Pearls in Mitigating Application Pain of Topical Nonsteroidal Agents

Steven Madsen^a Kyla N. Price^b Vivian Y. Shi^c Peter A. Lio^{d, e}

^aDepartment of Dermatology, UConn Health, Farmington, CT, USA; ^bCollege of Medicine, University of Illinois, Chicago, IL, USA; ^cDivision of Dermatology, Department of Medicine, University of Arizona, Tucson, AZ, USA; ^dDepartment of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; ^eMedical Dermatology Associates of Chicago, Chicago, IL, USA

Keywords

Topical nonsteroidal agents · Inflammatory dermatoses · Pain

Abstract

Background: Topical steroid-sparing agents (SSA), such as tacrolimus, pimecrolimus, and crisaborole, represent an important therapeutic option in the treatment of inflammatory dermatoses such as atopic dermatitis. While these agents lack the common side effects associated with topical corticosteroids, they all share application site pain as an important adverse effect. **Summary:** Based on the available evidence and our experience, we suggest the following 7 practical strategies for decreasing the pain associated with SSA use. (1) Use a topical corticosteroid for a few days to reduce inflammation before starting the SSA treatment. (2) Use SSAs strategically. (3) Apply moisturizer before applying SSAs. (4) Store moisturizers in the refrigerator. (5) Ask the patient to apply the SSA on a small test area before broader application. (6) Apply the SSA on dry rather than on damp skin. (7) Consider using aspirin when appropriate for the patient.

© 2020 S. Karger AG, Basel

Topical corticosteroids (TCS) have long been the backbone of dermatologic treatment and are used in myriad skin conditions [1], particularly inflammatory dermatoses such as atopic dermatitis (AD). Concerns about side effects as well as new developments in the past decade have led to increased interest in topical “steroid-sparing agents” (SSAs) such as the calcineurin inhibitors tacrolimus and pimecrolimus, and the PDE4 inhibitor crisaborole. These agents lack many of the common side effects associated with TCS (e.g., skin atrophy, telangiectasias, and hypopigmentation) [2]. However, application site pain such as burning or stinging is a prevalent adverse event when applying all of these agents, occurring in up to 50, 25, and 31%, respectively, of patients using tacrolimus [3, 4], pimecrolimus [5], and crisaborole [6]. Given that up to 78% of AD patients experience pain as a prominent symptom at baseline [7], the added pain caused by the SSA may be particularly troublesome.

The effects can be far-reaching when patients experience pain with the application of a medication, including a breakdown in the physician-patient relationship, the economic burden of filling a prescription that fails to bring clinical benefit, and permanent refusal of an important tool in the armament against inflammatory derma-

toses. Moreover, when children experience pain with the application of a topical agent, they may begin to perceive all topical treatments and moisturizers as potentially painful, and may then refuse *any* treatment, further complicating the already significant burden to caregivers of children with inflammatory dermatoses.

The mechanisms by which SSAs produce pain are poorly understood. The leading theories involve the up-regulation of nociceptive neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) via the activation of the cation channels TRPV1 and TRPA1 on sensory neurons [8–10]. The increased neurosensory response to itch and pain stimuli in AD patients may also partially contribute to increased application site pain with SSAs [11]. Additionally, it remains uncertain whether the active ingredient, the vehicle, or both cause the pain. Meta-analysis data did not demonstrate a dose-dependent increase in application pain with tacrolimus 0.03% versus 0.1% [12]. Furthermore, data between trials were inconsistent in demonstrating a significant difference in the frequency of pain between the active ingredient and the vehicle alone [12]. In the absence of definitive data, we propose that the pain may be caused by both the active ingredient and the vehicle. This approach allows us to develop strategies for pain mitigation that target both drug and excipient.

