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Review

Tachyphylaxis to topical glucocorticoids; what is the evidence?

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ABSTRACT

Background: Common belief holds that as topical glucocorticoids are used over time the less effective they become, a phenomenon called tolerance or tachyphylaxis.

Objective: To determine what evidence supports the concept of tachyphylaxis to glucocorticoids.

Methods: We searched Medline and Google Scholar for articles on tachyphylaxis to glucocorticoids published through October 2012.

Results: Rapid tolerance, tachyphylaxis, to non-clinical effects of glucocorticoids has been reported in literature. However, clinically significant tolerance to topical glucocorticoids has not been identified in clinical trials. We did not identify any evidence that clinical efficacy of glucocorticoids in inflammatory skin diseases significantly diminishes during long term continuous use.

Limitations: Tachyphylaxis or tolerance to clinical effects of topical glucocorticoids in inflammatory skin diseases is not fully characterized or well studied.

Conclusion: Based on available data in literature, there is no clinical trial supporting the concept that topical glucocorticoids lose effectiveness over time, nor that intermittent use of topical glucocorticoids is more effective than continuous use.

Background

Topical glucocorticoids are the foundation of dermatological treatment, with potent anti-inflammatory properties. Glucocorticoids act on a wide range of cells and have a wide range of mechanisms of action. Most of the effects of glucocorticoids on cells are mediated via the glucocorticoid receptor [1-3]. Glucocorticoids inhibit phospholipase A2, reducing the amount of arachidonic acid, decrease the release of interleukin (IL)-1α and IL-2, inhibit leucocyte migration to sites of inflammation, and interfere with the functions of endothelial cells, granulocytes, mast cells and fibroblasts [4-10]. Glucocorticoids also reduce T cell proliferation and increase T cell apoptosis, increase monocyte apoptosis, deplete the number of Langerhans cells, decrease histamine content of mast cells, and suppress eosinophil maturation, recruitment, and survival [11,12]. Topical glucocorticoids reduce protein synthesis

and have antimitotic effects. Antimitotic effects may explain some of the therapeutic actions of the drug in scaling dermatoses such as psoriasis [13]. Glucocorticoids inhibit natural vasodilators such as histamine, bradykinins and prostaglandins [14].

Whereas topical glucocorticoids are effective for a host of inflammatory skin diseases, dermatologic dogma contends that continued daily application of topical glucocorticoids eventually leads to a reduction in their clinical efficacy, especially in psoriasis [15-20]. Some effects of glucocorticoids, such as their vasoconstrictive effects, diminish even with just short term use [21]. However, long-term use of systemic glucocorticoids is the cornerstone of treatment of many autoimmune diseases and there is no concern with decreasing response to systemic glucocorticoids over time in rheumatologic diseases [1,17,22-26]. Intranasal glucocorticoids have been effective for long-term daily treatment of allergic rhinitis with no evidence of tachyphylaxis [27].

The purpose of this study is to review the literature to identify what information is available to support the notion that topical glucocorticoids lose their anti-inflammatory effects with long-term continuous use.

Methods

In this article, we sought to find out the scientific bases underlying the concept of tachyphylaxis to glucocorticoids. We searched Medline and Google Scholar for articles on tachyphylaxis to glucocorticoids published through October 2012. The search was performed using the terms "down-regulation", "tolerance", "tachyphylaxis", "bradyphylaxis", or "resistance" and "steroid", "corticosteroid", or "glucocorticoid". We also looked for the clinical trials using glucocorticoids for psoriasis in Medline. Another search also was done looking at multiple text books in dermatology, rheumatology, and physiology for the term "tachyphylaxis" in the index and appropriate pages studied. The relevant data were included in the article.

Results

Fifty-two relevant articles were found and included in the study. These articles were categorized into two groups: studies of tolerance to a specific effect of glucocorticoids and studies of long-term use of topical glucocorticoids in psoriasis.

