situation, the development of a new class of anti-inflammatory drugs will be highly welcomed, namely the topical inhibitors of calcineurin, which can apparently also be used safely for inflammatory dermatoses of the face.

However, although calcineurin inhibitors are a valuable and indispensable new therapy for atopic eczema, topical therapy with corticosteroids still remains an extremely important therapeutic strategy for atopic eczema. Their advantage is a very rapid onset of action (highly potent corticosteroid preparations can initiate relief of symptoms within 0.5 h after application), a well-established profile (evaluated over many years), of long-term effects and risks, and the availability of a variety of different base preparations.

Topical inhibitors of calcineurin is a relatively newly developed substance class for which long-term experience (>10 years) is lacking. Undoubtedly, very thoroughly designed and accomplished studies have demonstrated a very good efficacy of topical calcineurin inhibitors in atopic eczema with only few side effects [15, 54, 55, 65, 67, 79, 83]. However, the use of topical inhibitors of calcineurin in atopic eczema of children and adults has only been observed for 5–10 years. This is comparable to the era of topical corticosteroid treatment in the 1960s. Accordingly, long-term evaluation has to be carried out carefully in order to assess definitive tolerability and safety. Until this important task is concluded, it seems premature to declare the postcortisone era in clinical dermatology. For the time being, topical corticosteroids remain the first-line treatment option for acute exacerbated atopic eczema and also for the long-term management of this disease, with the mentioned exception of dermatitis occurring in the facial region.

Despite the lack of long-term experience, topical inhibitors of calcineurin have another disadvantage in the treatment of atopic dermatitis compared to topical corticosteroids. For experienced dermatological topical treatment strategies, the base of the drug has an almost as important value as the effective ingredient. Thus, the base has to be chosen according to the acuity of the disease, the body region where the drug is to be applied, and the skin type of the patient. For topical corticosteroids, a variety of vehicles with many different corticosteroid molecules are available and can expertly be chosen for a given indication, body region, and phase of the disease. Now we have one tacrolimus ointment preparation and one pimecrolimus cream preparation available on the market, which makes treatment difficult for certain areas such as the scalp and intertrigo. Another advantage of topical corticosteroids is the quicker onset of clinical efficacy.

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