Calcipotriol
A Review of its Pharmacological Properties and Therapeutic Use in Psoriasis Vulgaris

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Summary

Calcipotriol (calcipotriene) is a vitamin D3 analogue which inhibits epidermal cell proliferation and enhances cell differentiation. In patients with chronic plaque psoriasis involved in short term studies of 6 to 8 weeks' duration, calcipotriol ointment applied twice daily was significantly more effective than betamethasone valerate and dithranol (anthralin).

Pooled data from clinical trials show that calcipotriol is well tolerated, with the majority of adverse events being mild and transient local reactions. Topically applied calcipotriol has low hypercalcaemic potential and, in contrast to topical corticosteroids, oral retinoids and orally administered calcitriol, methotrexate and cyclosporin, calcipotriol does not appear to be associated with a risk of serious adverse events.

Thus, at this early stage in its clinical development, calcipotriol appears to be an effective and well tolerated topical therapy for the management of psoriasis; if promising preliminary clinical findings are confirmed, calcipotriol will represent a major advance in this difficult area of therapeutics.

Pharmacological Properties

Calcipotriol has pharmacodynamic properties similar to those of calcitriol (1,25-dihydroxycholecalciferol), the active metabolite of vitamin D3. In several in vitro models, calcipotriol and calcitriol markedly inhibit cell proliferation and enhance cell differentiation over a range of concentrations from approximately $10^{-10}$ to $10^{-6}$ mol/L. For example, both drugs reduce cell numbers, total DNA content and incorporation of radiolabelled thymidine into DNA, and increase the number of human keratinocytes with cornified envelopes and activity of the enzyme causing protein cross-linking in the envelopes. In patients with psoriasis, calcipotriol also reduces epidermal cell proliferation and enhances differentiation in lesional skin.

Calcipotriol binds to intestinal calcitriol receptors with affinity similar to that of calcitriol, but is 100 to 200 times less potent than calcitriol in its effect on in vivo calcium metabolism in rats. Intraperitoneal calcipotriol 1 and 10 µg/kg/day administered to rats for 7 days did not significantly affect serum and urinary calcium levels, or dry weight and calcium content of tibial metaphyses. Conversely, calcitriol 0.5 µg/kg/day significantly altered these parameters.

Calcipotriol inhibits interleukin-1-induced mouse thymocyte proliferation in vitro and, in patients with psoriasis, reduces the amount and distribution of epidermal interleukin-6 and the number of activated epidermal T-lymphocytes. However, the relevance of these findings to the mechanism of action and clinical efficacy of calcipotriol in psoriasis remain uncertain.

In patients with psoriasis, less than 1% of calcipotriol is systemically absorbed after a single application of 0.3 to 1.7g of radiolabelled calcipotriol ointment 50 µg/g. Calcipotriol is thought to undergo rapid hepatic conversion to MC 1046 and MC 1080, metabolites with negligible pharmacological activity, and has an affinity for human vitamin D binding protein 30 times less than that of calcitriol in vitro. Only traces of calcipotriol (< 1%) are recovered in urine and faeces after topical application.

Therapeutic Efficacy

In patients with psoriasis, calcipotriol cream 1200 µg/g is significantly superior to cream base alone, and dose-response relationships have been identified for cream (10 to 100 µg/g) and ointment (25 to 100 µg/g) formulations of the drug. Marked decreases in physician-assessed mean clinical scores for severity of skin erythema, thickness and scaling were observed after cream (about 17 to 49%) and ointment (about 50 to 90%) application, and investigator global assessments of overall clinical response showed significant improvement. After calcipotriol ointment 25, 50 and 100 µg/g application, 40, 63 and 88% of patients with psoriasis, respectively, demonstrated 'marked' improvement or total clearance of lesions; the 50 µg/g concentration was significantly superior to 25 µg/g (n = 20), but not significantly different from 100 µg/g (n = 17). Additionally, calcipotriol ointment 50 µg/g significantly reduced mean psoriasis area and severity index (PASI) score by 67% in 161 patients with psoriasis treated for up to 1 year.