Review

"Apply sparingly"? A review of topical corticosteroids

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Case

A 20-year-old woman presents to a family practice office. She has a four-week history of itchy, red, scaly skin on the flexural surfaces of her elbows and knees, as well as across the top of her abdomen. This itching has been interfering with her sleep. The patient has a history of asthma, and facial dermatitis as a baby. She finds her skin is often dry, especially through the winter months. You diagnose her with a flare of atopic dermatitis and consider prescription of a topical corticosteroid for treatment.

Introduction

Topical corticosteroids are a frequently prescribed treatment for many dermatologic conditions, such as atopic dermatitis and psoriasis. When prescribed and used appropriately, these topical agents are safe and effective. However, failure of topical corticosteroid treatment is common, and often the result of incomplete or incorrect instructions to the patient leading to inadequate use.[1] Patients often receive inadequate or conflicting counselling which leaves them confused, or even anxious, about how to use topical steroids and their risk of experiencing adverse effects.[2] This review aims to highlight the key considerations when prescribing and counselling on topical corticosteroids.

Mechanism of Action

Corticosteroids are widely used as anti-inflammatory and immunosuppressive agents in a variety of dosage forms for many different medical conditions. When applied topically, one common mechanism through which corticosteroids act is to inhibit phospholipase A, reducing the production of arachidonic acid and downstream inflammatory products such as prostaglandins and leukotrienes.[3]

Additionally, topical steroids bind to receptors in the epidermis and inhibit the synthesis and mitosis of DNA, resulting in decreased epidermal proliferation.[3] This is an important mechanism for the treatment of scaling dermatoses, but can also lead to adverse dermal thinning with prolonged use of potent agents.[4]

Adverse Effects

The concern for adverse effects is a common source of anxiety for patients, and a common cause of under-treatment. In one study of 200 outpatients in the U.K., 72.5% were worried about using topical steroids on their child's skin, and 24% admitted to non-adherence due to these concerns.[2]

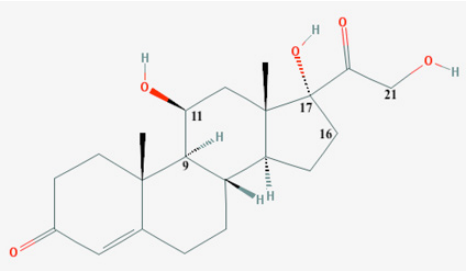
Possible local adverse effects of topical corticosteroids include striae, telangiectasia, tissue atrophy, allergic sensitization, and acneiform eruption.[3-5] Possible systemic adverse effects include suppression of the hypothalamic-pituitary-adrenal (HPA) axis, development of cushingoid appearance, and hyperglycemia.[3-5] Topical corticosteroid withdrawal ("steroid addiction") has not been well described in the literature, but appears to be a unique adverse effect after withdrawal of inappropriately used long term potent topical corticosteroids.[4] This has been primarily described on the face and genital areas, manifesting as a burning or stinging pain with erythema.

These adverse effects are relatively rare with appropriate steroid choice and duration, and almost always reversible. In one randomized trial allowing for unrestricted continuous use of 0.1% triamcinolone acetonide (trunk and limbs) and 1% hydrocortisone (face, neck, intertriginous areas) for one year in 330 adults, only 1% developed striae.[6] Trials demonstrating biochemical evidence of HPA axis suppression (i.e. decreased plasma cortisol) with extensive use of more potent topical corticosteroids have showed reversibility of this effect upon discontinuation of the medication.[2] Additionally, the clinical significance of this biochemical change remains unclear.[5]

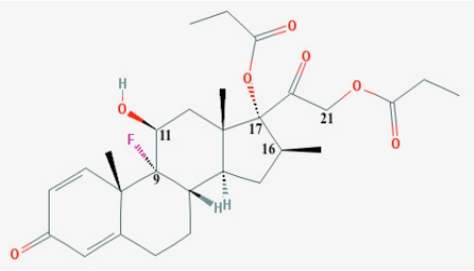
A statement by a U.K. Dermatology Working Group highlighted that the literature has failed to show significant HPA-axis suppression or skin thinning with topical corticosteroid use, particularly with intermittent treatments of lower potency agents.[2] Though these adverse effects are possible, in most instances they are minor and reversible with proper use. This relatively low risk of adverse effects must be weighed against the benefits of treatment, which can be substantial, and the risks of not treating the dermatologic condition. For example, atopic dermatitis left untreated can lead to insomnia from nocturnal symptoms, and the lesions can become secondarily infected.