Articles studying tachyphylaxis to glucocorticoids

One of the possible mechanisms of cell desensitization to the effect of glucocorticoids is glucocorticoid receptor down-regulation that results in a temporary decrease of receptor expression (an approximately 75% reduction) upon treatment with hormone [22-24,26,28-30].

Agonist-mediated down-regulation of glucocorticoid receptors are time-dependent and tissue specific and may possibly also be influenced by developmental and disease status [31,32]. In mouse epithelial cells, the level of glucocorticoid receptor decreases 24 hours after one application of topical glucocorticoid, but returns to normal level 48 hours after the application [29].

The ACTH-secreting, glucocorticoid-responsive AtT-20 mouse pituitary tumor cell has been a commonly used model for investigations of glucocorticoid agonist action. In the AtT-20 cells exposed to glucocorticoids, receptor is depleted to 50% of the initial value in 30 h. After 4-5 days of exposure, a plateau is reached. Receptor is reduced to 20-30% of the initial value and this does not change further even if the exposure is continued for another 2 weeks [33-35]. After termination of exposure to glucocorticoids, the level of glucocorticoid receptor returns gradually toward initial values in four days or more [36].

Although there are conflicting findings [2,3,31,37,38], one week application of intra nasal glucocorticoid can reduce glucocorticoid receptor mRNA levels (50-75% reduction) in human nasal mucosa. One week after termination of medication, glucocorticoid receptor mRNA levels may not yet reach the initial values [39]. In human lymphocytes, the level of glucocorticoid receptor may decrease 30-70% with systemic glucocorticoids and remain lower than normal for one week after discontinuation of treatment [31,40-44].

Although in neoplastic cells an association between the number of the glucocorticoid receptors and efficacy of the glucocorticoids has been reported [31,45,46], the physiologic significance of glucocorticoid receptor down-regulation in human tissues after glucocorticoid therapy is not well characterized [47]. Some authors suggest that some cells have a large number of "spare" glucocorticoid receptors; only a fraction of the cell's receptors need to be filled for the agonist to be fully active [48]. Therefore, a

reduction in the number of the glucocorticoid receptors may not affect the potency or maximum efficacy of the glucocorticoids. Three weeks incubation of AtT-20 cells with dexamethasone showed that even after dexamethasone had depleted the cell's receptor content to only a fraction of its initial value, its agonist action and biopotency was not diminished [33,34].

Tolerance to the antiproliferative effects of topically applied glucocorticoids occurs [49-51]. In one study, daily application of fluocinonide inhibited DNA synthesis of mouse epidermis in less than six hours. The maximum inhibition was achieved in 30 hours, followed by an increase in DNA synthesis that reached normal values in 100 hours and exceeded normal values despite continued application of the glucocorticoid [50]. In another study on mouse epidermis, an every-other-day-regimen of topical fluocinolone was used to prevent glucocorticoid receptor down-regulation and keep the receptors fully functional during the course of skin treatment. After the second applications of drug, the proliferation of keratinocytes including the cells in hair follicles and sebocytes in sebaceous glands was blocked. When a 50% depletion in the number of basal keratinocytes was achieved (day 7), some keratinocytes started to develop tolerance to the growth inhibitory effect of glucocorticoids and began to proliferate [29]. This tolerance may not have been due to glucocorticoid receptor down-regulation. Tolerance to the antiproliferative effects of glucocorticoids also has been reported after five days of exposure in cultured human skin fibroblasts [52].

In spite of the reduction in the *in vitro* antiproliferative effects of glucocorticoids in fibroblasts and keratinocytes over time, long-term continuous use of topical glucocorticoids causes epidermal and dermal atrophy [53,54]. In one study, with daily use of a potent topical glucocorticoid on dog skin, epidermal thinning was evident on histological examination after one week of treatment. In the dermis, collagen bundles were hyanalized after three to four weeks of treatment. At the end of week four, treatment was stopped and two weeks after the end of the treatment, the epidermis was thinner than at the end of treatment [55].

