Review

CALCIPOTRIOL - A VITAMIN D3 ANALOGUE (MC 903) IN THE TREATMENT OF PSORIASIS VULGARIS: A REVIEW

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SUMMARY

Calcipotriol, a vitamin D3 analogue, is an effective and well tolerated topical therapy of mild and medium intensive plaque psoriasis. Calcipotriol reduces epidermal cell proliferation and enhances differentiation in lesional skin. Calcipotriol ointment, applied twice daily, may be more effective than betamethazone valerate and dithranol. In combination with other antipsoriatic treatments (UVB, PUVA, Cyclosporin), it is used in therapy of severe psoriasis. The most frequently occurring adverse events are lesional and perilesional skin irritations. There is no risk of hypercalcemia if calcipotriol is used in recommended doses not more than 100 g weekly. Calcipotriol ointment is today an effective and safe alternative therapy for psoriasis vulgaris in children. For the treatment of scalp psoriasis a calcipotriol solution can be used. In this article, the literature is reviewed and different calcipotriol therapeutic modalities are discussed.

KEY WORDS

vitamin D, calcipotriol, plaque psoriasis, review

Calcipotriol is a vitamin D3 analogue, which was used for the first time in dermatology in 1985 when a group of Japanese researchers found that in a patient with senile osteoporosis, associated psoriatic lesions disappeared unexpectedly during the treatment with oral active vitamin D3 (1, 2).

Some facts about vitamin D3 and skin are well known:

- cholecalciferol - vitamin D3 is synthesized in the epidermis under the effect of UVB light from 7-dehydrocholesterol
- hypocalcemia can cause exanthemas of psoriatic type (as a result of deficiency of vitamin D in food, deficiency of UV light or hypoparatiroidism) (3, 4, 5, 6).
- specific receptors for calcipotriol have been found in skin (7).

The skin has an important role in metabolism of vitamin D3.

Under the effect of UVB light 7-dehydrocholesterol changes in the epidermis in cholecalciferol. The cholecalciferol produced in such way is carried to the liver for the 25-hydroxylisation and 25 hydroxicalciferol is synthesized (25 OHD3). It is further

hydroxilized with one hydroxilization in the kidneys in 1-alfa-25-dihydroxy-D3, calcitriol, a metabolite of vitamin D3, which is 100 times more active than vitamin D3. In vitamin D3 deficiency the skin is capable of producing vitamin 1,25 (OH) D3. 1-hydroxylization is stimulated by deficiency of calcium and phosphates and by parathyroid hormone.

Specific receptors for 1,25 (OH) D3 have recently been found not only in the skin but also in other tissues as muscle, pancreas (7, 8, 9) and in some tumors (10). Receptor-mediated effects on cell proliferation and cell differentiation have been observed (11, 12, 13).

The most characteristic feature of psoriatic lesions is an abnormally increased proliferation of epidermal keratinocytes as well as an incomplete differentiation (14). Overall, in patients with psoriasis the transit time of epidermal cells is reduced from 28 to approximately 4 days, the epidermis appears about 3 to 5 times thicker than normal (15).