The Steroid Molecule and Potency

The Compendium of Pharmaceuticals and Specialties (CPS) lists 22 different corticosteroid molecules used in topical products.[7] Considering the various vehicles in which these steroid molecules are compounded, there are roughly 50 different topical corticosteroid products on the market in Canada.[7] A basic understanding of the steroid molecule and potency is key in selecting the



Hydrocortisone (low potency)



Betamethasone 17,21 dipropionate (ultra-potent)

Figure 1. Examples of the molecular structure of glucocorticoids.[8,9,10]

appropriate steroid for a given condition.

All pharmacologically active steroids are based on chemical modifications of the basic steroid skeleton. Some modifications increase glucocorticoid activity while minimizing mineralocorticoid activity. An example of this is the addition of a hydroxyl group at position 11 on the hydrocortisone molecule in figure 1.[8] Substitution at position 16 and fluorination at position 9 further increases glucocorticoid activity and virtually eliminates mineralocorticoid activity. This can be seen in the structure of betamethasone dipropionate.[8] Also, specific changes can be made to increase topical potency. The esterification at position 17 and 21 seen in betamethasone dipropionate further increases its topical activity.[8] These chemical modifications make this topical corticosteroid roughly 1000 times more potent than hydrocortisone when applied topically.[4]

Many clinicians are under the impression that topical corticosteroid potency ranking is directly determined by either the glucocorticoid's treatment efficacy or its tendency to cause adverse effects. In actuality, though correlated with its anti-inflammatory effect, the potency of a topical corticosteroid is directly determined by a standard vasoconstriction bioassay, with more potent corticosteroids causing more cutaneous vasoconstriction.[4] This bioassay is used to subdivide the topical corticosteroid molecules into seven classes, with class one being the most potent and class seven being the least.[7] Examples of agents in each potency class, along with their approximate cost, can be found in Table 1.

The differences in relative potency between the topical corticosteroid classes is significant. For example, hydrocortisone, the lowest potency agent, is roughly 100 times less potent than the commonly prescribed class five steroid betamethasone valerate.[11] Though commonly known as "low potency" and "intermediate potency" agents, the relative difference in potency between them is substantial. In fact, due to its safety profile, 1% topical hydrocortisone preparations were recently approved for sale as non-prescription products in Canada. Topical corticosteroid packaging instructions and counselling from clinicians often includes the universal advice "apply sparingly". This can incorrectly inflate the patient's fear of adverse effects, particularly with low potency agents such as hydrocortisone, and lead to poor treatment response from underuse.

Table 1: Examples of topical corticosteroids by potency class[5,7]

Class	Example Agents	Approximate Cost (per 30g)
I	Clobetasol 17-propionate (Clobex) Betamethasone dipropionate glycol (Diprolene)	< $10 $10 - $25
II	Desoximetasone (Topicort) Halobetasol propionate (Ultravate)	$10 - $25 $25 - $50
III	Amcinonide (Cyclocort) Betamethasone dipropionate (Diprosone)	< $10 < $10
IV	Mometasone furoate (Elocom) Triamcinolone acetonide (Aristocort)	< $10 $10 - $
V	Betamethasone valerate (Prevex B) Hydrocortisone 17-valerate (Hydroval)	< $10 < $10
VI	Desonide	< $10
VII	Hydrocortisone (Emo-Cort, Prevex HC, Topiderm HC)	< $10
Non-Steroidal Topical Agents	Pimecrolimus (Elidel) Tacrolimus (Protopic)	$50 - $75 $50 - $75

Additionally, factors other than the corticosteroid molecule itself contribute to the potency of a given product. Increasing the concentration of the steroid within the vehicle can increase potency to a certain degree. The choice of vehicle also impacts potency. Ointment-based products are more occlusive and generally yield better absorption percutaneously. Occlusive dressings applied over topical corticosteroids can similarly have a dramatic impact, increasing potency up to 100-fold.[4] Also, the integrity of the skin barrier itself, as well as the age of the patient can impact the clinical potency of a topical corticosteroid agent.[4]

The severity and type of dermatologic condition must be weighed against the anatomic regions involved when choosing the appropriate topical corticosteroid potency, as percutaneous absorption is increased in areas with a thinner epidermal layer. For example, the percent of total dose absorbed percutaneously is 0.14% on the sole of the foot (thick epidermal layer) vs. 13% on the skin overlying the mandible (thin epidermal layer).[4] Table 2 highlights general recommendations for steroid potency given the anatomic region involved, however the severity and type of dermatologic condition must always also be taken into consideration.

