Topical Corticosteroids: Pharmacology

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Abstract

Topical corticosteroids are widely used for inflammatory and hyperproliferative disorders in dermatology. Numerous topical corticosteroids with high local activity have been developed over the years, with a focus to develop drugs with high efficacy locally and minimum risk for adverse drug reactions. They are available in a number of formulations. Their therapeutic effects are a result of their anti-inflammatory, immunosuppressant, vasoconstrictive and anti-proliferative actions. An appropriate topical corticosteroid is selected on the basis of the dermatological condition to be treated, patient-related factors and the physicochemical properties of the drug. Their use is associated with mainly local adverse drug reactions, but prolonged use and/or use of high-potency topical corticosteroids may cause systemic effects.

Keywords

Topical corticosteroids • Anti-inflammatory • Anti-proliferative • Potency

Learning Points

1. Topical corticosteroids are used extensively by dermatologists for inflammatory and hyperproliferative disorders of the skin.
2. Their anti-inflammatory, anti-proliferative and immunosuppressant actions are responsible for the clinical efficacy.
3. A number of topical corticosteroids, in varying strengths and formulations, are available.
4. Selection of a topical corticosteroid is made on the basis of dermatological condition to be treated, physicochemical properties of the topical corticosteroid and patient-related factors.

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K. Lahiri (ed.), *A Treatise on Topical Corticosteroids in Dermatology*,
DOI 10.1007/978-981-10-4609-4_2

5. Local adverse drug reactions are more common than systemic adverse drug reactions (ADRs) with the use of topical corticosteroids.
6. Research in this field is focused on developing molecules with high topical activity and better safety profile.

The successful use of dermatosis patients with hydrocortisone by Sulzberger and Witten in 1952 ushered in a new era in pharmacotherapy of dermatological conditions [1]. Since that time, numerous modifications have been made to develop topical corticosteroid molecules with favourable pharmacokinetic properties, improved efficacy and minimal adverse drug reactions. Topical corticosteroids are now used extensively by dermatologists for myriad conditions.

2.1 Structure-Activity Relationship

Corticosteroids have a C21 structure, consisting of a four-ring cyclophenanthrene nucleus and side chains. There are four rings, named A–D, with three six-membered rings and one five-membered ring. The synthetic corticosteroids used are derived from the natural corticosteroid, cortisol or hydrocortisone [2]. Cortisone was the first corticosteroid tested for dermatological disease but was devoid of topical activity [3]. Hydrocortisone was then developed by reduction of carbonyl group on C11, which was the first topical corticosteroid used and continues to be used in dermatology practice [4]. In the last 4–5 decades, many structural modifications have been made to the molecule in an effort to improve the topical activity of the molecule, while at the same time minimizing the adverse drug reactions.

The presence of double bonds between C4 and C5 and a keto group at C3 provide glucocorticoid and mineralocorticoid property to the corticosteroid molecule. Most of the synthetic molecules also have an –OH group at C21 position on ring D as is also found in the natural corticosteroid molecules. Halogenation, done at 6 α or 9 α position, increases the glucocorticoid and mineralocorticoid activity due to increased binding of the molecule to the glucocorticoid receptor [2]. Addition of a second fluoride or chloride group causes an additional increase in potency. Introduction of a double bond between C1 and C2 improves the glucocorticoid action and decreases the rate of metabolic inactivation, e.g. prednisolone, formed by insertion of double bond C1–2 to hydrocortisone, has a much higher anti-inflammatory activity as compared to hydrocortisone. Triamcinolone and betamethasone are other such examples (Fig. 2.1) [5].

Esterification of the corticosteroid increases its lipophilicity; thus it improves the percutaneous absorption and potency of the corticosteroid, e.g. betamethasone 17-valerate, produced by esterification of betamethasone at C21, has a higher potency than betamethasone and has a higher affinity for the glucocorticoid receptor [5]. Lipophilicity can also be enhanced by masking or removing the 17-dihydroxy acetone side chain or 16-α-hydroxyl group: this results in improved penetration through the stratum corneum [6].

Introduction of an acetonide group between positions C16 and C17 also helps to increase the skin penetration of the topical corticosteroid molecule and subsequent percutaneous absorption. An additional advantage is mitigation of mineralocorticoid effects caused by fluorination at C9 [5].

