Current Threats and Problems in the Topical Use of Steroids?: Review

Topikal Kortikosteroid Kullanımında Güncel Tehlike ve Problemler

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Geliş Tarihi/*Received:* 01.06.2008
Kabul Tarihi/*Accepted:* 08.09.2008

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ABSTRACT Corticosteroids are valuable in the management of many dermatoses. On the other hand, adverse effects commonly develop due to systemic as well as topical delivery of corticosteroids. It is well known that prolonged systemic use of corticosteroids may lead to suppression of the hypothalamic-pituitary-adrenal axis. Therefore, there has been a push to replace systemic corticosteroids with its topical preparations, whenever possible. Topical corticosteroids became the cornerstones of therapy for a wide variety of dermatoses, which also serve as adjuvant therapy for various other inflammatory, hyperproliferative and pruritic conditions. However, the potential risks of percutaneous absorption of topically applied corticosteroids are still unclear, though there are ever-increasing reports calling attention to this problem. Considering the easy availability of the topical corticosteroid ointments, which are among the most commonly prescribed medications, detailed information is needed to accomplish effective and safe therapy. Therefore, this review goes back to basics and discusses relevant issues through the latest related literature according to the historical development of corticosteroids, their mechanism of action, formulations, potency and local side effects including allergic contact dermatitis, rebound erythema and tachyphylaxis, systemic side effects due to their percutaneous absoption including iatrogenic Cushing's syndrome and Addisonian steroid dependency, factors affecting the occurrence of side effects, and their safety during pregnancy and finally summarizes the diagnosis and management of adrenal suppression.

Key Words: Glucocorticoids, topical administration, adverse effects, Cushing's syndrome, adrenal insufficiency

ÖZET Kortikosteroidler birçok deri hastalığında değerlidir. Diğer taraftan genellikle sistemik kullanımına, aynı zamanda topikal kullanımına da bağlı olarak yan etkiler görülebilmektedir. Uzun süreli sistemik kortikosteroid kullanımının hipotalamus hipofiz adrenal döngünün baskılanmasına sebep olabileceği iyi bilinmektedir. Bu nedenle, sistemik steroidlerin tedavi için mümkün olan ölçülerde topikal formları ile yer değiştirilmesine gayret edilmektedir. Topikal kortikosteroidler geniş bir yelpazedeki deri hastalıklarının tedavisinde esas ajan olmuşken aynı zamanda birçok diğer enflamatuvar, hiperproliferatif ve pruritik hastalıklarda da yardımcı tedavide yer almaktadır. Öte yandan topikal kortikosteroidlerin ciltten emilimi sonucu oluşabilecek potansiyel tehlikeleri, bu konuya dikkat çeken ve giderek artan olgu bildirimleri olmasına rağmen, hâlâ yeterli ölçüde bilinmemektedir. En çok reçete edilen ilaçlardan biri olan topikal kortikosteroidlerin oldukça kolay ulaşılabilir olduğu dikkate alındığında, ilacın etkilerinden etkili ve güvenli olarak faydalanabilmek için hakkında detaylı bilgi sahibi olunması gerekir. Bu nedenle bu derleme ilacın temel özelliklerine geri dönerek ilgili konuları; kortikosteroidlerin tarihsel gelişimi, etki mekanizması, formülasyonları, sınıflaması, allerjik kontak dermatit, rebound eritem ve taşifilaksiyi de içeren lokal yan etkilerini, iyatrojenik Cushing sendromu ve Addison hastalığı benzeri steroid bağımlılığını da içeren ilacın ciltten emilimi sonucu olan sistemik yan etkilerini, istenmeyen etkilerin ortaya çıkmasını etkileyen faktörleri, gebelikteki güvenliğini son literatürler eşliğinde tartışmış ve son olarak da adrenal baskılanmanın teşhis ve tedavisini özetlemiştir.

Anahtar Kelimeler: Glukokortikoidler, topikal uygulanan, yan etkiler, Cushing sendromu, adrenal yetmezlik

Turkiye Klinikleri J Med Sci 2009;29(1):194-201

Topical corticosteroids are among the most commonly prescribed medications. They are not only the cornerstones of therapy for a wide variety of dermatoses, they also serve as an adjuvant therapy for various other inflammatory, hyperproliferative and pruritic conditions. However, many adverse systemic effects may develop, due to the topical use of corticosteroids including iatrogenic Cushing's syndrome and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. As exogenous steroids including their topical formulations suppress pituitary adrenocorticotropic hormone (ACTH) production, they hence reduce cortisol production by the adrenal cortex. Sometimes the underlying disease may even lose its significance with the development of side effects such as iatrogenic Cushing's syndrome and Addisonian steroid dependency. Moreover, adrenal insufficiency can be life threatening in case of steroid withdrawal. Considering the easy availability of the topical corticosteroid ointments which are among the most commonly prescribed medications, detailed information about topical corticosteroids is needed.

