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Topical Corticosteroids in Dermatology: From Chemical Development to Galenic Innovation and Therapeutic Trends

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Abstract

Topical corticosteroids are the cornerstone therapy for many inflammatory skin conditions. In recent decades, the development of new molecules with improved benefit/risk ratio and innovative galenic formulations has boosted the field of topical corticosteroid therapy. Alternative classifications of topical corticosteroids have been introduced taking into consideration the potential adverse effects of each molecule in order to provide useful information for clinical practice. Concurrently, new therapeutic regimens with topical corticosteroids have been proposed to provide long-term approaches for the management of chronic relapsing inflammatory skin diseases.

The aim of this review is to provide an overview of topical corticosteroids focusing on the recent research performed in the fields of classification methods, galenic formulations and therapeutic strategies.

Keywords: Topical corticosteroid; Therapeutic index; Mometasone furoate; Vehicle; Formulation; Adherence; Proactive treatment

Introduction

Topical Corticosteroids (TCs), play a major role in the treatment of a large number of inflammatory skin diseases. Available for dermatologic therapy since 1952, when Sulzberger and Witten successfully treated selected dermatoses with hydrocortisone [1], TCs are by far the most commonly prescribed medication in an out-patient dermatology setting. TCs exhibit potent anti-inflammatory and antiproliferative effects responsible for their efficacy in skin. However, inappropriate use of TCs can lead either to local adverse effects such as skin atrophy and telangiectasia, or to systemic adverse effects, such as Hypothalamic-Pituitary-Adrenal (HPA) axis suppression and diabetes mellitus [2]. Moreover, TCs are the cornerstone of treatment for many chronic inflammatory skin conditions and addiction to therapy and withdrawal are common situations that healthcare practitioners need to face. Bearing all that in mind, comprehensive knowledge of TCs is essential in order to optimize therapeutic outcomes, avoid improper prescriptions and minimize the risk of adverse effects.

In the last decades, corticosteroid derivatives have been designed in order to simultaneously improve efficacy and reduce the incidence of adverse effects. Beyond this, the development of new formulations to enhance penetration through the skin and biological activity of the active compound on one hand, and to fulfil patients' needs (e.g. less greasy vehicles, shampoo formulations) for improving adherence to topical therapy on the other hand, has centred the research in recent years, all together with the ultimate objective of improving treatment effectiveness [3,4].

Topical Corticosteroids

TCs are hydrocortisone-derivative compounds with differentiated anti-inflammatory potency and adverse-effects profile [5]. Corticosteroids display a dual action at the cellular level. On one hand, they act via the glucocorticoid receptor (genomic pathway). By binding this receptor, they promote the transcription of several genes with anti-inflammatory functions and down-regulate the expression of pro-inflammatory genes. On the other hand, they act via membrane-bound receptors and second messengers (nongenomic pathway) by modulating the level of activation of target cells such as T cells and platelets. This pathway does not require protein synthesis and is responsible for the rapid effects of corticosteroids. This dual mechanism of action leads to the anti-inflammatory, antimitotic, apoptotic, vasoconstrictive and immunomodulatory functions of corticosteroids [6].

Chemical masking or removal of one or both of the 16- or 17-hydrophilic hydroxyl groups, or addition of long carbon side-chains (acetonides, valerates or propionates) increase topical steroid's lipophilicity [7]. The ideal TC should have the ability to achieve a therapeutic concentration in the target cell of the skin by running through the *stratum corneum*, yet without reaching the systemic circulation to avoid systemic adverse effects [8]. TCs lipophilicity is directly related to this penetration capacity, and recent advances in TCs development have focused on enhancing these molecular characteristics. In the same way, chemical substitutions in the steric configuration are able to modify their biological activity. For example, halogenation increases the potency but also the potential adverse effects, whereas esterification has been reported to enhance potency while improving the safety profile of the molecule [9]. More recently developed TCs incorporate some of these favourable molecular attributes to provide improved efficacy while minimizing the risk of adverse effects.

