The most powerful topical anti-inflammatory: the cautionary and enlightening story of SKIN-CAP

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Abstract

Topical treatment with glucocorticosteroids is a mainstay therapy for many dermatologic conditions. Though efficacious in many, topical therapies often fail to achieve desired positive results in clinical practice. SKIN-CAP spray (Cheminova Laboratories International SA, Madrid, Spain), a product containing activated zinc pyrithione, and subsequently found to have contained clobetasol, provided unprecedented clearing of psoriasis even when ultra-high potency topical glucocorticosteroids had failed. A PubMed for terms related to corticosteroids, topical therapy, patient adherence, and SKIN-CAP spray was performed. Articles from 1997 to 2023 were included in the review of SKIN-CAP spray. In this review, we report the background of SKIN-CAP as well as studies that were performed in an attempt to explain its perceived high efficacy. The remarkable efficacy that occurred with SKIN-CAP over other delivery systems for high potency topical corticosteroids was initially speculated to be a consequence of an interaction between the zinc pyrithione and the clobetasol. However, no synergistic efficacy was identified, and there was no greater drug delivery. Better adherence to the SKIN-CAP product may explain the efficacy. The SKIN-CAP story provides insights into the need for healthy skepticism, the importance of treatment adherence, and ways to encourage better adherence to topical medications.

Keywords: adherence, adulterated, clobetasol, corticosteroid, psoriasis, pyrithione, zinc

Introduction

The management of many dermatological conditions includes topical treatment, the mainstay of therapy for most patients. Topical formulations enable application of potent treatments directly to the site of inflammation while reducing the chance of systemic side effects or general toxicity. Although topical treatments have excellent efficacy in clinical trials, patients often fail to achieve the same benefit in clinical practice [1-3]. In large part, this may relate to abysmal topical treatment adherence, in part caused by challenging, time consuming, messy topical delivery systems.

The treatment of psoriasis vulgaris is exemplary of this dilemma. Topical corticosteroid therapy has long been a mainstay in the management of psoriasis, especially in cases of mild-to-moderate psoriasis [2,4]. In the clinical trial setting, clobetasol propionate 0.05% clears or almost clears psoriasis and improved quality of life in 75% to 85% of patients with moderate to severe plaque psoriasis [3]. Despite the efficacy of topicals in clinical trials, psoriasis is challenging to manage and patients commonly fail to obtain relief. Patients and their providers often find themselves struggling with non-remitting skin lesions despite prescription of one or more highly effective topical treatments.

SKIN-CAP—a truly remarkable, extraordinarily effective over-the-counter product—overcame this frustration. SKIN-CAP spray (Cheminova Laboratories International SA, Madrid, Spain), a product

containing activated zinc pyrithione, provided unprecedented clearing of psoriasis even when prescription medications had failed. In this article, we describe this history of SKIN-CAP and its implications for topical management of skin disease.

We searched PubMed using terms related to topical therapy, corticosteroids, patient adherence, and SKIN-CAP spray. We reviewed all reports covering SKIN-CAP topical therapy from 1997 to 2023.

Marketed by Cheminova International in the mid 1990s, SKIN-CAP was sold with the claim to be effective for numerous indications, including dermatitis and psoriasis. The sole active ingredient listed was zinc pyrithione [5-8]. The medication was distributed as an over-the-counter product and became widely used by patients, especially patients with psoriasis (**Figure 1**). It soon became apparent from patient experiences and small clinical trials that SKIN-CAP was stunningly effective for plaque psoriasis, providing rapid clearing with no side effects beyond occasional reports of skin irritation or flares after terminating treatment [5,7].

"I don't have any psoriasis practice any more. They all use SKIN-CAP," reported a physician during SKIN-CAP's peak in 1997 [9]. "No longer do patients need steroids inuncted, ingested, or injected, and no more methotrexate or PUVA visits" doctors Shelley and

Figure 1. *SKIN-CAP Spray by Cheminova International, sold over the counter.*

Shelley noted enthusiastically as they report 'miracles' of large psoriasis plaques remitting and psoriasis patient loads decreasing [9]. Within a two-week treatment period, biopsies with classic psoriatic presentation showed near complete resolution; reductions in inflammation were observed in mere hours [7]. Though not approved by the Food and Drug Administration (FDA) for psoriasis or other dermatoses, SKIN-CAP impressed patients and dermatologists alike with its unprecedented efficacy [5,9,10].

That effectiveness led to investigations into the nature of SKIN-CAP's formulation [5,11,12]. In 1997, samples of SKIN-CAP spray sold commercially in the United States were investigated by several laboratories. Mayo Clinic reported that samples analyzed by capillary electrophoresis-mass spectrometry (CE-MS) contained corticosteroid compounds similar to clobetasol propionate [5,10]. Despite claims by Cheminova that the product did not contain corticosteroids, the FDA was notified of these findings and they further confirmed the presence of clobetasol in SKIN-CAP cream, spray, and shampoo formulations [5,10].

Consumers were subsequently warned of inclusion of prescription-strength corticosteroids in this over-the-counter product, as well as the risks of continued use [13]. Despite this, many patients with psoriasis, grateful for availability of SKIN-CAP, continued to seek it out. Mail order accessibility for the spray from Europe prompted further investigation into the SKIN-CAP formulation. Detection of corticosteroid constituents was again documented but this time as tandem mass spectrometry revealed ion spectra consistent with betamethasone [6].

