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Review Article

TOPICAL CORTICOSTEROIDS AND ITS ADVERSE EFFECTS: A REVIEW

Harini M[1] and Kavya Balusu[2]*

[1]Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, 12-5-31/32, Vijayapuri Colony, Tarnaka, Secunderabad, Telangana, India - 500017
[2]*Gandhi Medical College, Musheerabad, Secunderabad, Telangana, India – 500003

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A B S T R A C T

Topical corticosteroids are one of the most commonly used treatments for dermatological disorders. They are highly preferred due to their strong immunosuppressive and anti-inflammatory actions. They are used as different formulations, but topical formulations such as ointments, creams are used widely. Adverse effects outweigh the efficiency. These drugs are extensively prescribed by the consultants because of their rapid action. This practice has led to quite frequent overprescribing of these drugs and, thereby, increasing adverse drug reactions. Misuse of TCs is a widespread phenomenon among young people, especially women. Systemic adverse effects of topical corticosteroids like Cushing's syndrome and hypothalamic–pituitary–adrenal (HPA) axis suppression is caused due to extended use. Withdrawal signs include erythema, itchiness, and burning; secondary lesions. Side effects are mostly reversible on termination of use. But prolonged use leads to serious adverse effects which cannot be reversible. Awareness of these effects reduces misuse, overprescribing of topical steroids.

INTRODUCTION

In dermatology, topical corticosteroids are the most commonly used topical medicines. Many people suffer from common skin problems that are common in all age groups. The dermal problems that are usually found are acne, burn scars, hyperhidrosis, psoriasis, scabies, vitiligo, pediculosis, herpes simplex infection, varicella, herpes zoster, erythema, urticaria. Topical corticosteroids (TC) are an effective anti-inflammatory agent and give rapid relief for the patients from different inflammatory dermatoses even from most of the infective conditions (e.g., dermatophyte infection, candidiasis, and viral)[1].

Indications

TC treatment is indicated for conditions characterized by inflammation, hyperproliferation, and immunological involvement. They can also alleviate symptoms of burning and pruritic lesions, inflammatory skin conditions such as psoriasis, and atopic dermatitis[1].They are indicated in several diseases, the most common are skin and musculoskeletal conditions. Others include allergic, immunological diseases, eye, respiratory system, gastrointestinal system (GIS) diseases, some infectious diseases, various malignancies, and neurological diseases[2].Indications for using steroids ranged from acne, pigmentation, as a general-purpose cream to various undiagnosed dermatosis[3].

Corresponding author:* **Kavya Balusu
Gandhi Medical College, Musheerabad, Secunderabad, Telangana, India – 500003

Formulations

TC's are available as ointments, creams, gels, lotions, shampoos, foams, and mousses. Compared with other preparations, corticosteroid ointments provide more occlusion and lubrication and also increase steroid absorption. Creams are generally less potent than ointments. Gels offer the least occlusion. Shampoos, foams, and mousses are effective for treating the scalp[1].

TC's are categorized into seven classes according to their potency as given in table 1. The potency of a TC depends on the formulation, the specific molecule type, level of skin absorption, and amount that reaches the target cell. Strength is also increased when a formulation is used under occlusive dressing areas. In general, ointments are more potent than creams or lotions[1].

Table 1 World Health Organization Classification of Topical Corticosteroids[1]

Group	Drugs
I (Ultra-high potency topical corticosteroids)	Clobetasol propionate cream (0.05%), Diflorasone diacetate ointment (0.05%)
II (High potency topical corticosteroids)	Amcinonide ointment (0.1%) Betamethasone dipropionate ointment (0.05%) Desoximetasone (cream or ointment) (0.025%) Fluocinonide (cream, ointment, or gel) (0.05%) Halcinonide cream (0.1%) Betamethasone dipropionate cream (0.05%) Betamethasone valerate ointment (0.1%)

III	Diflorasone diacetate cream (0.05%)
	Triamcinolone acetonide ointment (0.1%)
	Desoximetasone cream (0.05%)
IV	Fluocinonide acetonide ointment (0.025%)
(Moderate potency	Hydrocortisone valerate ointment (0.2%)
topical corticosteroids)	Triamcinolone acetonide cream (0.1%)
	Betamethasone dipropionate lotion (0.02%)
	Betamethasone valerate cream (0.1%)
V	Fluocinonide acetonide cream (0.025%)
	Hydrocortisone butyrate cream (0.1%)
	Hydrocortisone valerate cream (0.2%)
	Triamcinolone acetonide lotion (0.1%)
VI	Betamethasone valerate lotion (0.05%)
(Low potency topical	Desonide cream (0.05%)
corticosteroids)	Fluocinolone acetonide solution (0.01%)
	Dexamethasone sodium phosphate cream (0.1%)
VII	Hydrocortisone acetate cream (1%)
	Methylprednisolone acetate cream (0.25%)

