SEXUAL MEDICINE REVIEWS REVIEWS

Topical Corticosteroids in the Treatment of Vulvar Lichen Sclerosus: A Review of Pharmacokinetics and Recommended Dosing Frequencies

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ABSTRACT

Topical corticosteroids are often utilized as the first-line treatment for vulvar lichen sclerosus (VLS). However, there is wide variability in dosing regimens, as well as a lack of consensus on maintenance dosing. Available guidelines on dosing frequency and regimen continuation for VLS are based on clinical expert opinion and do not necessarily reflect the pharmacokinetics of topical corticosteroids. Over the past few decades, there have been many advances in the techniques used to measure the local and systemic absorption of topical corticosteroids. These techniques have led to a greater understanding of the pharmacokinetics and bioavailabilities of these medications. However, it is not clear how this new information has been applied in evaluating dosing regimens and commonly cited risks when considering short- and long-term use in different vulvar dermatoses. This purpose of this review is to evaluate the available evidence on pharmacokinetics, absorption rates, and concentration levels of topical corticosteroids in lesional and nonlesional skin. Additionally, the evidence regarding commonly cited risks of topical corticosteroid use, including dermal thinning, adrenal suppression, systemic immunosuppression, and tachyphylaxis are reviewed. Differences in the effects of topical corticosteroids on the varied tissues of the vulva are specifically explored. Finally, these considerations are applied to evaluate the current treatment guidelines for VLS to provide direction in determining an evidenced-based dosing regimen and to inform future research in this area. **Mautz TT, Krapf JM, Goldstein AT. Topical Corticosteroids in the Treatment of Vulvar Lichen Sclerosus: A Review of Pharmacokinetics and Recommended Dosing Frequencies. Sex Med Rev 2021;XX:XXX–XXX**

Key Words: Corticosteroids; Pharmacokinetics: Vulvar lichen sclerosus; Vulva

INTRODUCTION

Potent and superpotent (ultrapotent) topical corticosteroids are the gold-standard treatments for vulvar lichen sclerosus (VLS). Despite common use and well-demonstrated efficacy, there is no consensus on ideal treatment regimens (ie, dose, frequency of application, length of use).[1,2] The variation in dosing regimens is the result of a lack of randomized controlled studies evaluating optimal dosing, due to ethical concerns of prescribing a placebo or potentially less effective regimen when the efficacy of superpotent topical steroids is well-established.[3,4] The most recent 2018 British Association of Dermatologists (BAD) Guidelines for the Management of Lichen Sclerosus acknowledges "aware[ness] of the lack of high-quality evidence for [its] recommendations" because of a lack of randomized controlled trials.[1] While there are many studies that examine the efficacies of particular topical corticosteroid regimens, the chosen dosing frequencies are not typically based on the pharmacokinetics of the medication. Additionally, the perceived risks of corticosteroids, namely dermal thinning, adrenal suppression, systemic immunosuppression, and tachyphylaxis, are often stated without significant data to support the incidence or severity of these risks, especially regarding use on the vulva. Fears regarding long-term corticosteroid application have implications for patient and physician acceptance of long-term treatment regimens, patient compliance, and motivation to study and utilize other treatment options, which may be less effective. Even the package insert for clobetasol propionate, the most commonly used topical steroid for VLS, cautions against excessive usage (which it defines as more than two consecutive weeks of treatment, or more than 50g per week) without citing data to support these recommendations.[5]

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As such, our aim is to provide a comprehensive review of the literature on the pharmacokinetics, adverse effects, and dosing regimens of topical corticosteroids that are used to treat VLS. We will examine the following questions:

- What are dermal and systemic absorption levels for topical corticosteroids on lesional and non-lesional skin?
- What is the evidence in regard to commonly cited risks of long-term topical corticosteroid use, including dermal thinning, adrenal suppression, systemic immunosuppression, and tachyphylaxis?
- Do current dosing recommendations for VLS reflect available pharmacokinetic data on these medications?

PHARMACOKINETICS OF TOPICAL CORTICOSTEROIDS

Topical corticosteroids alter the immune system's function via impacts on inflammatory mediators, inflammatory cells, and lysosomal enzymes.[6] After passing through the cell membrane, corticosteroids bind with glucocorticoid receptor α-isoform in the cytosol to form a steroid-receptor complex (Figure 1). This complex translocates to the cell's nucleus and binds to a region called the corticosteroid responsive element. The binding event impacts the transcription of DNA into mRNA and subsequently the translation of mRNA into proteins.[7] Corticosteroids often upregulate the production of glycoproteins called lipocortins. Lipocortins inhibit the activity of phospholipase A2, which results in inhibited release of arachidonic acid, a precursor of the inflammatory mediators prostanoids and leukotrienes.[7] The increase in lipocortins can also reduce the amount of mitotic activity in skin cells.[8] In addition, corticosteroids inhibit the mRNA that produces interleukin-1, a key cytokine in the regulation of inflammatory responses.[7] Together, these actions result in an anti-inflammatory effect.