Not only is it difficult to predict which patients will experience pain with the application of these agents, the severity and duration of the pain are also unknowns. As such, it is important that the clinician is aware of pain as a potentially limiting side effect when SSAs are used to treat AD and other inflammatory dermatoses, and that there are strategies in place to prevent, reduce, or otherwise manage such pain. Here, we present practical tips to prevent or reduce the application site pain associated with SSAs like tacrolimus ointment, pimecrolimus cream, and crisaborole ointment. These tips may also be useful for other topical agents, including moisturizers [13], where there are concerns about discomfort or poor tolerance.

1. Use a TCS for a Few Days to Reduce Inflammation before Starting SSA Application

While SSAs are often used in lieu of TCS, it may be advantageous to strategically implement SSA application after briefly using TCS when the patient or family is amenable. The recent American Academy of Dermatology (AAD) and European guidelines for the treatment of AD both recommend the use of TCS prior to topical calcineu-

rin inhibitor use [14–16]. Patients with more acute eczematous lesions, in particular, may benefit from a short course (from several days to 2 weeks) of TCS to reduce inflammation and repair the skin barrier prior to initiating SSAs. In our experience, the presence of any cracks, fissures, or erosions appears to confer a higher risk of application site pain with SSAs, and such patients may be better suited to first have a course of TCS to improve the skin.

2. Use SSAs Strategically

While effective and versatile, SSAs are not appropriate in every situation. They appear to be best-suited for mild-to-moderate disease on the trunk and extremities and used with caution on sensitive areas such as the face and periocular areas [3, 4, 6]. As discussed, the application of SSAs should be avoided on broken skin (with fissuring, oozing, or obvious signs of excoriation), or in areas that are severely inflamed. The current recommendation is to use SSAs twice daily during exacerbations [14–16]. Both the AAD and European guidelines also recommend the proactive use of topical calcineurin inhibitors to reduce the number of flares and prolong the flare-free interval. Anzels and Burkhart [17] also recommend allowing the epidermis time to heal prior to initiating crisaborole as well as using crisaborole prophylactically to prevent future inflammation and irritation.

3. Apply Moisturizer before Applying SSAs

As noted above, SSAs are more likely to cause pain when the patient has broken or damaged skin. Applying a moisturizer can rapidly repair the defective skin barrier within 10 min [18] and reduce entry of and reactions to irritants and allergens. Some of the mitigating effect may result from decreased or slowed penetration and effective dilution of the medication, although there is reasonable evidence from the application of TCS that the order of application does not ultimately affect potency [19].

4. Store Moisturizers in the Refrigerator

Storing moisturizers in the refrigerator will not disturb the efficacy of the active ingredient in the SSA and will provide a cooling sensation to soothe skin itching and

burning. Anzelc and Burkhart [17] recommend a similar approach, i.e., to cool the application site with an ice pack to numb and soothe the area prior to SSA application. Cooling also decreases cutaneous vascular instability and inflammatory cell infiltrate [20]. Recently, the cold-sensing channel TRPM8 has been implicated as the mechanism for this cold-induced analgesia. Cold stimuli incite the release of the inhibitory neurotransmitter glutamate from TRPM8 channels, thus decreasing the transmission of noxious stimuli to the central nervous system [21]. Tacrolimus has recently been shown to activate TRPM8 [10], which may suggest an additive effect when the overlying moisturizer is cooled before it is applied.

5. Ask Patients to Use the SSA on a Small Test Area before Applying It Broadly

Patients who are new to SSAs should first test the medication on a small, noncosmetically sensitive area where there is no active inflammation. We recommend using the outer arm or outer thigh for this purpose. Patients who experience pain with application to a smaller area will be spared the pain of large-scale application.

6. Apply SSAs on Dry rather than on Damp Skin

In pivotal studies on crisaborole, the rate of application site pain was listed at 4.4%, while a more recent retrospective study found that nearly 32% of patients reporting burning or stinging. While the cause of this disparity is not certain, one possibility is that the medication was applied in the office for at least 1 application on dry skin during the clinical trials. In non-trial settings, many patients are instructed to apply medication after bathing when the skin permeability is increased [22]. We speculate that this may enhance the likelihood of stinging and burning.