Pharmacological action

Corticosteroids alter the functions of epidermal, dermal cells, and leukocytes participating in proliferative and inflammatory skin diseases. They act on binding to nuclear (steroid) receptors with an effect on protein synthesis. After passage through the cell membrane corticosteroids binds with receptor proteins in the cytoplasm to form a steroid-receptor complex, this then moves into the nucleus and binds to DNA. Binding to DNA changes the transcription of messenger RNA (mRNA). As mRNA acts as a template for protein synthesis, it can either stimulate or inhibit the synthesis of specific proteins. Hence, corticosteroids are known to stimulate the production of a glycoprotein called lipocortin. The produced lipocortin inhibits the activity of phospholipase A2, which releases arachidonic acid, the precursor of prostanoids and leukotrienes, from phospholipids. In distinction, corticosteroids inhibit mRNA responsible for interleukin-1 formation. These are the pharmacological actions of corticosteroids through arachidonic acid metabolism and interleukin-1 formation. Thus, corticosteroids act as anti-inflammatory, immunosuppressive, and anti-mitogenic effects[4].

Corticosteroids alter the inflammatory response and thus provide therapeutic benefits through actions on mediator release and function, inflammatory cell function, and release of lysosomal enzymes. Drawbacks of corticosteroid activity include the possibility of adrenal suppression, epidermal and dermal thinning, and local effects such as purpura, striae, and steroid-induced rosacea and perioral dermatitis. The dermal pharmacokinetics, particularly of absorption of topical corticosteroids, must be examined in corresponding with their pharmacodynamic effects to gain a more complete understanding of the activity. Numerous factors can affect transcutaneous steroid absorption: drug lipophilicity and solubility, drug concentration, anatomical site, age of the patient, presence of skin disease, and use of occlusive dressings.All of these influence the degree to which topically applied corticosteroids achieve their intended therapeutic results. Cutaneous metabolism is a less understood process at present. Although some gaps persist in present knowledge of the pharmacology and pharmacokinetics of this important class of drugs, there can be no denying the contribution of topical corticosteroids to the therapy of dermatoses[5].

Adverse effects

Cutaneous adverse effects occur regularly with prolonged treatment and are dependent on the chemical nature of the drug, the vehicle, and the location of its application[6]. Prolonged use of topical steroids can cause systemic side effects along with local effects[7]. The documented adverse effects are:

- Suppression of the hypothalamic-pituitary-adrenal (HPA) axis
- Iatrogenic Cushing's syndrome
- Growth retardation in infants and children
- Ocular: glaucoma and loss of vision
- Avascular necrosis of femoral head
- Severe disseminated cytomegalovirus infection resulting in death in infants.
- Osteoporosis and fractures
- Weight gain
- Hyperglycemia
- Cardiovascular disorders
- Dyslipidemia
- Myopathy
- Psychiatric disturbances
- Immunosuppression
- GI and dermatologic events

Misuse of TCs is a widespread phenomenon among young people, especially women. The practice is associated with significant adverse effects and poor awareness of these effects among the general public[8,9]. These drugs are extensively prescribed by the consultants because of their strong immunosuppressive and anti-inflammatory actions[10]. This exercise has led to quite frequently overprescribing of these drugs and, thereby, increasing adverse drug reactions. The topical corticosteroids were introduced in the early 1950s; since then, they are widely prescribed medication in dermatology clinics. This requires essential care in the selection of corticosteroid drugs for use and their dosage regimen[10]. Another study showed that fairness and skin lightening was the main indication of steroid abuse which was also the most common reason[11].

Although mometasone furoate 0.1% demonstrates greater anti-inflammatory activity and a longer duration of action than betamethasone relative to other topical corticosteroids with similar or weaker potency, topical formulations of mometasone furoate 0.1% have been shown to be associated with a low risk of corticosteroid-related adverse events, such as skin atrophy and other local events, and to have a very limited potential to induce systemic adverse effects, including hypothalamic-pituitary-adrenal axis suppression[12].

Adverse effects over face: Acneiform lesions, erythema, telengiectasias, dyspigmentation, hypertrichosis, perioral dermatitis, tinea incognito, photosensitivity, and burning sensation[3]. The risk of adverse effects increases with prolonged use, a large area of application, higher potency, occlusion, and application to areas of thinner skin such as the face and genitals. The face is the most common and most severely affected site of such misuse and steroid dependence resulting in a phenomenon that has been labelled as Topical steroid-damaged/dependent face (TSDF). TSDF is basically a form of drug dependence[13,14]. TSDF is defined as the semi-permanent or permanent damage to the skin of the face precipitated by the irrational, indiscriminate, unsupervised, or prolonged use of TC's resulting in a variety of cutaneous signs and symptoms and psychological dependence on the drug.

***Adverse effects in children**:* Among all age groups children are more prone to the effects of TC. The systemic reactions are high of topically applied medication because of their higher ratio of total body surface area (BSA) to body weight (BW). Thus, while prescribing low potent and short duration topical corticosteroids are preferred. Infants who are exposed to TCare at greater risk for Cushing's syndrome or adrenocortical insufficiency due to suppression of the HPA axis as glucocorticoids are highly absorbed through the diaper area[15,16,17.]