CORTICOSTEROID HISTORY

In 1950 "Nobel Prize in Physiology or Medicine" was given to Edward C. Kendall, Philips S. Hench and Tadeus Reichstein for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects. Kendall isolated and identified a series of compounds from the adrenal gland cortex, and developed cortisone by partial synthesis. Subsequently, the topical potential of the associated class of compounds was quickly sensed. However, cortisone demonstrated no topical activity. There remains no satisfactory explanation as to why cortisone is effective systematically but not topically. Because, cortisone is absorbed to the same degree as hydrocortisone.[1] Additionally, human skin can transform cortisone to hydrocortisone in vitro.[2] Shortly after the inconclusive trials with cortisone, hydrocortisone became available whose efficacy was firmly established.[3] After the first application of hydrocortisone in 1952, its halogenated derivatives became available and led to the development of the analogues now in use.[4]

PHARMACOKINETIC PROFILE

The plasma half-life ranges between 80 and 270 minutes. Endogenous circulating cortisol predominantly binds to the plasma protein corticosteroid-binding globulin with high affinity. However, most synthetic steroids bind predominantly to albumin. Glucocorticoids are metabolized in the liver and excreted by the kidney (95%) and the gut (5%).[5]

MECHANISM OF ACTION

Reports suggest that the clinical effects of topical corticosteroids are mediated by their anti-inflammatory, vasoconstrictive, anti-proliferative, and immunosuppressive properties.[6] They act via glucocorticoid receptors, which were first discovered in the late 1960s. Studies showed that the steroid bound to the receptor within the cytoplasm of cells, forming a complex that is rapidly transported to the nucleus of the cell, a process known as translocation.[7] The steroid-receptor complex then binds to a region on the DNA known as the glucocorticoid responsive element (GRE) and is then able to stimulate or inhibit transcription of genes and through this mechanism, it can regulate the inflammatory process.[7] Its effects include the inhibition of cytokine gene transcription, T-cell proliferation, and T-cell dependant immunity.[8] The anti-inflammatory effects of glucocorticoids include inhibition of dermal edema, capillary dilation and the movement of inflammatory cells within the skin. They also suppress fibroblast, endothelial cell, and leukocyte function hence they attenuate the humoral inflammatory process also. Glucocorticoids inhibit vascular permeability and the transmission of leucocytes through the vessel wall.[7,9] Mechanism of anti-inflammatory action of the topical glucocorticoids are summarized in Table 1.

FORMULATIONS

Most topical corticosteroids are available in many formulations including ointment, cream, lotion, gel, solution, and aerosol. In addition to being a carrier for the active drug, the vehicle may function to hydrate the skin and enhance drug penetration. Ointment formulations are effective in enhancing percutaneous absorption of topical corticosteroids by increasing the hydration and tempe-

TABLE 1: Mechanism of action of the topical glucocorticoids.

Action	Effect
•Inhibition of phospholipase A_2 activity	• Decreased production of prostaglandins, leukotrienes, platelet activating factor
•Inhibition of cyclooxygenase induction	• Decreased prostaglandin production
•Inhibition of nitric oxide synthase induction	• Decreased nitric oxide production
•Inhibition of cytokine production	• Suppression of cell-mediated inflammation and attenuation of humoral inflammatory process
•Inhibition of mast cell activity and reduction of mast cell number	• Decreased levels of mast cell inflammatory mediators like histamine
•Vasoconstriction	• Decreased local blood flow

rature of the skin.[10,11] They have a hydrophilic greasy base, usually soft paraffin, which forms an occlusive layer over the skin preventing loss of heat and water. Creams are emulsions of water in oil or oil in water. The oil in water emulsions do not feel greasy which is an important factor for some patients. Lotions contain topical corticosteroids in an aqueous or alcoholic suspension and gels are transparent semi-solid emulsions. Ointments are best used for dry, lichenified, hyperkeratotic and scaly plaques leading to rehydration of the stratum corneum.[7] Creams are best used for exudative lesions. Nonocclusive vehicles are preferred for application on hairy areas and flexures.