Undesirable mineralocorticoid activity of the topical corticosteroids can be reduced by adding 16-α-methyl, 16-β methyl or 16-α-hydroxyl group to the halogenated corticosteroid [7].

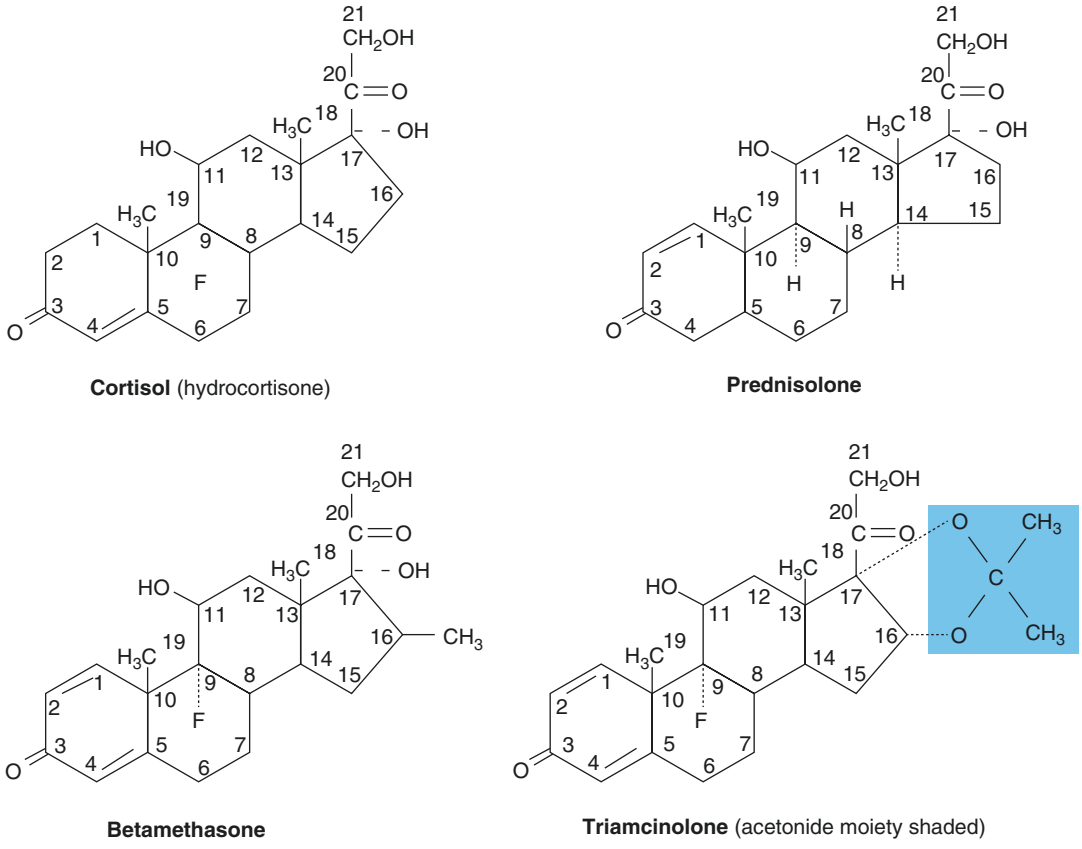

Fig. 2.1 Chemical structure of corticosteroids [9]. Copyright © McGraw-Hill Education. All rights reserved

Medicinal chemists have introduced structural changes to achieve high local glucocorticoid activity, with low potential to cause systemic effects. Analogues which undergo rapid inactivation after absorption are one such example: carbothioate glucocorticoid esters are metabolized to 21-carboxylic acid. Diesters like methylprednisolone aceponate, 17,21-hydrocortisone aceponate, mometasone furoate and carbothiates like fluticasone propionate are glucocorticoids with high topical activity and less propensity to cause skin atrophy and undergo rapid metabolism. They are also termed as 'soft corticosteroids' [8].

Another modification is inactive analogues which get activated at the site of action, e.g. glucocorticoid C21 isobutyryl or propionyl esters that are hydrolyzed to active C21 alcohols by airway-specific esterases [2].

2.2 Potency of Topical Corticosteroids: How to Determine

Many assays using laboratory animals and human volunteers have been used to estimate the clinical efficacy of the topical corticoste-

roids. Cell cultures, laboratory animals and tests using human volunteers are also used to assess atrophogenic potential of the molecules, as skin atrophy is a common adverse drug reaction reported with the use of topical corticosteroids.

