Facial Use of Low Potency Steroids With Anti-microbials and Retinoids

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***Introduction**:* There have been many reports of topical corticosteroids used on the face causing perioral dermatitis, steroid acne, and steroid rebound phenomenon. Even 0.5% hydrocortisone has been implicated. There is very little published data, one way or another, regarding low potency topical corticosteroid compounded with precipitated sulfur for its anti-microbial properties. Sulfur and hydrocortisone have been ordered for decades by compounding dermatologists for help with rosacea and seborrheic dermatitis.

***Methods**:* In a retrospective study, the first 508 returning patients were interviewed from the dermatology clinic who had used, or were continuing to use on an as needed basis, pharmacy compounded 0.75% hydrocortisone acetate and 0.5% precipitated sulfur lotion for up to 15 years for common facial problems. Inclusion in the review was based on three criteria: (1) The patients had not used topical steroids previously on the face; (2) They specifically used the compound 0.75% hydrocortisone acetate and 0.5% precipitated sulfur lotion, for strategies with seborrheic dermatitis, sensitive rosacea, acne with topical medication tolerability problems, and perioral dermatitis; and (3) Patients had returned for follow up at least twice after starting the compound.

All review patients were examined and interviewed for steroid side effects, including perioral dermatitis, steroid acne, and rebound phenomenon.

***Results**:* None of the 508 patients experienced steroid acne, rebound phenomenon or perioral dermatitis associated with facial use of 0.75% hydrocortisone and 0.5% precipitated sulfur. Five patients were unable to tolerate 0.5% sulfur because of either irritation or peeling and one reported itching. Acne patients (169 subjects) were using this compound as needed to directly manage retinoid tolerability problems. Of these sensitive acne patients, 64% reported being able to tolerate 75% to 100% more applications of their topical retinoids using the compound as needed.

***Conclusion**:* Facial use of 0.75% hydrocortisone acetate compounded with sulfur, was useful as a part of several dermatologic therapies, without significant risk of perioral dermatitis, steroid acne, or rebound phenomenon.

Introduction

Compounding dermatologists in the 1960s were using sulfur with hydrocortisone for both rosacea and seborrheic dermatitis. These two therapeutic products were the "blockbusters" of those days. Today these two products are grandfathered, perhaps even "great-grandfathered", into the dermatologic therapy world. There is considerably less published now about low potency topical steroids used on the face.

Speakers at dermatology meetings have implicated 0.5% hydrocortisone acetate in causing acneiform eruptions of the lower face. Other reports of topical corticosteroids causing perioral dermatitis, steroid acne, and facial 'steroid addiction', contribute to perceptions that topical steroids cannot be used on the face, under any circumstances. Dermatology training may emphasize these concerns, but may not provide exposure to teaching staff ordering topical compounds of corticosteroids with sulfur, or steroids with topical antibiotics for facial use.

'Steroid acne' most often occurs when naked corticosteroids are used on the face for an extended period of time. Steroid acne may also occur when systemic steroids are used by transplantation or oncology services. An occasional patient using large amounts of topical steroids on the extremities for psoriasis, develops steroid acne on the face or trunk from systemic absorption.

Topical 'steroid addiction' occurs when patients overuse corticosteroids on the face, groin, or the genitalia to the point of erythema and "burning" symptoms. The erythema and burning sensation rapidly worsen when the steroid is withdrawn, demonstrating "rebound phenomenon."

However, there is evidence that when topical steroids, particularly low potency steroids, are used on the face in combination with an antimicrobial agent, rebound phenomenon and steroid acne does not occur. This was reported in the 1976 dermatologic literature with a report[1] that included 19 subjects with rosacea. In this report, facial topical steroids were used in conjunction with oral tetracycline for rosacea. These subjects did not experience rebound phenomenon when the steroids were discontinued.

Our retrospective review of 508 patients, including 55 with rosacea, was possible because of similar clinical experiences. Experience that when precipitated sulfur is compounded with 0.75% hydrocortisone acetate, neither acneiform eruptions, nor rebound phenomenon were seen, even after prolonged use.