Topical glucocorticoids have a vasoconstrictive effect that is subject to rapid diminution with continued exposure. Three times daily application of triamcinolone acetonide or fluocinonide on human skin for four days resulted in a diminished vasoconstriction response to glucocorticoids, but after a four-day rest period the response returned [21,51]. Glucocorticoids can suppress histamine induced wheal formation, and tolerance to this effect occurs, too. In one study, with daily application of clobetasol or fluocinolone under occlusion, maximum wheal suppression was observed on the eighth day. By the 14th day, there was tolerance to the effect of glucocorticoids with only minimal suppression of histamine wheal formation [56-58].

On the basis of clinical experience, perhaps supported by the short term effects of glucocorticoids described above, a dogma has developed that continued daily application of topical glucocorticoids eventually leads to loss of efficacy especially in the treatment of psoriasis [15-20]. The term tachyphylaxis has been used for this loss of efficacy even though this loss of efficacy occurs much more slowly than the tachyphylaxis, the rapid loss in agonist effect, observed in the *in vitro* and *in vivo* studies described above. This tachyphylaxis dogma prevails despite the mechanism of action of topical glucocorticoids in the treatment of psoriasis being mainly through immunosuppression that may be unrelated to the experimental demonstrations of tachyphylaxis that have been reported.

We identified two short-term and one long-term study examining the effect of topical glucocorticoids on immune function in psoriatic lesions. In two 2-week-studies of topical glucocorticoids in psoriasis, T-cell infiltration in the epidermis and dermis were reduced without any evidence of tachyphylaxis [59,60]. In a 6-week-study, a reduction in CD4+ and CD8+ T-cells from baseline was observed in the epidermis and dermis after 4 weeks of therapy. At week 6, CD4+ and CD8+ T-cells in the epidermis were less than week 4. In the dermis, CD4+ T-cells were less than baseline but slightly more than week 4. In this study, severity scores of the lesions were reduced progressively up to week 6 without any evidence of tolerance [61].

The effect of daily use of clobetasol propionate shampoo treatment on the expression levels of individual genes in psoriasis has been studied. Some of the inflammation-related genes that were significantly upregulated in the hair follicles of psoriasis patients were significantly repressed by the clobetasol propionate at week 2. At the fourth week of treatment, three additional genes were significantly repressed [62]. No evidence of tolerance was observed in this study.

Articles studying the long term use of topical glucocorticoids in psoriasis

To our knowledge, there is only one clinical study looking for tachyphylaxis to the antipsoriatic effects of topical glucocorticoids [17]. Twenty seven subjects with plaque psoriasis applied betamethasone dipropionate ointment twice daily for 12 weeks to their plaques of psoriasis. In each patient, an isolated plaque of psoriasis, representative of all the plaques, was left untreated to allow

for the evaluation of the natural course of the disease. Plaques were evaluated every 2 weeks. Tachyphylaxis was defined as "an increase in plaque elevation (at least 2 score on a 9 point scale) occurring after a detectable decrease in plaque elevation with topical glucocorticoid". In this study, maximal improvement in psoriasis scores was detected after 2 weeks of therapy. Then, average score was maintained between weeks 2 and 12, without any further improvement or worsening. No subjects met criteria for definition of tachyphylaxis throughout the 12-week period. The control lesions remained unchanged during the course of the study. The authors concluded that the study failed to demonstrate tachyphylaxis to therapeutic effects of glucocorticoids in psoriasis.

Table 1 shows the results of six clinical trials using topical glucocorticoids in psoriasis for 4-12 weeks. There is no evidence of tolerance in these studies.