7. Consider Using Aspirin when Appropriate for the Patient

For adults using tacrolimus, 500 mg oral aspirin taken 1 h prior to tacrolimus application has shown promise in reducing the pain associated with its application [23]. Aspirin directly inhibits the TRPV1 channel, which in turn decreases the release of substance P by the afferent nerve fibers. This, combined with the inhibition of prostaglan-

din synthesis, may explain this effect [10]. Evidence of this practice is limited, and, importantly, its use for children has not been reported; it may nonetheless be a reasonable option for certain patients.

Conclusion

The advent of SSAs for the treatment of inflammatory dermatoses has offered safe and effective alternatives to TCS. It is important that clinicians are aware of potential side effects and are prepared to address these before they derail the planned therapy. We believe that the above practical tips for alleviating the pain associated with SSA application can facilitate improved patient-physician relationships, enhance the confidence of both patients and caregivers, increase treatment adherence, potentially reduce costs with fewer wasted prescriptions, and ultimately lead to better outcomes for patients with inflammatory dermatoses.

Disclosure Statement

P.A.L. reports research grants/funding from the National Eczema Association, Regeneron/Sanofi Genzyme, and AbbVie; is on the speaker's bureau for Regeneron/Sanofi Genzyme, Pfizer, and L'Oreal; and reports consulting/advisory boards for UCB, Dermavant, Regeneron/Sanofi Genzyme, Dermira, Pfizer, LEO Pharmaceuticals, AbbVie, Kiniksa, Eli Lilly, Microcos, La Roche Posay/L'Oreal, Pierre-Fabre, Johnson & Johnson, Unilever, Menlo Therapeutics, Theraplex, IntraDerm, Exeltis, AOBiome, Realm Therapeutics, Franklin Bioscience/Altus Labs, Verrica, TopMD, Arbonne, Amyris, and Burt's Bees. V.Y.S. is a stock shareholder of Learn Health, and has served as an advisory board member, investigator, and/or received research funding from Sanofi Genzyme/Regeneron, AbbVie, Eli Lilly, Novartis, SUN Pharma, LEO Pharma, Pfizer, Menlo Therapeutics, Burt's Bees, GpSkin, the National Eczema Association, Global Parents for Eczema Research, the Foundation for Atopic Dermatitis, and Skin Actives Scientific. There were no incentives or transactions, financial or otherwise, relevant to this manuscript. S.M. and K.N.P. have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

All authors contributed to drafting and revising the manuscript and approved the final version for submission.