Successful administration of topical corticosteroids is dependent on a number of factors. These factors include: (i) choosing the right corticosteroid, (ii) selecting the appropriate potency, or the amount of drug needed to produce a desired therapeutic effect, (iii) using the best vehicle through which the drug is administered, and (iv) applying the medication at the proper frequency.[8] The United States classification divides topical corticosteroids into seven classes, ranging from Class I (superpotent) to Class VII (least potent).[8] Table 1 lists these seven classes, as well as examples of corticosteroid types that fall into each class. The five main vehicles used to deliver topical corticosteroids are: ointments, creams, lotions, gels, and foams.[8] Ointments are the most potent because they are the most occlusive. The latter four are less occlusive and less greasy than ointments, which can make them more desirable for certain application sites (for example, to deliver corticosteroids to the scalp), but they are also less potent as a result.[8]

Many factors can impact the rate of absorption of topical corticosteroids, including drug lipophilicity, solubility, concentration, and site of application.[6] The steps that govern absorption of topical corticosteroids are: release from the excipient, penetration into and permeation through the stratum corneum, passage into the viable epidermis and dermis, and diffusion within viable epidermis/dermis to bind to the corticosteroid receptors.[9] The rate-limiting step is penetration of the stratum corneum.[9] The thickness of the stratum corneum is a major factor in determining rate of absorption. This may be especially important when

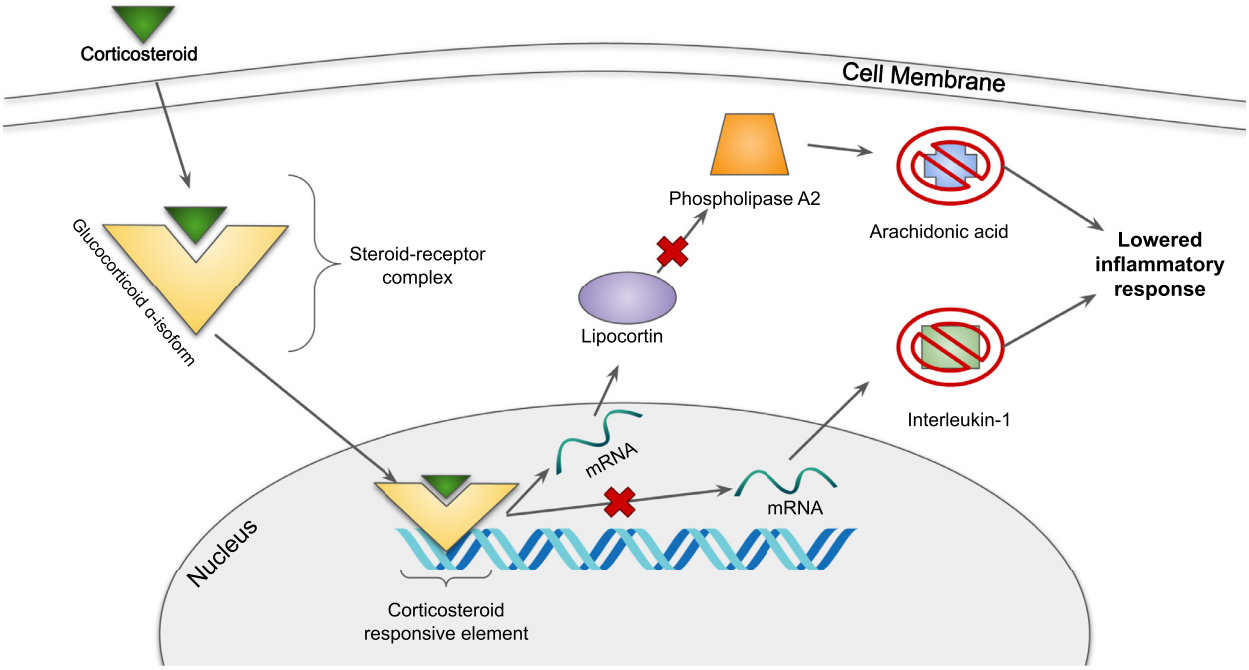

Figure 1. Pharmacokinetics of corticosteroids. Developed from Kragballe 1989.[7]