Mometasone Furoate (MF) is a (2') furoate-17 ester with chlorine substituents in the 9α- and 21- positions [10,11]. According to the ATC/DDD Index (Anatomical Therapeutic Chemical classification and Defined Daily Dose), MF 0,1% belongs to Class III (potent) topical corticosteroids [12]. However, it has a low percutaneous absorption and undergoes rapid hepatic biotransformation, thus it is characterized by low systemic availability. Moreover, MF molecular biotransformation in the skin brings lower affinity to dermal than to epidermal cells and is responsible for the low atrophogenicity of MF [13-15]. These attributes confer MF a low risk of both local and systemic adverse effects. Similarly, Fluticasone Propionate (FP), a 17-carbothioate synthetic corticosteroid, and methylprednisolone aceponate (MPA), a non-halogenated diester corticosteroid, share some molecular advances and metabolic characteristics with MF, showing enhanced lipophilicity and rapid hepatic biotransformation which lead to a reduced risk of systemic adverse effects. Likewise, FP and MPA belong to the ATC/DDD Index Class III (potent) topical corticosteroids [14,16].

Several human models such as the vasoconstriction test, the ultraviolet erythema test and the pyrexial erythema test have been developed in order to assess TCs potency and efficacy [17]. In addition to the anti-inflammatory tests, the skin atrophy test is important to determine the degree of antiproliferative effect of TCs. Regarding the vasoconstrictive properties of TCs, the vasoconstrictor assay (VCA) is used to measure their relative potencies. Developed by McKenzie and Stoughton, the VCA measures the degree of visible blanching caused by various dilutions of corticosteroids when applied to human skin [18,19]. The ability of a TC to induce vasoconstriction ("blanching effect") has been associated with its anti-inflammatory properties. Therefore, the VCA provides a useful method for predicting the clinical effectiveness of TCs [20]. Nevertheless, the anti-inflammatory effect of TCs in daily clinical practice is influenced not only by the strength of the formulation but also by several other factors such as the anatomical site of application, duration and frequency of administration and patient adherence [21,22].

TCs can be classified into different groups according to their potency. Several classifications have been proposed. The most commonly used in Europe are the ones from the ATC/WHO, the British National Formulary and Niedner's classification [12,23,24]. All of them propose four potency groups with Class I grouping the least potent molecules (e.g. hydrocortisone) and Class IV the most potent (e.g. clobetasol propionate). In contrast, the American classification considers seven potency groups in reverse order, with Class I TCs being the most potent and Class VII the least potent [25].

	Mometasone furoate	**Methylprednisolone aceponate**	**Prednicarbate**	**Hydrocortisone butyrate**	**Clobetasol propionate**	**Betamethasone valerate**	**Triamcinolone acetate**	**Hydrocortisone**
Vasoconstriction (4)	8	8	8	8	12	8	8	4
Efficacy for atopic dermatitis compared to other TCs (5)	10	10	10	10	15	10	10	5
Total A	**18**	**18**	**18**	**18**	**27**	**18**	**18**	**9**
Skin atrophy (6)	6	6	6	6	12	12	12	6
HPA axis suppression (2)	2	2	2	2	4	2	4	2
Allergenic potential (1)	1	1	1	1	1	1	1	1
Total B	**9**	**9**	**9**	**9**	**17**	**15**	**17**	**9**
Therapeutic Index (Total A/ Total B)	**2**	**2**	**2**	**2**	**1.5**	**1.2**	**1.06**	**1**
ATC/DDD Index	III	III	III	II	IV	III	II	I
HPA: Hypothalamic-Pituitary-Adrenal; TC: Topical Corticosteroid								

Table 1: Therapeutic Index (TIX) of commonly used topical corticosteroids. (Adapted from the German Guidelines [25]). The TIX is calculated as the ratio between efficacy criteria (Total A) and adverse effects criteria (Total B). Each criteria is scored between 0 and 3 and weighted by a correction factor (in brackets).

Classification of Topical Corticosteroids: The Therapeutic Index

Besides the anti-inflammatory potency of TCs, adverse effects are of great importance in their clinical application. Given that not all the available corticosteroids from the same potency group have similar potential to induce skin atrophy and systemic adverse effects, Luger et al. introduced the Therapeutic Index (TIX) as an attempt to classify TCs according to the relationship between the desirable and undesirable effects [26]. The TIX differs from the classic classifications of TCs that are only based on the potency of the molecule, and takes into consideration the risk adverse effects of each TC. A TIX score of 1 or lower indicates a poor ratio of desirable versus undesirable effects whereas a TIX score of 2 or higher indicates an advantageous relation between therapeutic and adverse effects.

The criteria used for the TIX are listed in Table 1. On one hand, vasoconstriction potency and literature-based efficacy for atopic dermatitis compared with other TCs are used as parameters related to desirable effects. On the other hand, skin atrophy, hypothalamic-pituitary-adrenal axis suppression and allergenic potential are the potential adverse effects taken into account. Each item is scored from 0 to 3 and weighted by a correction factor. Afterwards, the total score of desirable effects is divided by the total score of undesirable effects to obtain the final TIX score.