The pure element Sulfur is a reducing agent and has antimicrobial properties[2]. Sulfur is mined and processed to remove impurities. After pharmaceutical grade purity is reached, it's available as a yellow dry powder called precipitated sulfur. At 5% concentration, sulfur has keratolytic properties in the skin. In our review, we found that 1% of patients will find even 0.5% sulfur keratolytic, producing peeling or irritation. Precipitated sulfur is widely applicable, as it is not related to "sulfa allergy", which is reported by many

patients. Sulfa allergy is an immunologic reaction to the organic benzene ring moiety in the sulfa antibiotics.

Precipitated Sulfur has been used for both demodex folliculitis and rosacea for a century. There was demonstrated a relationship that many flares of rosacea were related to a proliferation of demodex in the skin. Forton et al[3] reported a concentration of less than 1 demodex/cm^2 in healthy skin and 30-60/cm^2 in flared rosacea patients.

Compounds with 5% precipitated sulfur have been used in acne and rosacea regimens, and were the treatment of choice in pregnant and lactating mothers with scabies.[4] Since the 1960's, many dermatologists have also compounded steroids with precipitated sulfur for treating psoriasis on the extremities. On hairy skin, sulfur was compounded with steroids empirically to help reduce iatrogenic folliculitis from topical psoriasis therapy.

Material and Methods

Fifteen years of seborrheic dermatitis therapy data and over five years of data managing retinoid tolerability in acne treatments were accessed.

The sample included the first 508 patients returning to the dermatology clinic who were included in the chart review and follow up interviews meeting four criteria: (1) No previous use of topical steroids on the face; (2) Patients used the pharmacy compounded 0.75% hydrocortisone and 0.5% precipitated sulfur in a lotion base on the face for the problems of either seborrheic dermatitis, rosacea, acne with tolerability problems, or perioral dermatitis; (3) Patients had returned for follow up at least twice and had been seen in follow up within the past two years; and (4) Patients were either teenagers using prescription acne therapies or were adults.

By diagnosis, patients were asked if they tolerated the compound, how often they used it, and asked to evaluate its overall effect on their skin as not significant, slightly more stable, more stable, or much more stable. Patients and their charts were reviewed for atrophy, steroid addiction/rebound phenomenon, and steroid acne at follow up exams. All 508 patients were asked specifically, either in person or by telephone interview, if they had ever experienced a problem with pimples or acne on the face from the compound.

Medications used concurrently with the compound were reviewed. Acne patients were separated by their use of topical retinoids, tretinoin, tazarotene, and adapalene and surveyed for tolerability issues. They were asked about the effect of the compound on their overall results and the effect on retinoid tolerability. Some acne patients started the compound with their retinoid because of a history of "sensitive skin" at presentation. The majority of the acne patients started using the compound after they could not tolerate topical retinoids every day. These patients were asked how many days each week they

could apply topical retinoid prior to using the compound, and how many retinoid applications were possible when the compound was used in conjunction.

Patients were asked which facial areas they primarily used the compound, upper face, lower face, mid face, or any combination of these. Data from chart review, clinic visits, and telephone follow-up interviews were entered into a spreadsheet.

Results

There were no cases of atrophy, rebound, or steroid acne from facial use of 0.75% hydrocortisone and 0.5% sulfur. Patients from the dermatology clinic who used the compound for less than one year and stopped, and those who used the compound for over 15 years, demonstrated the same safety results.

Isolated involvement and location of use on the face were recorded and did not contribute to significant additional findings. Efficacy was supported by the patients using and reusing the product on a prn basis, under physician supervision, and by patients rating the effect of the compound on their skin as not significant, slightly more stable, more stable, or much more stable (See Table 1).

Regarding managing tolerability of other topical products in the review, 305 patients reported that they believed the compound allowed them to better tolerate topical prescription products. Other patients were using the compound as monotherapy for seborrheic and perioral dermatitis, and some were not able to answer this question retrospectively.

Of 508 patients sampled, 95 had used the product and discontinued its use after two months to five years. Of these, (88) stopped after benefiting for months to years, and (7) stopped with no benefit or not sure of benefit. Three patients out of 229 seborrheic dermatitis patients stopped using the compound because of no subjective effect. Five patients stopped because of irritation and/or peeling. One of those reported itching. No patients stopped as a result of any other adverse event. None of the patients experienced steroid rebound after discontinuing the compound.