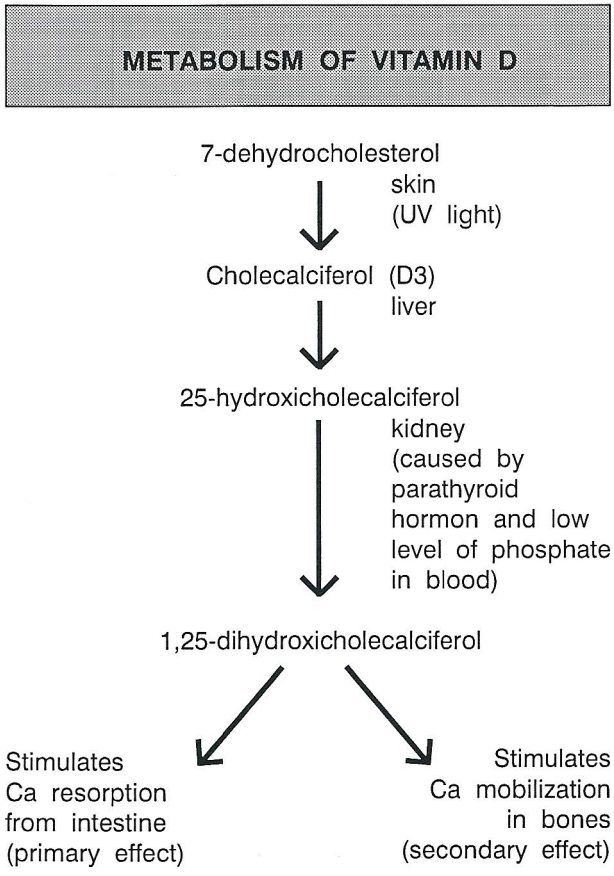

Fig. 1. Schematic presentation of vitamin D metabolism. Mardešić, D., Pedijatrija, Metabolism of vitamin D, Zagreb, Šk. Knjiga, 1991; 244.

Calcitriol markedly suppresses proliferation and enhances differentiation of epidermal keratinocytes (14) but the use of highly active vitamin D3 derivatives to control cell proliferation and to promote cell differentiation is limited by their potent effects on calcium metabolism. Hypercalcemia is induced by oral systemic doses higher than a few mg per day, and topical application is complicated by the risk of increased transdermal absorption of the active compound in areas of psoriatic skin lesions (16).

It has therefore been necessary to develop new vitamin D3 analogues with potent effects on cell proliferation and cell differentiation, but with a lower risk of inducing the classical vitamin D associated side effects: hypercalciuria, hypercalcemia and induction of bone resorption (13).

As a result of chemical and pharmacological research, a new vitamin D3 analogue calcipotriol (MC 903) has been developed.

Calcipotriol is a colorless crystalline substance with a molecular weight of 412.62, melting point of 166-8°C and a summation formula of $C_{27}H_4O_3$ (Fig. 2). Calcipotriol demonstrated effects on cell proliferation and differentiation similar to those of calcitriol in many *in vitro* experiments (17). So it was expected from calcipotriol to exhibit cellular antiproliferative and differentiation enhancing effects *in vivo*.

In patients with chronic plaque psoriasis calcipotriol influences all three main mechanisms of psoriasis pathogenesis. It shows antiproliferative, anti-inflammatory effects and enhances differentiation in lesional skin (16).

Calcipotriol is 100 to 200 times less potent than calcitriol in regulating the in vivo calcium metabolism in rats. Calcipotriol 1 and 10 mg/kg/day administrated intraperitoneally to rats for 7 days did not significantly affect serum and urinary calcium levels and calcium content of tibial metaphysis. Conversely, calcipotriol 100 mg/kg/day and calcitriol 0,5 mg/kg/day significantly altered these parameters (17).

EFFECTS ON IMMUNOLOGICAL AND INFLAMMATORY MEDIATORS

Effects of calcipotriol on interleukins 1 and 6 (IL-1 and IL-6), immunological and inflammatory mediators in the pathogenesis of psoriasis require special attention, but are still not fully explained.

In vitro calcipotriol inhibited mouse thymocite proliferation in response to human IL-1 in a dose dependant fashion (18).

In the patients with plaque psoriasis, calcipotriol ointment 50 mg/g:

- reduces the accumulation of polymorphonuclear leukocytes during the first week of treatment (19)
- reduces the number of epidermal cells after two weeks of treatment (19), and
- after four weeks treatment, the number of keratin-16-positive cells and the number of T lymphocytes decreased significantly (19).

The number of CD 14 cells and Langerhans cells remained unaffected during the treatment (19, 20, 21, 22).

The role of vitamin D3 *in vivo* studies can be concluded: an influence on epidermal proliferation and accumulation of polymorphonuclear leukocytes is an early effect, whereas the modulation of the number of T cells, monocytes and macrophages are late effects (23).