The TIX is useful for selecting TCs of the same potency group for the management of chronic inflammatory skin diseases in order to minimize adverse effects derived from long-term therapy. Since an important criterion for TIX estimation is the efficacy of the evaluated molecule for atopic dermatitis, the TIX score cannot be directly inferred to the treatment of other dermatoses without some constraints. Nevertheless, it provides valuable information about the risk-benefit profile of a specific TC. In fact, the appropriate use of TCs with a TIX of 2 or more minimizes the risk of producing the feared irreversible adverse effects such as skin atrophy or telangiectasia [27].

New Pharmaceutical Formulations of Topical Corticosteroids

The success of topical treatment is determined not only by the intrinsic activity of the active molecule, but by the characteristics of the vehicle that directly influence patient's compliance and may modify penetration through the skin and, consequently, treatment potency. Optimizing penetration by altering the formulation of the vehicle should guarantee the solubility and chemical stability of the therapeutic agent and the hydration of the *stratum corneum* of the epidermis. Meanwhile, the formulation vehicle plays an important role in treatment adherence [28]. Adherence to topical treatment is generally poor and worsens in chronic conditions such as psoriasis and atopic dermatitis [29,30]. Indeed, non-adherent patients account for almost 40% of patients with psoriasis [31]. Choosing the right therapeutic agent yet in the wrong vehicle might jeopardize patient adherence and, consequently, the achievement of treatment goals. Despite the proven efficacy and safety of modern TCs developed in the last decades, there was still a long way to go in developing vehicles with improved cosmetic properties. For this reason, progress in the field of TCs in recent years has been focused on new formulations in order to both fulfill patient's preferences and adapt to anatomical region characteristics.

In the case of MF, the available mometasone cream (original and generic products) is a fatty cream (W/O formulation) containing less than 5% of water, whereas the available solutions are alcoholic formulations with an increased risk of skin drying and burning sensation when applied to the scalp [11]. Given all the aforementioned, new formulations of MF have been recently developed to broaden the clinical spectrum of MF indications and to improve patient adherence. Already available, a new MF light cream with 33% of water content on the base of an oil in water (O/W) formulation has been created to overwhelm classical MF formulations [32]. Studies have assessed similar bioavailability, efficacy and tolerability compared to the previous MF cream although with the enhanced cosmetic properties of a lighter cream [32,33]. Concurrently, an innovative MF non-alcoholic emulsion with 36% water content has been developed to provide emollient properties and avoid the risk of skin irritation and dryness derived from the use of alcohol-containing solutions. This new fluid emulsion has demonstrated similar efficacy and safety results compared to the previous MF formulations, with improved cosmetic attributes and is suitable for the treatment of inflammatory conditions of the scalp (e.g. scalp psoriasis, atopic dermatitis), among others [34,35]. A staining test performed to assess the external phase of the different MF formulations available highlights the cosmetic improvements of the latest MF formulations (Figure 1) [4]. The external phase of the new MF cream and emulsion stain with blue colour, indicative of the hydrophilic nature of the external compound, whereas the previous MF creams and both ointments stain with red colour, indicative of the hydrophobic nature of the external compound. The previous cream and ointment show an external oil phase and are W/O formulations. By contrast, the new MF cream and emulsion have an external aqueous phase and are real O/W formulations that make them also suitable for the treatment of acute inflammatory conditions.

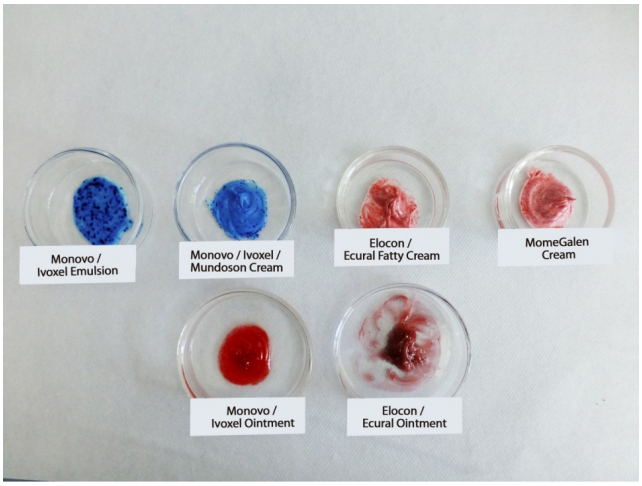

Figure 1: Staining test of the external phase. Reddish staining with Sudan III of the lipophilic component of water in oil (W/O) and ointment formulations, and bluish staining of the hydrophilic component of genuine oil in water (O/W) formulations [26].