CLASSIFICATION

Since the introduction of topical hydrocortisone, various topical corticosteroids have been developed to improve the degree of potency. Chemical alterations such as halogenations or esterification have increased the potency of these agents. Topical corticosteroid preparations are categorized according to their relative potency, which is determined by their vasoconstrictive activities.[12] However, the vasoconstrictive activity may not always correlate with therapeutic efficacy.[13] Classification of commonly prescribed corticosteroids are summarized in Table 2.

GENERAL PRINCIPLES AND APPROACHES

The indications and contraindications of topical corticosteroid therapy in dermatologic disorders are summarized in Table 3. As a rule, topical corticosteroid therapy should be initiated with the lowest potency agent that will sufficiently control the disease while avoiding prolonged use of anagent with insufficient potency.[14] The potency of the medication can always be increased if the disease fails to respond. In areas where the skin is inherently thicker or for resistant dermatoses, hyperkeratotic and lichenified lesions highly potent agents are often required.[15] High potency agents should be avoided in areas of high permeability, such as face or intertriginous areas. In rare instances when a resistant dermatosis such as discoid lupus erythhematosus occurs on an area with thin skin such as the face, a potent topical corticosteroid is preferentially used by closely monitoring the side effects. Generally, higher potency agents should be used for relatively short periods (≤2 weeks) with less than 45 g per week in an adult and no more than 15 g per week in a child with a maximum of twice-daily application.[14] If the dermatosis is in remission, the therapy should be discontinued. If the dermatosis involves more than 20% of the body surface area, combination therapies should be considered to maximize efficacy and minimize adverse events

TABLE 2: Classification of commonly prescribed topical corticosteroids.

Relative potency	Generic name
• Super high potency	•Clobetasol propionate, bethamethasone dipropionate, halobethasol propionate
• High potency	•Fluocinonide, halsinonide, desoximethasone, amsinonide, fluocortolone
• Intermediate potency	•Hydrocortisone valerate, triamcinolone acetonide, bethamethasone valerate, momethasone furoate, fluticasone propionate, prednicarbate
• Low potency	•Hydrocortisone, dexamethasone, prednisolone

TABLE 3: The indications and contraindications of topical corticosteroid therapy in dermatologic disorders.

Indications	Contraindications
• Most responsive dermatologic disorders	• Absolute
Seborrheic dermatitis	A-Primary bacterial infections
Atopic dermatitis	Impetigo
Localized neurodermatitis	Furuncules
Anogenital pruritus	Carbuncules
Psoriasis	Paronychia
Inflammatory phase of xerosis	Ecthyma
Allergic contact dermatitis	Erysipelas
Irritant dermatitis	Cellulitis
Lichen simplex chronicus	Lymphangitis
Nummular eczematous dermatitis	Erythrasma
Stasis dermatitis	B- Herpes simplex infection of eye
• Less responsive dermatologic disorders	• Relative
Discoid lupus erythematosus	*Candida*
Psoriasis of the palms and soles	Angular cheilitis
Necrobiosis lipoidica diabeticorum	Tinea
Sarcoidosis	
Lichen planus	
Pemphigus	
Familial benign pemphigus	
Vitiligo	
Granuloma annulare	
Parapsoriasis	
Photodermatitis	
Pityriasis rosea	

combination therapies should be considered. The aim of the combination therapy is to use agents with different or non-overlapping mechanisms of action to achieve additive or synergistic efficacy, which helps to reduce dosages of the individual agents and possible side effects.[14] Possible combination therapies with topical corticosteroids are summarized in Table 4.

SIDE EFFECTS

Topical corticoids have potential side effects due to their local effects and systemic absorption. These are summarized in Table 5 and 6. Absorption varies among individuals and with respect to anatomical location.[15] Variable percutaneous absorption is caused by the thickness of the stratum corneum and its lipid composition. Penetration varies between the eyelid and the plantar skin for about 300-fold.[15] Skin atrophy results from the direct antiproliferative action that topical corticosteroids have on fibroblasts.[16] There is a reduction of collagen synthesis secondary to fibroblast inhibition, resulting in loss of dermal support. Striae, telengiectasias and purpura may develop due to these atrophic changes. Exogenous steroids including topical corticosteroids suppress pituitary ACTH production and hence reduce cortisol production by the adrenal cortex, which can be life threatening in case of steroid withdrawal. Another side effect of systemic absorption of topical steroids is iatrogenic Cushing's syndrome.[17-32]