DOSAGE AND ADMINISTRATION

One gram of calcipotriol ointment contains 50 mg calcipotriol. It should be applied sparingly to the affected skin twice a day, no more than 100 g per week. A higher dose may be associated with an increased risk of hypercalcemia. Initially it was recommended that the course of calcipotriol treatment should not exceed 6 weeks, but later on clinical studies which lasted 12 months have shown that it was an effective and well tolerated preparation. Today calcipotriol is accepted as a treatment, which can be used for months without risk of lasting skin or systemic side effects when the dosage is lower than 60-100 mg per week (24).

TOLERABILITY

In the course of clinical trials, it was shown that the most common adverse effects were: lesional and perilesional skin irritation (qualified by patients as burning, itching and stinging), erythema, scaling and peeling of the skin (overall incidence 8,8 to 19,5%) (25).

Calcipotriol ointment should not be applied to psoriatic lesions on the face because it may give rise to irritation (25, 26). Facial dermatitis caused by calcipotriol ointment was generally mild and transparent in nature (14, 27). Often the facial dermatitis is caused by unintentional transfer of calcipotriol ointment from hands to the face, therefore careful handwashing after use of the ointment is recommended (24, 28).

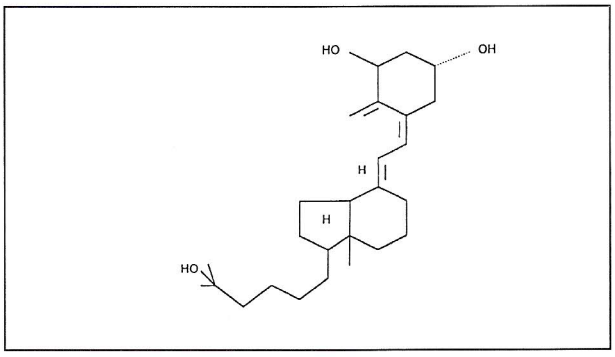

Fig. 2. Structural formula of calcipotriol

In a few clinical trials with a very large number of patients treated with calcipotriol ointment 50 mg/g twice daily total serum calcium levels were not significantly altered (29, 30, 31).

There are still no reports about using calcipotriol ointment during pregnancy. Although studies in experimental animals have not shown any teratogenic effect, it is not advisable for pregnant women to use calcipotriol ointment.

CALCIPOTRIOL OINTMENT IN CHILDHOOD PSORIASIS

Clinical trials for assessing the safety and efficacy of calcipotriol use for psoriasis vulgaris in children, showed no serious side effects, including those relating to calcium and bone metabolism, hematological and biochemical parameters.

Calcipotriol ointment has proved to be an effective, well-tolerated, acceptable and safe alternative therapy for psoriasis vulgaris in children (32, 33, 34).

The efficacy of calcipotriol in psoriasis can not be compared to systemic antipsoriatic treatments, but the simultaneous use of both improves the therapeutic results, allows lower doses than those used in single agent therapy and consequently reduces the risk of side effects arising from systemic antipsoriatic treatment.

COMBINATIONS OF VARIOUS OTHER TREATMENTS WITH CALCIPOTRIOL

Calcipotriol + UVB

Clinical trials with this combined therapy showed that calcipotriol enhances UVB therapy (35, 36, 37, 38, 39). Calcipotriol ointment should never be applied immediately before the application of UVB light because it can decrease the minimal erythema dose (MED) (40, 41, 42). When applied after the UVB therapy, calcipotriol did not show any adverse interactions, neither to artificial UVB light nor to sun exposure (40, 41).

Calcipotriol + PUVA

PUVA therapy is one of the most effective treatments for psoriasis, but high-dose or long-term PUVA treatment increases the risk of cutaneous malignancies, especially basalioma (43, 44, 45). Combination of calcipotriol ointment and PUVA reduces total UVA dose required for clearance of skin lesions and shows no interactions if calcipotriol is applied after the application of UVA (41, 42, 46, 47).