Table 2: Recommendations for use of topical corticosteroids by anatomical location.[4,5]

Topical Corticosteroid Potency	Clinical Indication for Use
Ultra-High	• Severe Dermatologic conditions • No involvement of face or intertriginous skin • Disease involving palms and soles
Medium to High	• Dermatologic conditions of mild-moderate severity involving body/scalp • Generally, not involving facial/intertriginous skin
Low	• Dermatologic conditions involving facial/intertriginous skin; particularly skin of eyelids or genitals

Prescribing and Counselling

Prescription of systemic medications is relatively simple. There is rarely confusion on the patient's part of how much medication to take, and rarely difficulty on the prescriber's end with deciding how much medication to provide. The same cannot be said for the prescribing of topical agents.

One objective measure for the application of topical products is the fingertip unit (FTU). One FTU is the quantity of ointment expressed from a tube with a 5mm diameter nozzle from distal skin crease to the tip of the index finger (figure 2).[12] The average weight of one FTU is approximately 0.5 grams.[12]

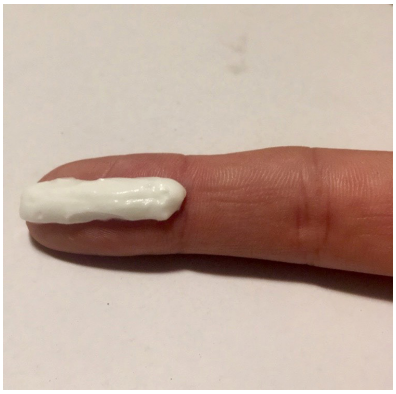


Figure 2: One fingertip unit

With this standardized measure, the appropriate number of FTUs to adequately treat a given body surface area was deduced. This provides clinicians with a guide to estimate the appropriate application-quantity for patients. As a quick reference, one FTU should adequately treat an area the size of two adult handprints with the fingers together.[5] For pediatric topical applications, infants require roughly one-fifth the adult dose, children two-fifths the adult dose, and adolescents two-thirds the adult dose.[13] Patients should be counselled to rub-in the appropriate quantity of cream or ointment until they disappear, as there is no advantage in leaving a thick layer of the topical product on the skin.[4]

The total weight of a topical product to be dispensed is also an important consideration. Too little can put the patient at risk of an inadequate treatment response, and too much at risk of adverse effects and delayed follow up. Using the average weight of an FTU, the number of FTUs required per application, and the frequency of application, clinicians can calculate the weight of topical product required per day. For convenience, many tables exist which have done this calculation for various body surface areas (table 3).

Table 3: Amount of topical product to treat various areas twice daily for one week.[12]

Area	Number of FTUs per appliction	Quantity of topical required
Face and neck	2.5	18g
Front of trunk	7	49g
One arm*	3	21g
One hand	1	7g
One leg	6	42g
One foot	2	14g

**Example calculation:*
(#FTUs required per application) x (weight of FTU) x (frequency) x (duration) = quantity
(3 FTUs) x (0.5g/FTU) x (2/day) x (7 days) = 21g

It is important patients receive accurate and consistent counselling from clinicians on topical corticosteroids. Patients can easily forget the details of application instructions and may only be left with the product packaging to guide usage, which often uses cautionary language such as "apply sparingly" or "apply thinly."[2] This can be avoided by detailing explicit usage instructions on the prescription so that the pharmacy labelling matches with the prescriber's intent. For example, when prescribing a potent agent, the prescriber may include the labelling instructions "Apply to lesions on the palms and soles for 2-4 weeks. Do not use on face." Additionally, it is important that pharmacists clarify the indication and duration with patient and/or prescriber as required to reinforce the correct application instructions. Ideally, patients should be provided with a personal chart outlining which areas to treat, with how many FTUs, frequency of application, and expected duration of treatment.[2] Most skin eruptions that do not improve significantly within 2 weeks of topical corticosteroid use should be reassessed.[5]

Case Resolution

You prescribe your patient betamethasone valerate 0.1% cream applied twice daily to the affected areas. Knowing the surface area of the palmar surface of two hands requires roughly one FTU per treatment, you estimate your patient will require three FTUs per treatment to cover the involved body surface areas. You prescribe 45g for two weeks of treatment (3FTU x 0.5g/FTU x 2/day x 14days = 42g), demonstrate the measurement of an FTU, and inform her it should take roughly three FTUs per application to adequately treat the involved areas. You educate the patient on atopic dermatitis, and the importance of the use of non-medicated topical emollients. You arrange follow-up in 14 days to reassess the patient's condition.

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