Table 1. Clinical trials using topical glucocorticoids in psoriasis

Study	Treatment period (week)	Results
Comparison of topical calcipotriene with fluocinonide (twice daily) [63]	6	Both treatments had more psoriasis severity score reduction per week, in the first two weeks, compared with the rest of the treatment period. The mean severity score showed a continuous reduction up to the end of treatment period with both treatments.
Comparison of topical clobetasol with placebo (twice daily) [64]	4	Success rate was increased gradually in the four-week-treatment period in the treatment group. After stopping treatment at week 4, a recurrence was observed.
Comparison of topical clobetasol with placebo (twice daily) [65]	4	Success rate was increased gradually in the four-week-treatment period in the treatment group. After stopping treatment at week 4, a recurrence was observed.
Comparison of topical clobetasol with calcipotriene – betamethasone	4	Success rate was increased gradually in the treatment period and a recurrence occurred after stopping therapy in both treatment groups.

combination ontment[66]

Comparison of topical clobetasol with tazarotene (once-daily)[67]	12	Severity scores decreased gradually during the treatment period in both groups. Clobetasol cream was more effective than tazarotene cream throughout the treatment period. At week 16 (four weeks after stopping therapy), clobetasol-treated lesions (but not tazarotene treated lesions) showed some degree of recurrence.
Comparison of topical clobetasol (once daily) for 2 weeks versus 1 week of active treatment and 1 week of vehicle alone [68]	1-2	Two-week-continuous treatment was slightly but significantly more effective than one week active treatment.

Kragballe K et al. conducted a double-blind clinical trial comparing the efficacy of continues versus intermittent use of glucocorticoids [63]. Patients with psoriasis vulgaris were randomized to once daily treatment when required with either: 52 weeks of calcipotriol/betamethasone-two-compound product (two-compound group), 52 weeks of alternating 4-week periods of two-compound product and calcipotriol (alternating group), or 4 weeks of two-compound product followed by 48 weeks of calcipotriol (calcipotriol group). The patients were followed every 4 weeks. Absent or mild disease activity was considered to be a satisfactory response. In this study, continues use of betamethasone was more effective than intermittent use of the drug (figure 1) [63]. There was no evidence of tolerance to the glucocorticoid even over one year of use.

Discussion

The term tachyphylaxis is defined as a "rapidly decreasing response to a drug or physiologically active agent after administration of a few doses". Tachyphylaxis to glucocorticoids was first demonstrated by du Vivier and Stoughton who showed acute onset of tolerance to the vasoconstrictive action of topical glucocorticoids [21,51]. The standard definition of tachyphylaxis applies well to this rapid tolerance that is observed in vasoconstrictor assays. The suppressive effect of glucocorticoids on histamine induced wheal formation is also subject to tolerance [56-58]. However, the clinical significance of tachyphylaxis to the vasoconstrictive and antihistaminic effects of glucocorticoids is not known. Whereas there is strong evidence demonstrating glucocorticoid receptor down-regulation in tissues after glucocorticoid therapy [22-24,26,28-3133-36,39-44], the physiologic significance of glucocorticoid agonist-induced receptor down-regulation is also still not known and may not have any significant effect on glucocorticoid efficacy [33,34,47,48].

The standard definition of tachyphylaxis does not fit well with the more clinically significant, frequently observed phenomenon that our patients complain of, that slowly, over time, their topical glucocorticoid doesn't work as well as it used to. Tachyphylaxis may be a poor term for this latter phenomenon, which may be better labeled, "bradyphylaxis," and which can be defined as "a slow, progressive decreasing response to treatment over long periods of use [64]." In clinical studies, although topical

glucocorticoids may be more effective in treating psoriasis in the first two weeks of therapy [17,65], there is strong evidence that they remain effective for at least up to four weeks [66-69]. Efficacy for up to 52 weeks has also been reported in psoriasis [63,70]. Exacerbations or recurrences that have been observed after discontinuation of the drug at week 4 or 12 is evidence that the drugs were still having an effect after long-term continuous use [66-68,70]. Studies that compared short-term versus long-term use of topical glucocorticoids in psoriasis showed better results with long-term use [63,69,71-73].