Side effects due to systemic absorption of topically applied corticosteroids are much more commonly noticed in children,[17-26] though described in adults several times.[27-32]

ALLERGIC CONTACT DERMATITIS DUE TO TOPICAL CORTICOSTEROIDS

Allergic contact dermatitis due to topical corticosteroids may develop and should be considered in patients with dermatitis, which is resistant to therapy. Various components of the preparation such as propylene glycol and benzyl alcohol are common sensitizers. Hypersensitivity to the active steroid moiety itself has also been recognized.[33] Cross-reactivity to other structurally related corti-

TABLE 4: Possible combination therapies with topical corticosteroids.

1. Topical
Calcipotriene
Tazarotene
Calcineurin inhibitors
Tacrolimus
Pimecrolimus
Anthralin
Tretinoin (may prevent corticosteroid-induced atrophy)
Tar
Salicylic acid (reduces thickened plaques)
2. Phototherapy
UVB
Narrowband UVB
Bath PUVA
Systemic therapy (depends on the type of the dermatoses)

UVB: ultraviolet B, PUVA: Psoralen plus ultraviolet.

TABLE 5: Local side effects of topically applied corticosteroids.

1.	Epidermal atrophy
2.	Stria
3.	Telengiectasia
4.	Pigment changes (hypo and hyperpigmentation)
5.	Skin fragility
6.	Purpura and ecchymosis
7.	Acneiform eruption
8.	Rosacea
9.	Persistant erythema of the skin in sun exposed areas
10.	Contact dermatitis
11.	Photosensitivity
12.	Perioral dermatitis
13.	Rebound flare
14.	Delayed wound healing
15.	Increased localized fine-hair growth known as hypertrichosis
16.	Rebound erythema
17.	Aggravation of cutaneous infections
18.	Ocular changes (glaucoma, cataract, ocular hypertention)

TABLE 6: Systemic side effects of topically applied corticosteroids.

1.	Iatrogenic Cushing's syndrome
2.	Suppression of HPA axis and Addisonian steroid dependency
3.	Addisonian crisis in case of steroid withdrawal
4.	Hyperglycemia and diabetes mellitus
5.	Fractures or aseptic necrosis
6.	Decreased growth rate
7.	Electrolyte imbalance
8.	Posterior subcapsular cataract
9.	Glaucoma, posterior subcapsular cataract
10.	Hyperlipidemia
11.	Peptic ulcer, gastrointestinal bleeding
12.	Susceptibility to infections
13.	Hypertention
14.	Hypogonadism, delayed puberty, amenorrhea
15.	Mood changes, nervousness, insomnia, psychosis
16.	Pseudotumor cerebri
17.	Neurological complications
18.	Osteoporosis
19.	Muscle atrophy, myopathy

HPA: Hypothalamic-pituitary-adrenal.

costeroid compounds may occur.[33] It is often difficult to ascertain which topical corticosteroids will react with each other but it was shown that most patients who developed corticosteroid allergy did not react with the fluorinated topical corticosteroids.[34] As reported, the optimal approach is to use one from the group of the betamethasone esters, flumethasone esters or the halomethasone esters.[34]

REBOUND ERYTHEMA DUE TO DISCONTINUATION OF TOPICAL CORTICOSTEROIDS

Rebound erythema is a rare adverse effect that may occur after using potent topical corticosteroids. Severe exacerbation of the dermatoses may ensue as a result of abrupt discontinuation.[35,36] It may also occur due to the discontinuation of topical corticosteroids that initially cause vasoconstriction which is then followed by the development of excessive vasodilatation.[37]

TACHYPHYLAXIS

Tachyphylaxis is the development of acute tolerance to a pharmaceutical agent when the agent is used repeatedly. Tachyphylaxis has been reported to occur after long-term treatment with corticosteroids due to tolerance to the vasoconstrictive and antiproliferative effects of topically applied corticosteroids.[14] However, after a medication-free period for a few days, the initial vasoconstriction effect is achieved again.

INTRALESIONAL CORTICOSTEROIDS

Intralesional steroid injection is used commonly in steroid-resistant diseases with only small areas requiring treatment with injections every 3-4 weeks. Some disorders like keloids, hypertrophic scars, alopecia areata are very responsive to intralesional injections.[3] With this method, triamcinolone acetonide is diluted to the desired concentration depending on the lesion. This method allows bypassing the stratum corneum. Local side effects include subcutaneous atrophy, and pigment changes at the site of injection. Systemic side effects can develop due to prolonged use.