Table 1. Topical corticosteroid classes and potencies

Class	Potency Level	Corticosteroids
I	Superpotent	Clobetasol propionate 0.05% in any vehicle, augmented betamethasone dipropionate 0.05% gel or ointment, diflorasone diacetate 0.05% ointment, fluocinonide 0.1% cream, and halobetasol propionate 0.05% cream or ointment
II	High-potency	Amcinonide 0.1% ointment, augmented betamethasone dipropionate 0.05% cream or lotion, betamethasone dipropionate 0.05% ointment, desoximetasone cream or gel or ointment, diflorasone diacetate 0.05% cream, fluocinonide 0.05% cream or gel or ointment, and halcinonide 0.1% cream or ointment or solution
III	Medium-to-high potency	Amcinonide 0.1% cream, betamethasone dipropionate 0.05% cream, fluticasone propionate 0.005% ointment, and triamcinolone acetonide 0.5% cream or ointment
IV and V	Medium-potency	Betamethasone valerate 0.1% cream or lotion or foam, desoximetasone 0.05% cream, Fluocinolone acetonide 0.025% cream or ointment, fluticasone propionate 0.05% cream, hydrocortisone butyrate 0.1% ointment, hydrocortisone probutate 0.1% cream, hydrocortisone valerate 0.2% cream or ointment, mometasone furoate 0.1% cream or lotion or ointment, triamcinolone acetonide 0.025% cream or lotion or ointment, and triamcinolone acetonide 0.1% cream or lotion or ointment
VI	Low-potency	Alclometasone dipropionate 0.05% cream or ointment, desonide 0.05% in any vehicle, fluocinolone 0.01% cream, and hydrocortisone butyrate 0.1% cream
VII	Least-potent	Hydrocortisone 1% and 2.5% cream or lotion or ointment

Developed from Gabros, Nessel, and Zito, 2020.[8]

discussing vulvar dermatoses. In lichen sclerosus, the stratum corneum is thickened. In erosive lichen planus, the stratum corneum may be absent. It would stand to reason that absorption rates would be higher in dermatoses such as erosive lichen planus, where there is limited stratum corneum, and lower in dermatoses with thickened stratum cornei, such as lichen sclerosus. However, no study has compared absorption rates between these conditions.

WHAT ARE DERMAL AND SYSTEMIC ABSORPTION LEVELS FOR TOPICAL CORTICOSTEROIDS ON LESIONAL AND NON-LESIONAL SKIN?

Measuring Absorption of Corticosteroids

Most topical corticosteroids were developed in the 1950s.[6] Clobetasol propionate was first patented in 1968, came into medical use in 1978, and was FDA-approved in 1985 as Temovate ointment.[10] At the time of approval, absorption of these medications was measured by one of two techniques: horizontal stripping and sectioning of the skin.[11] To measure the potency of topical corticosteroids in particular, common assays included the tape-stripping procedure, vasoconstrictor assay, mitotic index suppression method, and atrophogenic potential assay.[6] However, in the last 30-40 years, researchers have developed more advanced techniques for assessing pharmacokinetics and bioavailability of topical medications. These new methodologies include heat separation, in vitro diffusion method, quantitative autoradiography, dermal open flow microperfusion (dOFM), and the use of induced follicle-free skin.[11,12] Advances in the technology of optical instruments has allowed researchers to quantify compounds in the skin using various spectroscopies in visual and infrared wavelengths, a technique referred to as heat separation.[11] The progression in the tools available to researchers to study these medications prompts a review of the commonly accepted pharmacokinetics of topical corticosteroids, and whether they are consistent with what we have learned using modern techniques.

Absorption Levels of Topical Corticosteroids for Dermatoses

The idea of once daily application of topical corticosteroids comes from a review article published in 1998. Similar to the current review, the authors investigated the dermatopharmacokinetics of topical corticosteroids to determine whether current standards of applying topical corticosteroids multiple times a day was supported by the science at the time.[13] Of note, they cite studies using the older methods for measuring absorption levels of corticosteroids: tape stripping and vasoconstrictor assays. The authors concluded that once a day application of topical corticosteroids is sufficient and preferable to twice or more applications per day due to reservoir effects of corticosteroids.[13]

However, since the publication of the previous review over 20 years ago, we have been able to study absorption rates using more advanced techniques. There were no studies that measured corticosteroid absorption in the setting of active or treated lichen sclerosus found in a comprehensive literature search. However, there is limited research on corticosteroid absorption in two other skin conditions that affect the vulva: psoriasis and vitiligo. An exploration of this data, which utilized more modern absorption assays, may give us insight on differences of absorption in lesional versus non-lesional skin.