Together with the new MF formulations, Clobetasol Propionate (CP) shampoo has been developed for short-term contact therapy of inflammatory scalp conditions [36]. CP and betamethasone valerate are also available as foams [37]. This pharmaceutical formulation has improved cosmetic acceptance although it is at greater risk of inducing skin irritation, especially in patients with atopic dermatitis, due to the lack of adequate emollient properties and to some alcoholic ingredients, such as stearyl- and cetyl-alcohol or ethanol.

Further research is currently being performed with microemulsion systems as the carriers for TCs. Lipid-core nanocapsules minimize the amount of drug that can reach the deeper skin layers to avoid systemic absorption without changing its accumulation in the *stratum corneum* [38,39]. Furthermore, vehicles with pseudoceramide-containing physiologic skin lipids have shown to provide boosted anti-inflammatory and skin barrier restorative effects in comparison to polyethylene glycol or ethanol-containing vehicles [40]. The addition of physiologic skin lipids in new formulations provides an opportunity to counteract the potential disruptive effect of TCs on the skin barrier function.

New Treatment Modalities with Topical Corticosteroids: Proactive Treatment

In the first decades after the introduction of TCs to dermatological practice, the increased risk of irreversible adverse effects of the first molecules, such as skin atrophy or telangiectasia, limited long-term treatment strategies. Nevertheless, the development of new corticosteroids with increased lipophilicity together with improved vehicles have opened the door to new treatment modalities with TCs. Proactive treatment provides an opportunity to extend remission period in chronic relapsing inflammatory skin conditions. Evidence of the efficacy and safety of this therapeutic approach has been published in recent years for some TCs with a TIX score of 2.0. FP has shown to delay relapses in atopic dermatitis when added twice weekly to emollient maintenance treatment [41]. Meanwhile, long-term proactive approach with MF applied twice weekly has been shown to be a safe option and to reduce the relapse rate in lichen sclerosus [42]. MF has also been proved to be as effective as clobetasol propionate (reference therapy) for the active phase of lichen sclerosus in a recently published randomized controlled trial [43].

Conclusions

Topical corticosteroids are the cornerstone of treatment for a large number of inflammatory skin diseases. A comprehensive knowledge in the field of TCs is essential for daily clinical practice in order to avoid adverse effects derived from their inappropriate use.

In the second half of the last century, chemical structure modelling obtained new TC molecules with improved pharmacological attributes. However, the absence of newly developed TC molecules in the last years might lead to the incorrect conclusion that no additional progress has been achieved. Efforts in recent years have been focused on the development of innovative formulations in order to fulfil patients' needs, improve bioavailability and minimize the risk of skin barrier function disruptive effect. For instance, mometasone innovative galenics provide real oil-in-water (O/W) formulations with high water content that offer better cosmetic acceptability, tolerability and patients' preference compared to the original formulations. These attributes make them also suitable for acute inflammatory skin conditions, might impact treatment adherence rates and improve treatment success in chronic inflammatory diseases.

Together with pharmacological development, clinical progress has been highlighted by the introduction of practical tools to further evaluate TCs. The TIX offers valuable information about the risk of adverse effects and provides a comparison between TCs of the same potency group. Moreover, the favorable benefit/risk ratio of modern TCs has allowed new therapeutic approaches for chronic relapsing inflammatory skin conditions. Proactive therapy based on long-term intermittent TC treatment has shown to have a substantial effect on preventing relapses in several inflammatory skin diseases.

Conflicts of Interest Disclosure

DA received consulting fees and/or honoraria from Almirall, Deutsche Akademie für Entwicklungsförderung und Gesundheit des Kindes und Jugendlichen e.V., GlaxoSmithKline GmbH, Govi Verlag, Infectopharm GmbH, L`Oreal Deutschland GmbH, MSD Sharp & Dohme, Nestlé Germany, Pierre Fabre Deutschland, Taurus Pharma GmbH.

Almirall S.A is the manufacturer of the Monovo cream® and Monovo emulsion® both formulation with mometasone furoate.

AG and IP received honoraria for medical advisory tasks from Almirall.

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