Discussion

Dermatologists sought to explain the efficacy of clobetasol in SKIN-CAP compared to that of prescription clobetasol ointment. SKIN-CAP seemed to be far more effective. The initial hypothesis was that the SKIN-CAP formulation of clobetasol propionate increased drug penetration of clobetasol. However, there was no significant difference found in the percutaneous absorption of corticosteroid in

the SKIN-CAP therapy compared to traditional, FDA approved, clobetasol propionate formulations [14]. In specific trial scenarios, cutaneous absorption of the FDA-approved products 'exceeded' that of the SKIN-CAP spray [14].

Next it was suggested that the efficacy of topical SKIN-CAP spray related to a pharmacologic synergy between zinc pyrithione and clobetasol (one rationale being that corticosteroid receptors have 'zinc fingers'), [15]. However, the use of zinc pyrithione did not have a synergistic effect with clobetasol propionate after two weeks of therapy in a clinical trial; clobetasol monotherapy foam and combination therapy with zinc pyrithione spray had similar efficacy [16].

Better adherence to treatment may explain the remarkable effectiveness of SKIN-CAP spray. Adherence to a therapeutic plan is central to any medical therapy including dermatologic treatment. Poor adherence to topical treatment is common and reduces treatment efficacy. Roughly 40% of psoriasis participants admit nonadherence to treatment and self-report overestimates adherence [2,17,18]. Scalp psoriasis therapy is especially prone to nonadherence—it is hard to treat through hair—and is one of the more challenging presentations of psoriasis [19,20].

Causes of poor adherence include unintentional lack of adherence, such as inadequate access to the treatment or forgetfulness, and deliberate lack of adherence, wherein the patient justifies non-engagement [17]. Topical treatments may not only be time consuming but obtrusive in their application. Patients are more likely to discontinue the use of medications which are messy and time consuming (for example, ointments used on the scalp), preferring the use of vehicles with quick and simpler application or even systemic treatment [17,21,22]. SKIN-CAP spray provided an easy to use, non-messy vehicle.

Fear of side-effects from corticosteroid use also causes nonadherence [23]. Adherence to SKIN-CAP treatment can be attributable to the product's 'perceived' safety, given the absence of disclosure of prescription strength corticosteroid in the contents. With the label stating, "activated zinc pyrithione," patients may have been much less apprehensive of adverse side effects, including those feared with long-term corticosteroid use or systemic therapy [17,18]. The assumed gentleness of zinc pyrithione likely played as major role by averting corticosteroid phobia.

Strict adherence to SKIN-CAP may also relate to the financial commitment patients made to obtain the product. SKIN-CAP spray was sold as an over-the-counter product, resulting in patients personally paying for the medication. Monetary investment is a powerful extrinsic motivator, prompting patients to commit to their chosen treatment to avoid the frustration of money wasted.

Conclusion

There are lessons to be learned from the SKIN-CAP spray and its efficacy in psoriasis patients that apply to the general treatment of management of dermatological conditions. The efficacy of any therapy, including topical corticosteroids for the treatment of psoriasis, is dependent on the consistent use of prescribed medication by the patient. The dogma that patients with dry, scaly psoriasis should be treated with an ointment may need to be reconsidered; the best vehicle may be the one which the patient will use.

Topical clobetasol is an exceptionally potent anti-inflammatory treatment. The SKIN-CAP saga reveals that a topical clobetasol formulation that is used by the patient can reduce skin inflammation faster than some of our more potent systemic treatments. The key, however, is that we must get patients to actually apply the product. Assuaging people's fear of treatment, prescribing vehicles patients are willing to use, and getting them personally invested in the treatment may be valuable tools to improve adherence and outcomes.

The SKIN-CAP story is also a cautionary tale about the relatively limited scrutiny of over-the-counter products, particularly if they have been marketed as conforming to FDA regulations [24]. Unlike FDA-approved drugs that have undergone rigorous scrutiny, the degree to which non-prescription safety

and efficacy have been documented to vary [24]. It remains prudent to be wary of products that specifically have not been heavily scrutinized or subject to trial, especially when showing extraordinary efficacy despite an 'all-natural' composition [25-26].

Potential conflicts of interest

Steven R Feldman has received research, speaking and/or consulting support from Eli Lilly and Company, GlaxoSmithKline/Stiefel, AbbVie, Janssen, Alovtech, vTv Therapeutics, Bristol-Myers Squibb, Samsung, Pfizer, Boehringer Ingelheim, Amgen, Dermavant, Arcutis, Novartis, Novan, UCB, Helsinn, Sun Pharma, Almirall, Galderma, Leo Pharma, Mylan, Celgene, Ortho Dermatology, Menlo, Merck & Co, Qurient, Forte, Arena, Biocon, Accordant, Argenx, Sanofi, Regeneron, the National Biological Corporation, Caremark, Teladoc, BMS, Ono, Micreos, Eurofins, Informa, UpToDate, Verrica, and the National Psoriasis Foundation. He is founder and part owner of Causa Research and holds stock in Sensal Health. The remaining authors declare no conflicts of interest.

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