One of the most robust studies to measure absorption levels of topical corticosteroids was conducted by Bodenlenz and

colleagues in 2016. They used dermal open flow microperfusion (dOFM), to investigate the absorption of the topical corticosteroid clobetasol propionate 0.05% in psoriatic skin.[14] Clobetasol was applied daily for 14 days to lesional and non-lesional skin, with dOFM performed on days 1 and 14. They found that after one day of treatment, the cumulated quantities of clobetasol in non-lesional skin was 2.142 ± 1.993 ng, whereas in lesional skin it was only 0.854 ± 0.422 ng (P = .033). The penetration of clobetasol into the dermis after the first day of treatment reached maximum concentration at 18 hours in non-lesional skin but did not reach the lower limit of quantification in lesional skin. After 14 days of treatment, the cumulated quantities of clobetasol in non-lesional skin rose to 4.439 ± 4.602 ng and in lesional skin rose to 2.768 ± 2.010 ng. These results indicate a slower penetration of clobetasol in lesional skin compared to non-lesional skin. The authors concluded that the thickened stratum corneum in psoriasis lowers the skin penetration rate for lipophilic topical drugs in lesional skin. However, as the lesional skin heals from daily clobetasol application, the stratum corneum decreases in thickness, which explains the significant increase in absorption from Day 1 to Day 14. Still, the cumulated quantities of clobetasol in lesional skin were about 60% of that found in non-lesional skin after 14 days of treatment. The acceptable baseline levels of clobetasol on Day 14 also indicate that clobetasol does not significantly accumulate in the skin following repeated dosing.[14]

Findings were starkly different in the setting of vitiligo. In contrast, Singh and colleagues (2015) found that topical clobetasol propionate 0.05% cream and fluticasone propionate 0.005% ointment had significant reservoir effects that last 5 days after a single application in vitiliginous skin.[15] The authors used a method called the histamine-induced wheal suppression test, initially designed by Singh and Reddy.[16] This method is effective because topical corticosteroids suppress the wheal and flare response triggered by histamines. The authors applied the topical corticosteroids to the skin in two locations (plus a control location), poured 1mL of 1% histamine phosphate solution over the areas, and then pricked the skin with a 2 mm long needle. After ten minutes, the diameter of the wheal and erythema produced at each site were measured.[15] They repeated the measurements at each site every day until all three sites had similar levels of wheal and flare responses again. The authors found that both clobetasol propionate and fluticasone inhibited the wheal and flare response for up to 5 days and therefore concluded that topical corticosteroids form reservoirs in the stratum corneum from which they are gradually released into deeper layers of the skin.[15]

It is possible to reconcile these divergent findings when considering the different natures of the two dermatoses investigated. Vitiligo, a skin disorder characterized by a loss of melanin pigment, does lead to some thickening of the stratum corneum, particularly when exposed to sunlight.[17] However, this thickening only amounts to a stratum corneum thickness of 34.09 ± 33.61 μm in sun-exposed vitiliginous skin.[17] Comparatively, one study found the average stratum corneum thickness in vulvar skin affected by lichen sclerosus to be 1200 μm,[18] while two studies found respective stratum corneum thicknesses in skin affected by psoriasis to be 41.6 μm and 98 μm.[19,20] Therefore, it is likely that the thicker stratum cornei of lichen sclerosus largely prevents the reservoir effects seen in vitiliginous skin described above.[15]

The potential or observed adverse effects that are cited most frequently in studies involving topical corticosteroids are dermal thinning, adrenal suppression, systemic immunosuppression, and tachyphylaxis.[4,21,22,23] Concerns over these potential adverse effects have led to significant fears among patients and healthcare providers, leading to general recommendations to limit frequency and duration of topical corticosteroids, especially super potent corticosteroids. In vulvar dermatoses that utilize topical superpotent corticosteroids as first-line treatment, these fears have clinical consequences related to physician prescribing and patient compliance. In the case of lichen sclerosus, not continuing long-term treatment may increase risk of malignant progression.[4] This underscores the need to critically evaluate the incidence and risk of these reported adverse effects to topical corticosteroid application.