Considering the results of the aforementioned studies, there seems to be no clinical trial evidence to support the dogma that tolerance to topical glucocorticoids develops in psoriasis or other inflammatory skin diseases. What dermatologists consider tachyphylaxis or tolerance to glucocorticoids in clinical practice may be the result of other factors. First, poor adherence of the patients to topical therapy over time may be a good explanation for cases of this phenomenon that we see in clinical practice. Non-compliance to topical treatment increases over time and is much more evident in clinical practice than in clinical trials [74-77]. The patient may report that the drug is not working anymore, but it may be that the drug is not used anymore.

Second, topical glucocorticoids may have a maximum effect on the severity score of psoriasis that may be achieved in the first few days or weeks. The lesions get better but do not clear. The drugs are still effective after the first few days or weeks but up to the certain limit. If this theory is correct, there may be a recurrence or deterioration of lesions after discontinuation of the drug that is still effective. In our review, all of the studies that followed the patients after discontinuation of the drug, showed such recurrences [66-68,70,78]. One should bear in mind that psoriasis is a chronic disease with fluctuating severity and frequent exacerbations unrelated to current or previous treatments. A natural flare of the disease that has been under control with glucocorticoids that have a maximum effect may give the impression of tolerance. These two theories can explain the factors that are responsible for many (perhaps most) cases of recurrence or drug resistance not only in psoriasis but also in most of the other chronic diseases treated with long term topical glucocorticoid treatment.

Conclusion

Whether called tachyphylaxis or bradyphylaxis, loss of clinical effects of topical glucocorticoids in inflammatory skin disease has been an accepted belief in dermatology for many years. Interestingly, after a thorough search of literature for the origin and a precise explanation behind this commonly held belief, not one clinical trial gave evidence supporting this widely accepted dogma. In the clinical trial setting, topical glucocorticoids appear to retain clinical effectiveness for at least 52 weeks.

Limitations

The loss of glucocorticoid efficacy over time in clinical practice is not fully characterized or well studied. One limitation of our review is that in the most long term study, the 52-week study done by Kragbelle K et al. [63], the glucocorticoid was used in combination with calcipotriol and there is the possibility that co-administration of a vitamin D analog can affect the pharmacodynamics of glucocorticoids [79,80].

This study compared the efficacy of calcipotriol/betamethasone-two-compound product (two-compound group) continuously with a regiment of alternating 4-week periods of two-compound product and calcipotriol alone (alternating group) and with 4 weeks of two-compound product followed by calcipotriol alone for the rest of the 52 weeks (calcipotriol group) in treatment of psoriasis. Continuous use did not show a loss of efficacy over the 52-week study period. In addition, whenever the topical corticosteroid was stopped, there was worsening of the disease. This indicates that throughout the 52-week period, the corticosteroid still contributed efficacy.
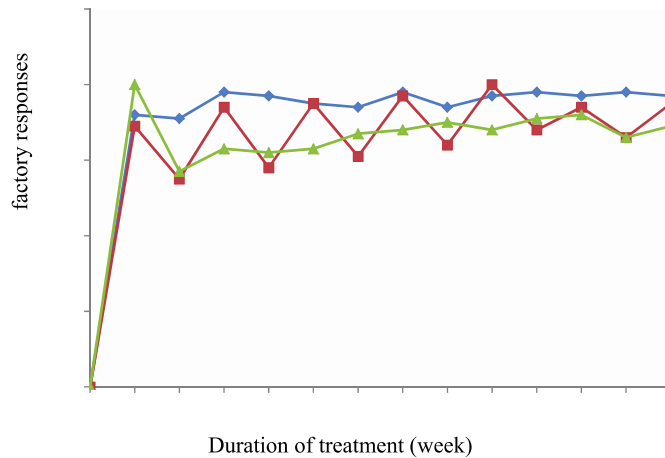
Figure 1. Clinical results in Kragballe K et al. [63] study. No apparent loss of activity with long term use of topical corticosteroids

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