Human vasoconstriction assay, developed by McKenzie and Stoughton, is a commonly used method to estimate the potency of topical corticosteroids. Different dilutions of the drug are applied to the skin and the degree of skin blanching is observed [10]. Some studies have shown a co-relation between the vasoconstriction activity and anti-inflammatory activity in clinical use [11, 12]. Vasoconstriction may not always co-relate with therapeutic assay [13]. A study which compared four ranking systems (vasoconstriction, clinical outcome, therapeutic index and efficacy/safety/cost) found that vasoconstriction assay co-related with clinical efficacy in 62% of agents studied [14]. Currently, however, vasoconstriction property forms the basis for classification of topical corticosteroids.

As the vasoconstriction assay is based on subjective assessment, efforts have been made to make the assessment more objective by laser Doppler velocimetry, capillaroscopy or transepidermal water loss.

Recently, Humbert and Guichard questioned the rationale of using vasoconstrictor effect, which is one of the many possible actions of corticosteroids, as a measure of their anti-inflammatory effect and therapeutic efficacy. They proposed a new classification of topical corticosteroids based on the condition for which it is to be used and measuring the relative effects of the different molecules [15].

The small plaque psoriasis bioassay proposed by Dumas and Scholtz is a modification of the vasoconstrictor assay. In this assay, the corticosteroid formulation is directly tested on psoriatic plaques, rather than on the normal skin, and its anti-inflammatory effect measured [16]. Rat thymus involution assay and anti-granuloma assay have also been used to measure the anti-inflammatory effect of topical corticosteroids. Fibroblast assay measures the atrophogenicity property of topical corticosteroids [6].

2.3 Classification of Topical Corticosteroids

The WHO classification divides the topical corticosteroids into seven classes/groups, with group 1 being the most potent and group 7 being the least potent. In this system, potency is based on activity of topical corticosteroid molecule, its concentration and nature of vehicle. The same drug can be placed into different classes with the use of different vehicles [17]. In this classification, the seven classes of corticosteroids are categorized into four groups, wherein class I is considered as ultrahigh-potency, classes II and III as high-potency, classes IV and V as moderate-potency and classes VI and VII as low-potency corticosteroids.

The British National Formulary classification divides the topical corticosteroids into four classes and does not take into consideration the vehicle [18]. Class I is considered to be very potent, while class IV includes drugs with low potency.

The high-potency formulations are recommended for short-term use only and are required for areas like palms and soles and also for chronic or hyperkeratotic lesions. Low- to medium-potency topical corticosteroids are useful for acute inflammatory lesions on the face and intertriginous areas and can be used for a longer term (Table 2.1).

Table 2.1 WHO classification of topical corticosteroids [17]

Potency	Class	Topical corticosteroid	Formulation
Ultrahigh	I	Clobetasol propionate	Cream, 0.05%
		Diflorasone diacetate	Ointment, 0.05%
High	II	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%
	III	Betamethasone dipropionate	Cream, 0.05%
		Betamethasone valerate	Ointment, 0.1%
		Diflorasone diacetate	Cream, 0.05%
		Triamcinolone acetonide	Ointment, 0.1%
Moderate	IV	Desoximetasone	Cream, 0.05%
		Fluocinolone acetonide	Ointment, 0.025%
		Fludroxycortide	Ointment, 0.05%
		Hydrocortisone valerate	Ointment, 0.2%
		Triamcinolone acetonide	Cream, 0.1%
	V	Betamethasone dipropionate	Lotion, 0.02%
		Betamethasone valerate	Cream, 0.1%
		Fluocinolone acetonide	Cream, 0.025%
		Fludroxycortide	Cream, 0.05%
		Hydrocortisone butyrate	Cream, 0.1%
		Hydrocortisone valerate	Cream, 0.2%
		Triamcinolone acetonide	Lotion, 0.1%
Low	VI	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Fluocinolone acetonide	Solution, 0.01%
	VII	Dexamethasone sodium phosphate	Cream, 0.1%
		Hydrocortisone acetate	Cream, 1%
		Methylprednisolone acetate	Cream, 0.25%

2.4 Mechanism of Action

Corticosteroids have anti-inflammatory, immunosuppressive, anti-proliferative and vasoconstrictor actions. Many of these actions are mediated by the nuclear glucocorticoid receptor which modulates transcription of proteins. This is considered to be the genomic mechanism and mediates many of the actions produced by the corticosteroids. Additionally, non-genomic mechanisms have been proposed to explain some of the immediate effects which cannot be explained by the classic glucocorticoid-receptor mechanism [19].