Dermal Thinning

Many studies have examined the potential for topical corticosteroids to cause skin atrophy, or dermal thinning.[21,24,25,26] In fact, atrophy is the most common adverse effect of topical corticosteroids.[27] Corticosteroids can cause atrophy via their upregulation of lipocortins. Lipocortins, whose anti-inflammatory properties were outlined above, also have antimitotic effects, leading to epidermal thinning.[8] Higher potency corticosteroids lead to higher risk of dermal thinning because the same amount of drug has greater effects on the skin, however the increase in risk based on potency has not been formally investigated.[8] Kao et al. (2003) found that even three days of use of a potent topical corticosteroid can change epidermal structure and function in mice by disrupting the skin-barrier homeostasis, reducing corneodesmosome density, and inhibiting epidermal lipid synthesis.[28] In a small study of human participants, Lubach and Kietzmann (1995) found that non-lesional skin thinned about 15% after 16 days of twice daily clobetasol propionate application.[29] The 15% thinning was maintained when clobetasol was applied only every 5th or 7th day. However, after decreasing application intervals to every 10th and 14th day, skin thickness returned to normal levels. In addition, skin thinning effects after a single application of clobetasol persisted for about three days.[29] Another study found that long-term use of topical corticosteroids led to an increase in transepidermal water loss (TEWL), which results in a lowered ability to maintain the permeability barrier of the epidermis via the intercellular lipid lamellae.[30] Draelos (2008) claims that because drug penetration of topical corticosteroids is highest in thinnest skin (as corroborated by Bodenlenz et al., 2016[14]), this could lead to some of the observed adverse cutaneous effects.[31]

In the vulva, the mucosal membranes and intertriginous regions, as well as the fact that the vulva is nearly always occluded

(by underwear, sanitary pads, or skin-on-skin contact), lead to differential risks of dermal thinning compared to other parts of the body.[32] Given these factors, it has been posited that the increased absorption rates of corticosteroids can lead to increased risk of dermal atrophy.[32,33,34] The first case report on glucocorticoid-related atrophy in the vulva specifically documented a case of a 55 year old woman who had significant atrophy in her vulva after 2 years of treatment with topical steroids of increasing potency and frequency (specific regimens not mentioned).[34] She had extensive loss of subcutaneous fat in her labia majora and labia minora and had a "web" of perineal skin with background telangiectasia in the perineum.

However, studies have not indicated increased atrophic changes, either clinically or histologically, when potent corticosteroids are applied to vulvar skin affected by lichen sclerosus. In a study of over 80 women with vulvar lichen sclerosus treated with clobetasol propionate 0.05% ointment once daily for 3 months, then 3 times per week until complete remission or 2 times per month if treatment continued longer than 12–18 months, "no systemic or local atrophic effects were observed" clinically in the median of 4.7 years follow-up.[35] Evaluating histological response to treatment, a small study found no histologic evidence of infection or skin atrophy in vulvar biopsy specimens collected from women with vulvar lichen sclerosus treated with twice daily application of clobetasol propionate 0.05% cream during the 22 month study period.[36] Given the results of these studies, the risks of dermal thinning in vulvar lichen sclerosus are most likely over-exaggerated, especially in long-term treatment regimens where the frequency of maintenance dosing is twice weekly. It is also worth noting that, as mentioned previously, the average stratum corneum thickness in vulvar LS to be 1200 μm,[18] which is over seven times thicker than the average epithelial thickness (including the stratum corneum) in normal vulvar skin (170 μm).[37] Therefore, some amount of atrophy can actually restore the stratum corneum to normal thicknesses.

Adrenal Suppression

Suppression of the hypothalamus-pituitary-adrenal (HPA) axis has been implicated in high doses of topical corticosteroids, leading to Cushing syndrome, decreased morning cortisol levels, and hyperglycemia. In one documented instance, in which the patient had been using 200 g clobetasol propionate 0.05% and 500 g of a 1:4 dilution of the same preparation each week as well as an unknown quantity of betamethasone valerate, corticosteroid-related Addison crises have even led to death.[22,26,35] Risk factors for these adverse effects include applying the corticosteroids to large surface areas of the skin, occlusion, higher concentrations of drug, and using more potent steroids.[26] Ohman and colleagues (1987) presented four case reports of patients with wide-spread psoriasis and eczema treated with 50 g of 0.05% clobetasol propionate cream per week who developed cushingoid features.[22] These patients demonstrated evidence of secondary adrenal failure by a metyrapone test. In each case, the patients had been treating their dermatoses with 0.05% clobetasol propionate for multiple years (2–5 years), although the dosages varied from 30 g per month to 100 g per week. Once each of the four patients stopped using 0.05% clobetasol propionate, within months their metyrapone tests returned to normal levels.[22] Similarly, Wolkerstorfer and colleagues found that a dose of 14g a week of clobetasol propionate ointment can suppress adrenal glands in children.[38] Less potent steroids, such as betamethasone dipropionate, required much higher dosages (49 g per week) before plasma cortisol levels were significantly reduced.[38] However, for the purpose of treating vulvar lichen sclerosus, the maximum recommended dosage is 10 g per month of clobetasol,[2] so the risks of adrenal suppression should be quite low, and there are no reported cases of adrenal suppression in women using corticosteroids for vulvar dermatoses.