References

- Bewley A; Dermatology Working Group. Expert consensus: time for a change in the way we advise our patients to use topical corticosteroids. *Br J Dermatol*. 2008 May;158(5):917–20.
- Nankervis H, Thomas KS, Delamere FM, Barbarot S, Rogers NK, Williams HC. Topical corticosteroids and topical immunomodulators. Scoping systematic review of treatments for eczema. Southampton, UK: Programme Grants for Applied Research; 2016. pp. 25–45.
- Reitamo S, Wollenberg A, Schöpf E, Perrot JL, Marks R, Ruzicka T, et al.; The European Tacrolimus Ointment Study Group. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. *Arch Dermatol*. 2000 Aug;136(8):999–1006.
- Remitz A, Harper J, Rustin M, Goldschmidt WF, Palatsi R, van der Valk PG, et al.; European Tacrolimus Ointment Study Group. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. *Acta Derm Venereol*. 2007; 87(1):54–61.
- Luger TA, Lahfa M, Fölster-Holst R, Gulliver WP, Allen R, Molloy S, et al. Long-term safety and tolerability of pimecrolimus cream 1% and topical corticosteroids in adults with moderate to severe atopic dermatitis. *J Dermatolog Treat*. 2004 Jun;15(3):169–78.
- Pao-Ling Lin C, Gordon S, Her MJ, Rosmarin D. A retrospective study: application site pain with the use of crisaborole, a topical phosphodiesterase 4 inhibitor. *J Am Acad Dermatol*. 2019 May;80(5):1451–3.
- Maarouf M, Kromenacker B, Capozza KL, Kempton D, Hendricks A, Tran K, et al. Pain and Itch Are Dual Burdens in Atopic Dermatitis. *Dermatitis*. 2018 Sep/Oct;29(5):278–81.
- Kita T, Uchida K, Kato K, Suzuki Y, Tomimaga M, Yamazaki J. FK506 (tacrolimus) causes pain sensation through the activation of transient receptor potential ankyrin 1 (TRPA1) channels. *J Physiol Sci*. 2019 Mar; 69(2):305–16.
- Ständer S, Ständer H, Seeliger S, Luger TA, Steinhoff M. Topical pimecrolimus and tacrolimus transiently induce neuropeptide release and mast cell degranulation in murine skin. *Br J Dermatol*. 2007 May;156(5):1020–6.
- Arcas JM, González A, Gers-Barlag K, González-González O, Bech F, Demirkhanyan L, et al. The Immunosuppressant Macrolide Tacrolimus Activates Cold-Sensing TRPM8 Channels. *J Neurosci*. 2019 Feb;39(6):949–69.
- Andersen HH, Elberling J, Sølvsten H, Yospovitch G, Arendt-Nielsen L. Nonhistaminergic and mechanical itch sensitization in atopic dermatitis. *Pain*. 2017 Sep;158(9):1780–91.
- Ashcroft DM, Dimmock P, Garside R, Stein K, Williams HC. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ*. 2005 Mar;330(7490):516.
- Oakley R, Lawton S. Views on unwanted effects of leave-on emollients and experiences surrounding their incidence. *Dermatol Nurs (Lond)*. 2016;15:38–43.
- Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al.; European Dermatology Forum (EDF), the European Academy of Dermatology and Venerology (EADV), the European Academy of Allergy and Clinical Immunology (EAA-CI), the European Task Force on Atopic Dermatitis (ETFAD), European Federation of Allergy and Airways Diseases Patients' Associations (EFA), the European Society for Dermatology and Psychiatry (ESDaP), the European Society of Pediatric Dermatology (ESPD), Global Allergy and Asthma European Network (GA2LEN) and the European Union of Medical Specialists (UEMS). Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol*. 2018 May;32(5):657–82.
- Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014 Jul;71(1):116–32.
- Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol*. 2018 Jan;120(1):10–22.e2.
- Anzelc M, Burkhart CG. Crisaborole: Application Pain and Prevention. *Open Dermatol J*. 2019;13(1):55–7.
- Arimoto H, Yanai M, Egawa M. Analysis of absorption and spreading of moisturizer on the microscopic region of the skin surface with near-infrared imaging. *Skin Res Technol*. 2016 Nov;22(4):505–12.
- Ng SY, Begum S, Chong SY. Does Order of Application of Emollient and Topical Corticosteroids Make a Difference in the Severity of Atopic Eczema in Children? *Pediatr Dermatol*. 2016 Mar-Apr;33(2):160–4.
- Maarouf M, Saberian C, Lio PA, Shi VY. Head-and-neck dermatitis: diagnostic difficulties and management pearls. *Pediatr Dermatol*. 2018 Nov;35(6):748–53.
- Proudfoot CJ, Garry EM, Cottrell DF, Rosie R, Anderson H, Robertson DC, et al. Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. *Curr Biol*. 2006 Aug;16(16):1591–605.
- Voegeli D. The effect of washing and drying practices on skin barrier function. *J Wound Ostomy Continence Nurs*. 2008 Jan-Feb; 35(1):84–90.
- Mandelin J, Remitz A, Reitamo S. Effect of oral acetylsalicylic acid on burning caused by tacrolimus ointment in patients with atopic dermatitis. *Arch Dermatol*. 2010 Oct;146(10):1178–80.