The corticosteroid receptor can be present in several isoforms. Corticosteroids produce their effects through the α-isoform, while relatively high levels of β-isoform may cause the

resistance to glucocorticoids [2]. The glucocorticoid receptors are found in most of the cells of the body, which accounts for their widespread systemic effects. In the skin, glucocorticoid receptors have been located in keratinocytes and fibroblasts within the epidermis and dermis [20, 21].

When the receptors are unoccupied by the corticosteroid molecule, they are usually present in the cytoplasm. The inactive receptor is bound to proteins like heat-shock proteins (Hsp) like Hsp90, Hsp70 and immunophilins. The glucocorticoid molecule, being lipophilic, enters the cell by passive diffusion. Within the cell, it binds to the receptor, the heat-shock proteins and immunophilins dissociate from the receptor and the corticosteroid-receptor complex then translocates to the nucleus [2].

Within the nucleus, this receptor-corticosteroid dimer complex then binds to a specific sequence of DNA, known as the glucocorticoid-response element. This interaction induces synthesis of anti-inflammatory proteins and regulator proteins involved in metabolic processes. This process is known as transactivation. The metabolic effects and some of the adverse drug reactions may occur through this process [22].

When the corticosteroid molecule directly/indirectly interacts with regulation of pro-inflammatory genes for transcription factors, such as activator protein 1 (AP1), nuclear factor κ B (NFκB) or interferon regulatory factor-3 (IRF-3), this process is termed as 'transrepression'. This negative regulation brings about anti-inflammatory and immunosuppressive effects [23].

The following non-genomic mechanisms for corticosteroids have been proposed to explain some of their rapid actions:

1. Corticosteroids interact with plasma membrane and mitochondrial membranes to alter their physicochemical properties and activities of membrane-associated proteins [19, 24].
2. Non-genomic glucocorticoid effects could mediate non-genomic effects on immune cells [25].
3. Some of the non-genomic effects could also be brought about by the corticosteroid receptors which are located on the cellular membranes, rather than the cytoplasm [24].

2.5 Pharmacological Actions of Corticosteroids

Corticosteroids are useful in varied dermatological conditions due to their anti-inflammatory, immunosuppressant, vasoconstrictive and antiproliferative effects (Fig. 2.2).

2.5.1 Anti-Inflammatory and Immuno-Suppressant Effects

Corticosteroids inhibit the functions of most of the cells involved in an inflammatory response: some of these actions are direct, while others are mediated through the receptors. The corticosteroids reduce inflammation actions by the following actions:

1. There is a decrease in the number of polymorphonuclear leucocytes and monocytes at the site of inflammation, and they have a reduced ability to adhere to the vascular endothelium. Their antibacterial and phagocytic activity of the polymorphs is also diminished.
2. There is a reduction of natural killer and antibody-dependent cellular cytotoxicity by lymphocytes.
3. The Langerhans cells are reduced in number and there is diminution of their antigen-presenting function.
4. They inhibit the release of phospholipase A_2 which is involved in the production of prostaglandins, leukotrienes, PAF and other derivatives of arachidonic acid pathway.
5. Decrease in T cell production and increase in T cell apoptosis, partly due to reduced IL-2.
6. There is a decreased expression of ELAM1 (endothelial-leucocyte adhesion molecule-1) and ICAM-1 (intracellular adhesion molecule-1) from the endothelial cells [2].