Systemic Absorption and Immunosuppression

Systemic absorption rates of topical corticosteroids can be measured through hematology and urinalysis.[39] Topical medications have poor total absorption (especially compared to oral medications) and less than 2% of a topical corticosteroid such as hydrocortisone is systemically absorbed after 1 day of application.[40,41] However, one study found that topical corticosteroids can be detected in the bloodstream up to 2 days after application. In 1983, Hehir and colleagues used the quantitative autoradiography method to measure the blood plasma levels of clobetasol propionate and clobetasone butyrate in patients with psoriasis or eczema.[42] They drew blood from patients following the application of either clobetasol propionate or clobetasol butyrate (both radio-labelled). Then, using a series of assays, they separated the radio-labelled corticosteroids from the plasma and measured the amounts of each. They found that there were measurable amounts of both corticosteroids in the blood plasma up to 48 hours after application and concluded that once daily or every other day application would be ideal for topical corticosteroids.[42] The vulva has been shown to have higher systemic absorption rates of topical corticosteroids than other parts of the body due to intertriginous regions and high TEWL rates.[32,43,44] However, Goldstein et al. (2011) found that even after daily clobetasol application to the vulva for treatment of lichen sclerosus, serum levels were assessed and clobetasol serum levels never reached pre-established cut-off levels of concern.[45] Other studies have found potential systemic adverse effects, including depletion of mast cells,[46] T-cell proliferation and apoptosis,[47] glaucoma,[26] hyperglycemia and the unmasking of latent diabetes mellitus,[26] edema and possibly hypocalcemia.[26] However, given the paucity of literature on these side effects, they are generally considered very rare.

Tachyphylaxis

The long-term use of topical corticosteroids has been associated with tachyphylaxis, which describes a diminished response to successive doses of the medication, making it less effective

with repeated use.[23] There are limited clinical trials examining the phenomenon of tachyphylaxis for topical corticosteroids.[48] Studies on topical corticosteroids in psoriasis have not demonstrated tachyphylaxis.[49,50] Some authors have proposed that poor patient compliance over time can be perceived as a reduction in drug efficacy, labeled as tachyphylaxis.[23,48,51] Although there are no studies that directly examine tachyphylaxis in the setting of VLS, a number of studies cite tachyphylaxis in their rationale for tapering dosing regimens,[52,53,54] and in some cases, in their rationale for treatment with topical calcineurin inhibitors instead of topical corticosteroids.[55,56]

Vulvar Dermatoses Versus Other Dermatoses

It is important to note that vulvar dermatoses have some different properties compared to dermatoses in other regions of the body. The vulva and vagina are comprised of a combination of keratinized, mucosal, and modified mucosal membranes, and consequently, the absorption rates of drugs are variable across these membranes.[57,58,59] The modified mucous membranes of the labia and clitoris are relatively resistant to corticosteroid-related side effects such as atrophy and telangiectasia related to treatment of lichenoid dermatoses.[58,60,61] Alternatively, the inguinal creases, hair-bearing areas of the labia majora, and perianal skin are more prone to atrophy with long-term corticosteroid use.[58,62,63] The reasons for these observed differences in tissue response has not yet been elucidated, but may be related to increased levels of inflammation related to the disease process in the targeted areas of the labia minora, peri-clitoral area, and the perineum. The labia majora have been shown to absorb greater amounts of hydrocortisone and methyl nicotinate compared to the forearm, likely due to differences in stratum corneum thickness and presence of apocrine (sweat) glands on the forearm.[43,44,64] The vulva has the lowest number of cell layers in the stratum corneum of anywhere on the body, with an average of 6 layers of stratum corneum, compared to an average of 15 layers on the extremities.[57] The vagina itself allows for far greater absorption of a drug than keratinized skin due to absence of stratum corneum, thin mucous membranes, and natural occlusion due to vaginal walls resting on each other.[57] There may be less atrophic changes experienced with application of corticosteroids in the setting of vulvar lichen sclerosus and other vulvar lichen conditions due to the high levels of inflammation, thickened stratum corneum impairing absorption, and location sites of the condition on the labia and clitoris, which appear to be more resistant to corticosteroids. Indeed, Table 2 illustrates that the actual observed adverse effects of topical corticosteroids applied to the vulva are typically nonexistent or mild. However, there are limited studies that examine histological changes specific to atrophy in regard to the treatment of vulvar lichen sclerosus and other vulvar lichen conditions.[36]

Do current dosing recommendations for vulvar dermatoses reflect available pharmacokinetic data on these medications?