Prolonged use of topical corticosteroids causes systemic adverse effects including Cushing's syndrome and HPA axis suppression, which is less common than that of the oral or parenteral route. About 43 cases with iatrogenic Cushing syndrome from very potent topical steroid usage (Clobetasol) in children and adults have been published over the last 35 years particularly in developing countries. In the children group, most are infants with diaper dermatitis. In the adult group, the most common purpose of steroid use was for the treatment of Psoriasis. Tempark et al., have reported that an 8-month-old female infant developed Cushing's syndrome and adrenal insufficiency after diaper dermatitis treatment through the misuse of Clobetasol without a doctor's prescription. A physiologic dose of hydrocortisone was prescribed to prevent an adrenal crisis for 3 months and discontinued when HPA axis recovery was confirmed by normal morning cortisol and ACTH levels[18].

Hypothalamic–pituitary–adrenal (HPA) axis suppression is a potential systemic risk of topical steroid use. Over usage may result in systemic adrenal insufficiency. Infants and those patients with damaged skin barriers are at high risk for the development of adrenal suppression. Adrenal suppression is diagnosed by measurement of plasma total cortisol, 24-hour steroid, adrenocorticotrophin hormone stimulation, and insulin tolerance. Various reportsfind strong laboratory evidence of adrenal hypofunction. Moreover, clinical reversible adrenal insufficiency has been observed on rare occasions. Therefore, topical corticosteroids should be used with an increased awareness of the potential for systemic adrenal suppressive effects [19,20].

Adverse effects in pregnancy: At present limited and inconclusive data are unable to detect the relation between topical corticosteroids and congenital abnormality, preterm delivery, or stillbirth. Evidence shows no statistically significant difference with the use of TC in pregnancy and without pregnancy. But there appears to be an association of very potent topical corticosteroids with low birthweight. Further cohort studies with comprehensive outcome measures, consideration of corticosteroid potency, dosage and indications, and large sample size are needed[21].

Other adverse effects: Kevin et al., have demonstrated a potential association between topical corticosteroid use and the risk of developing diabetes mellitus. This risk does not appear to be dependent on the potency of the topical medication, but relatively the cumulative dose and cumulative duration of use. Topical steroids have been previously associated with the potential for hyperglycemia and glucosuria and are thought to have a relatively safe side effect profile. In prolonged use, there is the potential for steroids to be absorbed through the skin and eventually reach systemic circulation[22].

Osteoporosis is one of the most threatening consequences of Cushing's syndrome. The weakening of the bone frame in osteoporosis develops the fragility of the bone and increased the risk of fractures. In younger patients, drug-induced osteoporosis is one of the most common causes. Drugs like glucocorticoids, L-thyroxine, heparin, and anticonvulsants may lead to the development of osteoporosis in patients treated with long-term therapies for chronic diseases. The outcome of glucocorticoids on the bones may arise through different mechanisms: i) Dysregulating calcium homeostasis; ii) an imbalance of steroid hormones, and iii) inhibition of bone formation and enhancement of bone resorption. The additional risk factor for osteoporosis determined by smoking may have contributed to the vertebral collapse[23]. Since patients with psoriasis are more likely to be smokers, the use of topical steroids over long periods in these patients will require additional monitoring[24].

Topical Steroid Withdrawal Signs

Topical steroid withdrawal is also identified as redskin syndrome. It has been found to be a distinct adverse effectof TC's overuse, particularly where there has been long-term inappropriate use of moderate to potent TC's on the face or genital area. It is most common in women due to improper use for cosmetic reasons. Symptoms include erythema, itchiness, and burningsecondary lesions [25].

Skin atrophy is the most common and important side effect of topical glucocorticoid (GC) therapy, with major consequences because it is irreversible and the thinned skin is fragile and has a weakened barrier function. The effects of GCs on the skin have shown reduced proliferation of GC target cells, keratinocytes, and fibroblasts, disturbed metabolism of ECM proteins, and also the disturbing synthesis of skin lipids. Many approaches and models determine a GCs atrophogenicity in vivo such as measuring skin thickness in hairless rats or mice[26].

CONCLUSIONS

The treatment of chronic inflammatory skin disease is associated with the use of topical corticosteroids. Their efficacy, tolerability, and adverse effects depend on several factors, specifically potency, type of preparation, extemporaneous dilutions, quantity used, the magnitude of the treated body surface, frequency of application, location, patient age, method of application, and condition of the skin barrier[6].
In conclusion, topical corticosteroids are effective and well-established therapeutic modalities. Though highly efficacious have a low safety profile. Side effects like itching, rashes can easily be reversible on discontinuation of therapy. Adverse effects like suppression of the hypothalamic-pituitary-adrenal axis, Iatrogenic Cushing's syndrome, growth retardation in infants and children are mostly irreversible. Topical corticosteroids when administered for a short duration show minor effects and are not severe. Prolonged administration shows many serious adverse effects due to the accumulation of drugs in tissues.

Topical corticosteroids are the most effective anti-inflammatory drugs but equally toxic due to misuse. The practice is associated with significant adverse effects and poor awareness of these effects among the general public.

Conflict of interest

The authors disclose that there is no conflict of interest.

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