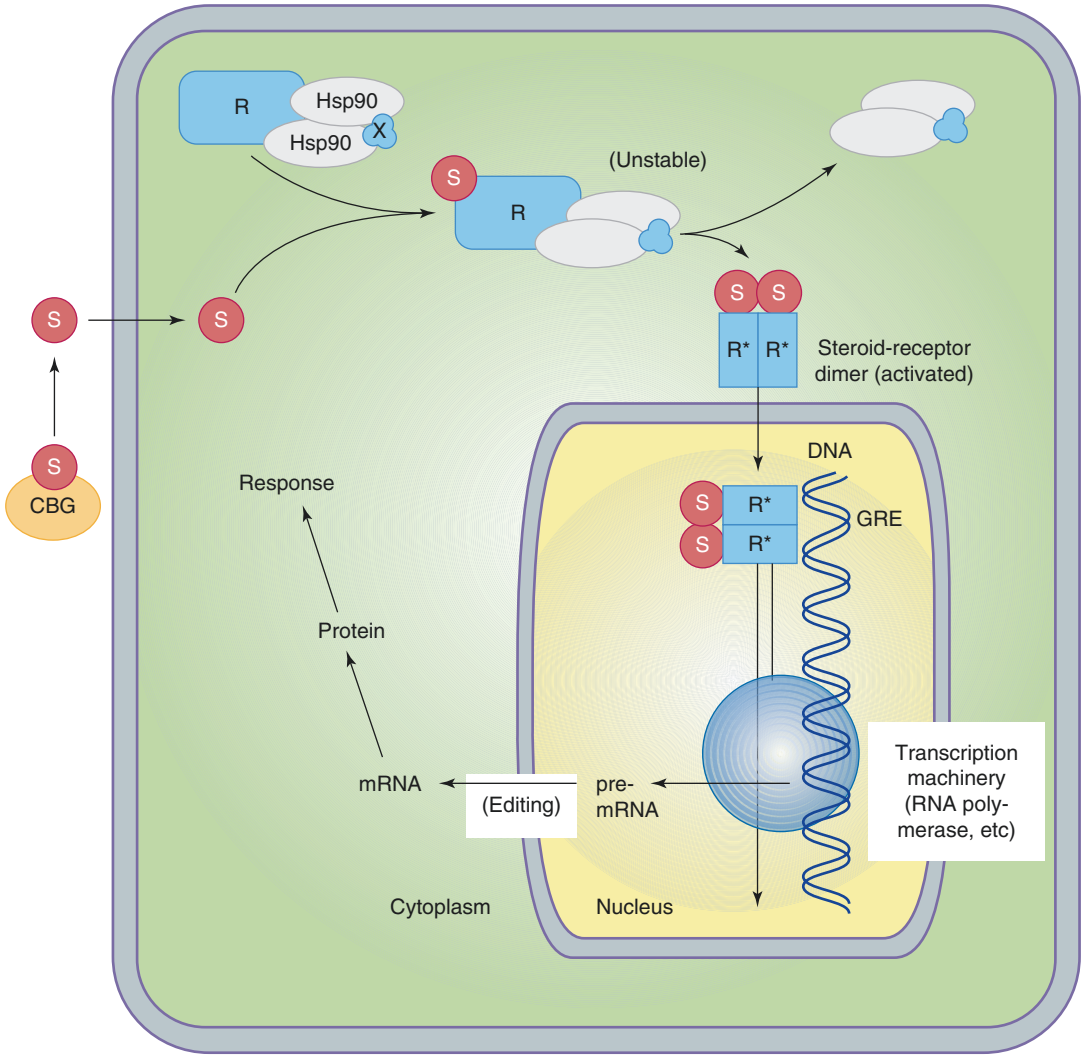

Fig. 2.2 Molecular level mechanism of action of corticosteroids [9]. Copyright © McGraw-Hill Education. All rights reserved

7. They inhibit transcription factors, such as activator protein 1 and nuclear factor κB, which activate pro-inflammatory genes. Lipocortin binds to membrane phospholipids, which is a substrate for phospholipase A_2 and makes it unavailable to form arachidonic acid which generates mediators like prostaglandins and leukotrienes [26, 27].
8. They decrease the release of IL-1α, IL-2, TNF and granulocyte-monocyte stimulating factor.
9. Glucocorticoid-receptor complex inhibits the inducible cyclooxygenase (COX 2) isoform, with minimal inhibition of COX 1. Cyclooxygenase is involved in prostaglandin synthesis [28].
10. They also reduce the levels of inducible nitric oxide (NO) synthetase, which increases NO synthesis. Nitric oxide is a vasodilator and a mediator for inflammation (Table 2.2) [28].