Dosing Regimens

Regarding frequency of application, numerous studies have examined the effects of various dosing intervals or topical corticosteroids on VLS.[4,36,65,66] These recommendations are based on clinical expert opinion and do not necessarily reflect the aforementioned newer knowledge of the pharmacokinetics of these medications. The first widely-cited study, by Dalziel, Millard, and Wojnarowska (1991) used the following dosing interval: twice daily treatment with clobetasol propionate 0.05% cream for twelve weeks to treat vulvar lichen sclerosus.[36] Others have varied widely; Table 2 illustrates a few example treatments, dosing intervals, results, and adverse effects reported by studies that have investigated topical corticosteroids to treat vulvar dermatoses. There is no standard dosing regimen investigated by these studies; and they are diverse in terms of the type of corticosteroid used, the potency of the steroid, the number of grams applied each week, and the frequency of application. These studies do not cite pharmacokinetic data to justify their chosen dosing regimens; instead, each seems to build off the work of their predecessors. Dalziel, Millard, and Wojnarowska (1991), who did not have many predecessors from whom to base their dosing regimen, simply cite that "many practitioners use potent topical steroids to treat LS" but do not explain further.[36]

There are two preeminent guidelines regarding the use of topical corticosteroids to treat VLS.[1,2] However, even these two guidelines have different recommendations and cite clinical studies using topical corticosteroids instead of studies that investigate the pharmacokinetic and absorption rates of topical corticosteroids.[1,2] The British Association of Dermatologists (BAD) Guidelines for the Management of Lichen Sclerosus (BAD guidelines) recommend applying 0.05% clobetasol propionate every night for four weeks, then every other night for four weeks, then twice a week for four weeks to treat anogenital lichen sclerosus in adult women.[1] These guidelines do not recommend universal maintenance therapy and instead write that maintenance therapy should only be used "as needed," and not in cases where remission is maintained.[1] Alternatively, the European Academy of Dermatology and Venereology (EADV guidelines) evaluates a number of treatments and reports that "there is no single strategy (medical or surgical) that can be recommended for the treatment of LS. Patients and their parents or 'carers' should be informed of the different options and their advantages and disadvantages explained enabling them to make a decision."[2] They also write that "there is no standardized treatment regimen [with topical steroids]; often clobetasol propionate 0.05% ointment (or cream) once or twice-daily for 3 months with a possible reduction in application frequency after 1 month in milder cases is applied. Usually a fingertip per application and a maximum amount of 10 g per month (possibly a little more for initial treatment) is recommended to avoid skin thinning."[2] Unlike the BAD guidelines, the EADV guidelines recommend maintenance therapy for all vulvar LS patients, but specify that some patients may only need to apply corticosteroids 2-3 times a month, while others might need maintenance therapy of 2-3 times a week.[2] As can be

Table 2. Example treatment regimens and results in studies using topical corticosteroids to treat vulvar lichen sclerosus (VLS)

Study	Patients	Treatment	Dosing interval	Results	Adverse effects
Dalziel, Millard, & Wojnarowska (1991)	15 adult females	CP 0.05% cream to treat VLS	2x a day for 12 weeks	Clinical appearance approved in all 13 patients; no longer possible to make clinical diagnosis of LS in 5 patients; no specific features of LS detected in 4 of the biopsies after treatment	1 patient had burning from clobetasol, other had contact sensitivity to clobetasol
Fischer & Rogers (1997)		0.05% BD* ointment to treat VLS in children	3x a day for 3 weeks, then 2x a day until appearance of vulva "returned to normal" (average 3 months of treatment)	8/11 children gained complete remission, 3/11 required maintenance therapy with mild topical corticosteroid	3/11 patients had mild telangiectasia of labia majora, 2/11 had transitory erythema at 12 weeks
Renaud-Vilmer et al. (2004)	83 adult females	CP 0.05% ointment to treat VLS	1x a day for 3 months, 3x a week until complete remission, 2x a week if remission not achieved by 12-18 months	All patients had improvements in symptoms after 3 months, 45 patients achieved complete remission, significant effect of age on the probability of complete remission	2 patients had local inflammation due to steroid application, 1 case of genital candidiasis
Garzon & Paller (1999)		CP 0.05%, DD* 0.05%, BD 0.05%, and BD without propylene glycol to treat VLS	2x a day for 6 weeks	All 10 prepubertal girls showed partial or complete subsistence of symptoms of LS	No adverse effects
Lee, Bradford, & Fischer (2015)		Individualized: either BD 0.05%, MA 0.1% ointment, CP 0.05% ointment, H 1% ointment to treat VLS	1x a day until symptom suppression achieved, then individualized gradual reduction of topical corticosteroid potency	93.3% fully compliant patients had suppression of symptoms, 58% partially-compliant patients had suppression of symptoms; adhesions and scarring occurred during follow-up in 3.4% compliant patients and 40% partially-compliant patients	Reversible atrophy induced by topical corticosteroids occurred in 1.1% of compliant patients and 2% of partially compliant patients; corticosteroid dermatitis in 2.2% of compliant and 4% of partially-compliant patients

*BD = betamethasone dipropionate; CP = clobetasol propionate; DD = diflorasone diacetate; H = hydrocortisone; MA = methylprednisolone aceponate.

seen, these two guidelines do not reach consensus as to the best method of using topical corticosteroids to treat vulvar lichen sclerosus.