The review found (450) that were continuing to use the compound daily or prn. Patients by diagnosis were recorded (See Table 1) as using the compound daily (306), weekly as needed (59), and less than weekly as needed (85).

Some (37) of our review patients had used the compound for over 15 years, (29) for seborrheic dermatitis, (8) as part of their rosacea therapy, and (1) as a part of adult acne therapy.

Of 229 seborrheic dermatitis patients in the sample, (80) or 35% were female and (97) or 42% of seborrheic dermatitis patients used the compound for over 5 years.

Our review sampled 57 patients with the diagnosis of perioral dermatitis. (53) were female, and (3) or 5% had used the compound for over five years. (17) used the compound alone. (31) used the compound with a topical antibiotic product. (21) initially used an oral antibiotic with the compound.

Our review sampled 55 rosacea patients. (37) or 67% were female, and (18) or 33% had used the compound for over 5 years. (24) used the compound alone. (25) used the compound with an oral antibiotic or topical rosacea medication.

Our review sampled 169 acne patients representing (94) or 56% females, and (13) or 8% had used the compound for over five years. All 169 used the compound with a topical retinoid to manage retinoid tolerability. (60) were also using a topical antibiotic, (80) used an oral antibiotic, with or without a topical antibiotic. (29) were using the compound with topical retinoid and benzoyl peroxide. (20) acne patients rated the compound as making their skin very much more stable. (121) acne patients rated the compound as making their skin more stable. (25) rated the compound as making their skin slightly more stable. (1) stated not more stable (See Table 1).

The number of acne patients using the compound for managing tolerability with topical tretinoin was (101), with topical tazarotene (66), and with 0.1% adapalene (2). Acne patients were specifically surveyed who had been given the compound after developing irritation from topical retinoids. Of the tazarotene users, 67% reported they were able to increase by 75%-100% the number of days per week applying and tolerating tazarotene. Of the tretinoin users, 62% reported they were able to increase by 75% -100% the number of days each week applying and tolerating tretinoin.

Among the sensitive acne patients were 18 (11%) who reported an increase in retinoid tolerability from 0 days per week to 7 days per week. Eleven of these were tretinoin patients, 6 were tazarotene, and 1 was an adapalene user.

Discussion

The patients in our retrospective study were teenagers using acne medications and adults. Over 24 years ago, the dermatology clinic began implementing topical pharmacy compounds containing both sulfur and hydrocortisone to help in the treatment of seborrheic dermatitis, perioral dermatitis, and rosacea. As of fifteen years ago, the majority of the prescriptions were for 0.75% hydrocortisone and 0.5% sulfur lotion. This formula was felt to optimize efficacy and tolerability, without side effects. For over five years, this compound has been used for directly managing retinoid tolerability problems in sensitive acne patients. Of 169sensitive acne patients, 64% were able to double their use of topical retinoids with prn use of the compound.

It was an important compound for treating chronic everyday seborrheic dermatitis. When ketaconazole products came along, they worked extremely well in combination with the compound. Our oldest patient using the compound for seborrheic dermatitis was 100 years old.

It was also learned from hydrocortisone assay that after a year, the pharmacy compounds could lose 90% of the active and were best used in the first two months.

There was no FDA approved product for perioral dermatitis. The compound was particularly important in combination with antibiotics for perioral dermatitis. Antibiotics alone require six to eight weeks for clearing of perioral dermatitis.[5] When using antibiotics in conjunction with the compound, clearing in two weeks was quite common.

Both rosacea and periorificial dermatitis possess poorly understood pathophysiology. Treatments have developed empirically. Acne patients experiencing perioral dermatitis is not uncommon, yet may be under-diagnosed and under-treated (see photograph Figure 1 - Patient presenting with acne and perioral dermatitis tendency). It's widely accepted however that these patients typically experience more tolerability problems with topical acne prescriptions. Dermatology patients with mixtures of problems tend to be under-discussed in publications.