Table 2.2 Important effects of glucocorticoids on primary and secondary immune cells [29]

Monocytes/macrophages
↓ Number of circulating cells (myelopoiesis, release)
↓ Expression of MHC class II molecules and Fc receptors
↓ Synthesis of pro-inflammatory cytokines (e.g. IL-2, IL-6, TNF-a) and prostaglandins
T cells
↓ Number of circulating cells (redistribution effects)
↓ Production and action of IL-2 (most important)
Granulocytes
↓ Number of eosinophile and basophile granulocytes
↓ Number of circulating neutrophils
Endothelial cells
↓ Vessel permeability
↓ Expression of adhesion molecules
↓ Production of IL-1 and prostaglandins
Fibroblasts
↓ Proliferation
↓ Production of fibronectin and prostaglandins

2.5.2 Vasoconstrictor Action

The mechanism of vasoconstrictor action is not clearly understood, but it may be due to blocking of action of vasodilators like histamine and bradykinin [30]. The erythema is reduced due to constriction of capillaries in superficial dermis. The vasoconstrictor action may contribute towards the anti-inflammatory effects. The correlation between vasoconstrictor activity and anti-inflammatory action has been used to grade the potency in the vasoconstrictor assay, mentioned earlier.

2.5.3 Anti-Proliferative Action

Topical corticosteroids are known to reduce mitosis in the epidermis and the basal cell layer becomes less thick. The stratum corneum and granulosum are thinned out. Keratinocyte proliferation and keratinocyte growth factors are also decreased. This is accompanied by a reduced melanocyte production. The dermis also shows signs of atrophy due to inhibition of fibroblast proliferation, migration, chemotaxis and protein synthesis [31]. There is reduced synthesis of collagen and glycosaminoglycans. The dermis volume shows a reduction due to loss of collagen and glycosaminoglycans and topical corticosteroid-induced vasoconstriction. As these processes continue, the elastin and collagen fibres begin to show abnormal aggregation [7]. These anti-proliferative effects are useful in psoriasis but are also the mechanism for the atrophogenic changes induced by topical corticosteroids.

2.6 Therapeutic Indications

Many inflammatory and hyperproliferative dermatological conditions respond very well to topical corticosteroids. Systemic corticosteroids are used for severe dermatological conditions.

Conditions like atopic dermatitis; stasis dermatitis; psoriasis, especially of genitalia and the face; and nummular eczematous dermatitis are some such examples. Discoid lupus erythematosus, sarcoidosis, pemphigus, vitiligo, etc., respond, but to a lesser extent. Some conditions like keloids and hypertrophic scars may require intra-lesional corticosteroid therapy [32]. Details of indications for the use of topical corticosteroid are presented in the next chapter.

2.7 Formulations

Topical corticosteroids are available in many formulations: creams, ointments, lotions, gel/hydrogel, sprays, shampoo and foam. Some of the newer formulations have a better patient acceptability and help to improve patient compliance.

Vehicles function as carrier for the active topical corticosteroid molecule, hydrate the skin and may help to increase the drug penetration [33]. The absorption and potency of drug depends on the vehicle used, in addition to the chemical structure of the corticosteroid molecule [34]. While selecting the vehicle, due attention needs to be paid to the interactivity of vehicle with the skin and drug molecule; stability, release rate and solubility of the drug in the vehicle; and skin area to be treated [35].

Creams are water-based formulations and have a low occlusive ability. Creams spread easily, without a greasy feel, and are thus preferred

by patients. They can be applied to most areas of the body, and preferred in hairy and intertriginous areas, and for wet lesions. The requirement of preservatives is a disadvantage [2, 29].

Ointments are preferred for dry or scaly, lichenified lesions and in areas with thick skin: palms and soles. They increase skin hydration and provide good occlusion. The drug penetration is thus improved. Drug action can be enhanced further by addition of propylene glycol, which increases the solubility of the drug in the vehicle. They are preferred for dry or scaly lesions and for palms and soles but should be avoided in intertriginous areas [2].

Lotions are generally oil-in-water emulsions. They are easy to apply and patient compliance is good. Lotions and foams are used for scalp lesions.

Gels are formulated with a gelling agent and offer ease of application.

Conventionally, ointments have been considered to be more potent than the rest of the formulations, but the use of an optimized vehicle has resulted in equipotent cream, ointment and gel formulations [33].

Besides these conventionally used formulations, there is a lot of interest in developing newer formulations such as nanoparticles, liposomes, microemulsions, ethosomes, etc. [36].