The recommendation for once daily application of topical corticosteroids is based upon concern for reservoir effects in non-lesional skin using older techniques to determine corticosteroid absorption.[13] More recent studies employing more advanced pharmacokinetic assays show that concentrations of potent steroids are less in lesional skin with a thickened stratum corneum, likely related to decreased absorption of medication with increased stratum corneum thickness. Even though local absorption increases as lesional skin heals and stratum corneum thickness normalizes, the two-week measured concentrations of corticosteroids are still closer to half of the concentrations found in non-lesional skin in the same time course of medication exposure.[14]

Decreasing dosing frequency as lesional skin heals seems reasonable and is in line with current guidelines for vulvar lichen sclerosus. Consideration of long-term maintenance dosing of topical corticosteroids should factor in the cause of the specific vulvar dermatosis. For example, the inciting factor in lichen simplex chronicus is typically an irritant or allergen exposure, so treatment with a shorter course of corticosteroids and avoidance of repeated external exposure is usually adequate. However, in the cases of lichen sclerosus, which has an autoimmune origin, maintaining low-level concentrations of corticosteroids in the tissue for a longer time course or indefinitely seems reasonable, as the inciting factor remains present. Animal and human studies that show potent steroids to be present in the tissue for approximately 3 days support a biweekly regimen for maintenance dosing.

Although dermal thinning is a commonly cited risk of topical corticosteroids, studies indicate only about a 15% tissue thinning with the ultra-potent corticosteroid clobetasol propionate. This level of thinning remained stable with long-term frequent dosing intervals (up to weekly), and reversed with increased dosing intervals of greater than a week.[29] The modified mucous membranes of the labia minora and clitoral tissue tends to not show as many corticosteroid-related side effects in the setting of vulvar lichenoid dermatoses.[57,62,63] This may reflect increased levels of inflammation and thickened stratum corneum related to inflammatory disease processes that target these specific parts of the vulva, with the most robust example being VLS. This has been supported by post-treatment vulvar biopsies showing no histological evidence of skin atrophy in women with VLS treated with long-term (up to 22 months) twice-daily clobetasol propionate.[36] However, this is based on limited evidence and more robust studies that include histological outcome measures are needed to further evaluate safety and efficacy of corticosteroid treatments for lichenoid vulvar dermatoses.

Based on the current review and available guidelines, the authors recommend treatment of VLS with an ultrapotent topical corticosteroid, such as clobetasol propionate 0.05% ointment. Ointment is preferred over cream due to increased tolerability and reservoir profile. Recommended dosing regimen is a large pea-sized amount, which equates to approximately 0.33 grams, applied to vulva and/or perianal areas once daily for 4 weeks, then every other day for 4 weeks, then twice weekly indefinitely. It is important to note that these recommendations reflect the authors' interpretations of available pharmacokinetic data and reported adverse risks. The rationale for this approach is that the stratum corneum is significantly thickened in VLS and reported adverse effects and systemic absorption are minimal. Continuous maintenance therapy is key to preventing pre-cancerous changes.[4,35]

CONCLUSION

The risks of topical corticosteroids are often stated without a solid pharmacokinetic basis to understand the true effects of these medications on lesional and non-lesional skin. In vulvar dermatoses such as VLS that utilize topical ultra-potent corticosteroids as first-line treatment, these fears have clinical consequences related to patient and physician acceptance, patient compliance, and guideline recommendation of dosing regimens and long-term maintenance therapy. In addition, these concerns have prompted searches for other treatment options that may not be effective, further delaying treatment and, in the case of VLS, increasing risk of progression to malignancy.[4,67] Historically, guideline dosing regimens for VLS have been based upon expert opinion with limited pharmacokinetic evidence guiding dosing recommendations. To fully understand the ideal dosing regimen to treat vulvar lichenoid disorders, more robust data on corticosteroid absorption rates, concentration, and histological effects is needed. This information must be specific to the varied tissues of the vulva and evaluated for separate vulvar lichenoid conditions, which have differing levels of inflammation. Further evaluating the current first-line treatment for vulvar lichenoid conditions from a pharmacokinetic basis is a necessary and worthwhile contribution to treating these disease processes.

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