None of the perioral dermatitis patients included in the review presented using topical steroids on the face. In our clinic's experience, most cases of adult perioral dermatitis are related either to a tendency for rosacea, barrier problems, concurrent atopy and seborrheic dermatitis, or to an exaggerated response to perioral microbial colonization.

No patient reported decrease in efficacy with their other prescription products. It was clear that when used properly (pea sized amount on the face), this compound does not cause perioral dermatitis, steroid acne or rebound phenomenon, nor does it interfere with treatment of acne. This is consistent with the experience other dermatologists who regularly compound hydrocortisone with sulfur for rosacea, or hydrocortisone with clindamycin for acne, and hydrocortisone with ketoconazole for seborrheic dermatitis.

"Overuse" of the compound was indicated by history and/or by an increase in telangiectasias in elderly patients. We saw no patient under 70 years of age who developed telangiectasias from overuse of the compound. When it was felt that a patient was overusing the compound, they were instructed to decrease the use while increasing their use of sunscreen and moisturizer. None of those patients experienced steroid rebound when reducing their use of the compound.

The concern that low potency topical corticosteroids actually interfere with treating cutaneous infections, acne, and rosacea is not supported by evidence. There is significant supportive clinical experience that when combined with appropriate antibiotic therapy, corticosteroids can enhance treatment of these problems.

There is little disagreement that highly destructive scalp kerion infection responds better to oral griseofulvin, when combined initially with some type of corticosteroid therapy. A dermatologist is qualified to treat the destructive inflammation of kerion with steroids, when it's felt to be important for preventing permanent hair loss. Acne nodules are often responsive to injection with intralesional steroids. It's also well known that some

nodulocystic acne patients taking oral isotretinoin require oral prednisone for extreme inflammation. The oral steroids reduce the inflammation and are intended to shorten the course of the isotretinoin treatment.

Dermatologists regularly observe that an atopic child with heavy overgrowth of staphylococcal bacteria will improve and the bacterial overgrowth will clear, with topical steroids alone. Topical steroids quell the inflammation supporting the staphylococcal super-colonization, producing effective treatment without necessarily using oral antibiotics.

Inflammation also appears to play a part in supporting actinic keratoses. Many of our Des Moines patients are farmers of Irish and German descent with Fitzpatrick Types I or II skin. As part of their extensive sun damage, many have a chronic red blotchy heliodermatitis with a background of seborrheic dermatitis, mild rosacea, or both. Many of our patients with this set of problems used the pharmacy compounded 0.75% hydrocortisone and 0.5% sulfur lotion for over 15 years, while they regularly came in for attention to hypertrophic actinic keratoses. None of these patients experienced perioral dermatitis or acne from this compound with long term use.

There is additional evidence that suggests topical retinoids prevent the skin atrophy and telangiectasias associated with topical steroid use.[6,7] Observations made in two reports indicate a protective effect from topical retinoid in combination with topical steroids on the face.

Similar evidence comes from widespread use of Triluma® cream. Triluma® cream is a very popular Rx-only product for melasma. It contains hydroquinone in combination with tretinoin and fluocinolone and is used on the face for extended periods. Atrophy, telangiectasias, and perioral dermatitis from the fluocinolone are not seen in any significant amount, nor is rosacea flared. This is some of the strongest evidence of the protective effects of retinoids, and how readily the side effects of low potency topical steroids on the face can be prevented.

Evidence suggests that the combination of retinoid, anti-microbial, or topical sulfur will modify the dermatologist's concerns with low potency steroids on the face.

Concerns regarding acne, rebound phenomenon, and perioral dermatitis caused by steroids should be kept in perspective. Dermatologists are certainly qualified to treat cutaneous infections, acne, and rosacea with steroids in combination with the appropriate antibiotic or retinoid therapy. These important strategies should not be deleted from the qualifications and training of dermatologists. Any dermatologist may order pharmacy compounding for a product similar to the agent of this study. Treating facial inflammation with low potency topical steroids does not appear to significantly incur adverse events when appropriate anti-microbials and retinoids are being used concurrently.

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Disclosure: Steven L. Harlan, M.D. is actively developing physician dispense products for dermatology for HTP Pharmaceuticals.