2.8 Selection and Use of Topical Corticosteroids

- Areas with thick stratum corneum, for example, palms and soles, require higher-potency preparations, whereas lower-potency topical corticosteroids are preferred for areas with a thinner stratum corneum, for example, parts of the face, the scrotum and intertriginous areas. There can be an increased penetration of the drug through the skin and, thus, an increased risk of ADRs [38, 39].
- Mild-to-moderate-potency corticosteroids can be used for highly responsive conditions; those which are less responsive need to be treated with higher-potency corticosteroids.
- Another consideration while selecting the topical corticosteroids is the extent of surface area of the skin involved. Systemic adverse drug reactions may occur if extensive skin surface is treated.
- Use of occlusive dressings can increase the permeability up to tenfold. Their use has decreased due to availability of super potent topical corticosteroids.
- The degree of absorption through the skin also varies with disease conditions, e.g. in atopic dermatitis, there is increased absorption of topical corticosteroids through the defective epidermis.
- The use of topical corticosteroids should be avoided on ulcerated or atrophied skin or if there is infectious dermatosis.
- If a systemic adverse drug reaction is suspected, then relevant laboratory investigations should be ordered [2, 37, 38, 39].

2.9 Adverse Drug Reactions (ADRs)

Topical corticosteroids tend to cause local ADRs more commonly, although systemic ADRs have been reported. The ADRs which have been seen commonly are listed in Table 2.3. The use of more potent agents and/or longer duration of therapy increases the chances of developing adverse drug reactions. Surface area of the skin, total amount of drug used, skin integrity and use of occlusive dressing are other risk factors [40].

Table 2.3 Local adverse drug reactions due to topical corticosteroids [13, 42, 43]

• Atrophic changes: striae, telangiectasia, purpura, stellate pseudoscars, ulceration
• Easy bruising
• Steroid acne
• Rosacea
• Aggravation and/or masking of infections
• Allergic contact dermatitis
• Ocular effects: cataract, glaucoma, increased susceptibility to infections, reduced ulcer healing
• Corticosteroid rebound, addiction, tachyphylaxis
• Miscellaneous: hypertrichosis, hypopigmentation

Systemic ADRs are not seen very commonly with the use of topical corticosteroids but may occur when they reach the systemic circulation via percutaneous absorption. High-potency corticosteroid used over large skin surface for prolonged periods increases the chances for developing systemic ADRs. Suppression of the hypothalamic-pituitary axis, growth retardation in children, cataract, glaucoma, avascular necrosis of femur and Cushing's syndrome have been reported; aggravation of diabetes mellitus, hypertension and osteonecrosis have been reported [41].

Children and the elderly have a higher risk of adverse drug reactions due to a higher ratio of total body surface to body weight (about 2.3–3-fold that of adults).

2.10 Contraindications

Topical corticosteroids should not be used when there is known hypersensitivity to the corticosteroid or any component of the vehicle. Ulceration or bacterial, fungal or viral infections being present are relative contra-indications to their use [7].

2.11 Topical Corticosteroids in Special Populations

2.11.1 Pregnancy and Lactation

A Cochrane review conducted in 2015 could not establish a co-relation between the use of topical corticosteroids and congenital abnormalities, preterm delivery or stillbirths, citing reasons of insufficient data. The use of very potent topical corticosteroids during pregnancy may increase the risk of very low-birthweight babies, but there is low evidence for this observation [44].

No adverse effects from the use of topical corticosteroids during lactation are documented, but it is advisable to avoid their use on the nipples before nursing [7].

2.11.2 Geriatric and Paediatric Patients

Low-potency corticosteroids are generally preferred for paediatric patients due to the greater risk of adverse drug reactions due to higher surface area to body weight ratio and fragile skin. In infants, use of diapers may increase drug absorption [39].

Geriatric patients also have a higher propensity to develop adverse drug reactions, more so if there is skin atrophy due to the ageing process [39].

2.12 Recent Advances

Remarkable progress has been made in the development of topical corticosteroids from the time that they were first introduced for treatment of dermatology diseases. Interest in developing new molecules with high topical activity and better safety profile continues. Another area of research is the use of newer formulations like nanosomes, liposomes, etc., for enhanced delivery of drug molecule into the skin [36]. Nitro-glucocorticoids are corticosteroids with an enhanced anti-inflammatory effect. Selective glucocorticoid-receptor agonists (SEGRAs) are drugs which are able to selectively induce transrepression with minimal induction of transactivation and are in various stages of development [45].

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http://www.springer.com/978-981-10-4608-7

A Treatise on Topical Corticosteroids in Dermatology
Use, Misuse and Abuse
Lahiri, K. (Ed.)
2018, XXI, 333 p. 152 illus. in color., Hardcover
ISBN: 978-981-10-4608-7