FACTORS AFFECTING THE DEVELOPMENT OF SIDE EFFECTS

There is some evidence that the side effects due to systemic absorption of topical corticosteroids are dose dependent. When more than 50 g clobetasol propionate ointment per week is applied topically, a significant number of patients may develop adrenal suppression, in case of less than

50 g per week suppression tends to be transient.[38] It seems that the younger the patient and the more inflamed the skin, more significant absorption will occur.[20] Additionally, in geriatric patient populations the skin becomes drier and thin, hence elderly patients are more susceptible to side effects of topically applied corticosteroids. Reduction of corticosteroid absorption when the epidermal barrier is restored has been suggested to be the reason of transient suppression of the HPA axis.[28,39] Sometimes patients even with low dose of topically applied corticosteroids may develop adrenal suppression when combined with occlusive dressing, which enhances their absorption.[26] Rarely, instances of low-potency steroids causing systemic side effects in patients with abnormal barrier function have been reported.[17] Because the barrier that normally prevents drug penetration into the skin is disrupted in some conditions such as erythrodermic diseases, skin may be more permeable to many medications. Factors affecting the development of side effects of topically applied steroids are summarized in Table 7.

DIAGNOSIS AND MANAGEMENT OF ADRENAL SUPPRESSION DUE TO CORTICOSTEROIDS

The history, clinical findings and laboratory tests assist the clinicians in making a diagnosis of adrenal suppression. Patients who are using topical steroids for a long time with/without cushingoid changes are candidates for developing adrenal suppression. In case the treatment is stopped suddenly, adrenal insufficiency may develop. On endocrinologic testing initial laboratory investigations of reduced morning cortisol (normal 5-25 μg/dL) and reduced ACTH level (normal 5-46 pg/mL) indicates suppression of endogenous adrenal steroids and pituitary ACTH. Three consecutive 24-hour urinary free cortisol levels are helpful for confirmation. ACTH stimulation test should be performed also. In this test 1 μg ACTH is given and cortisol levels are measured at 0, 30, and 60 minutes. A normal cortisol response to low-dose ACTH test is considered a peak of greater than 20 μg/dL. In case of low response, adrenal suppression can be diagnosed.[17-32,40]

Adrenal suppression can lead to severe symptoms and sudden cessation of treatment may result in adrenocortical insufficiency with anorexia, nausea, vomiting, abdominal pain and even death. Therefore, the diagnosis of adrenocortical insufficiency is very important. Oral glucocorticoid supplements should be given during episodes of stress such as surgery and intercurrent infections, both during the period of topical steroid use and for four months after discontinuing the cream.[25]

TOPICAL CORTICOSTEROIDS DURING PREGNANCY

The general opinion is that the treatment of pregnant women with topical corticosteroids is associated with little, if any, teratogenic risk. This belief is supported by the largest case-control study of corticosteroid use during pregnancy.[41] Systemic effects are generally limited. Approximately 3% of the medication in topical corticosteroid preparations is absorbed following eight hours after contact with normal skin. Topical corticosteroids are pregnancy category C (includes drugs with positive evidence of fetal risk, which may be used in cases where the potential benefit outweighs the risk).[42] Patients requiring treatment of large surface areas, particularly under occlusion, should be monitored for adrenal suppression and other potential side effects.[42]

TABLE 7: Factors affecting the development of side effects.

1.	Potency of steroid
2.	The amount of applied dose (more than 50g/ per week)
3.	Application area (areas with thinner skin such as intertriginous regions are more susceptible)
4.	Changes in the skin (impaired barrier function)
5.	Occlusive dressing (enhances absorption)
6.	Age of the patient (pediatric and geriatric patient populations are more susceptible)

CONCLUSION

Physicians should be alert for the side effects of topical corticosteroids. Considering the easy availability of the topical corticosteroid ointments, special information regarding length of treatment, frequency of use and possible adverse effects should be given to the patient stressing the importance.[43] Physicians should always keep in mind the factors that potentiate the risk for systemic absorption. Periodic clinical and laboratory testing may be indicated if the drug is to be used for long periods. If suppression of HPA axis is detected, slow weaning of the topical corticosteroid, reduction of application frequency or titration to a lower potency preparation is recommended.

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