Calcipotriol and cyclosporine

Calcipotriol was shown to augment the immunosuppressive effect of cyclosporine on interleukin 2 secretion (48, 49, 50). Taking synergistic effect of calcipotriol and cyclosporine into account, several studies were conducted in order to explore the possibilities of this combination with the objective of reducing side effects, especially renal toxicity, by decreasing the doses of cyclosporine (51, 52). The authors concluded that the combination of calcipotriol and cyclosporine enhanced the efficacy of antipsoriatic treatment, improved the risk-benefit ratio, and permitted the use of lower dosage of cyclosporine (52, 53).

Calcipotriol and oral retinoids

There is only one publication with quantitative data on combined therapy with calcipotriol and oral retinoids where authors concluded that calcipotriol/acitretin combination produced a significantly better therapeutic response with a lower cumulative acitretin dose (54).

We did not find a report on combined therapy with calcipotriol and methotrexate.

Calcipotriol solution

For the treatment of scalp psoriasis, a solution of calcipotriol (50 mg/ml) is available. It should be used twice daily; one to two drops of the solution to a psoriatic lesion of the approximate size of a coin, not exceeding 60 ml per week. In a double blind, four-week clinical trial, calcipotriol solution showed to be more effective than the vehicle alone (55). In double blind, four-week long clinical study, calcipotriol solution (50 mg/ml) was compared with betamethazone-17-valerate solution (1 mg/ml) in patients with scalp psoriasis. Although application of calcipotriol solution resulted in significant improvement, betamethazone-17-valerate solution was more effective (24, 56). Possible side effects of calcipotriol solution are irritation of the face and scalp; it is recommended to avoid contact of the solution with eyes and facial skin. In case of thick scales, the therapy should begin with salicylic acid and continued with calcipotriol solution. Salicylic acid should not be used with calcipotriol solution at the same time because it can inactivate calcipotriol.

Calcipotriol in treatment of nail psoriasis

Treatment of nail psoriasis is difficult, long-lasting and often without success. Some reports, which suggested that nail psoriasis might respond to topical calcipotriol, were therefore welcomed. Kokelj et al. treated 7 patients with calcipotriol ointment twice daily for 3 months and five of them experienced an improvement of their psoriasis (57). We also suggested to our patients who used calcipotriol for their skin lesions to apply calcipotriol ointment around the nail area twice daily: preliminary results were considered as satisfactory.

Other therapeutic modalities of calcipotriol

Calcipotriol could be used for treatment of skin disorders other than plaque psoriasis. The vitamin D3 receptors have been detected in various cell types in the skin including keratinocytes, Langerhans cells (58), melanocytes (59), fibroblasts (60) and endothelial cells (61). There are few reports about

using calcipotriol ointment in the treatment of intertriginous psoriasis (62), palmoplantar (63) and pustular psoriasis (64, 65), Reiter's syndrome (66), pityriasis rubra pilaris (67) and disorders of keratinization (68, 69, 70, 71). Recent reports suggest that the hyperproliferative variants of ichthyoses and keratodermas may respond to topical calcipotriol ointment, although the use can be limited due to theoretical risk of hypercalcemia. Namely, disorders of keratinization involve usually large areas of skin and it is easy to assume that patients can exceed the recommended weekly dose of 100 g of calcipotriol. Other mentioned diseases (intertriginous and pustular psoriasis, Reiter's syndrome, pityriasis rubra pilaris) responded positively to calcipotriol but more studies should be done to corroborate these preliminary results on a small number of patients (72).

CONCLUSION

Calcipotriol, a vitamin D3 analogue, is today a well-established and widely used effective treatment for mild and medium plaque psoriasis. In combination with other therapeutic modalities it is successfully used also in severe cases of psoriasis. Topically applied, calcipotriol has a low hypercalcemic potential and in contrast to all other available antipsoriatic therapies (topical corticosteroids, retinoids, methotrexate, and cyclosporin), it does not show a risk of serious adverse events. A limitation of treatment with calcipotriol is irritation of lesional and perilesional skin.

Today, vitamin D derivatives have already an important place in treatment of psoriasis, but it seems to be even more promising for the future. Namely, new analogues are available which seem to be more effective than calcipotriol due to altered chemical structure.

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