Active Vitamin D3 Ointments Suppress Ultraviolet B Irradiation-Induced Papilloma Formation in Mouse Skin

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Abstract

Background: Topical application of 1α, 25-dihydroxyvitamin D3 (1α,25-(OH)2D3) inhibits 12,12-dimethylbenz [a] anthracene (DMBA) and 12-α-tetradecanoylphorbol-13-acetate (TPA)-induced tumor formation of mouse skin. Ultraviolet irradiation (UV) may also induce skin tumors. However, no report exists regarding the effect of topical active vitamin D3, tacrolimus, or corticosteroids on UV-irradiation-induced skin tumors. 1.2. Objective Using ultraviolet B (UVB)-induced papilloma model, we compared the effect of active vitamin D3, tacrolimus, and corticosteroids ointments on the skin papilloma formation.

Methods: Various corticosteroids (betamethasionevaleate, betamethasonebutyrate propionate), active vitamin D3 (tacalcitol, carcipotriol, maxacalcitol), tacrolimus, or white petrolatum ointments were applied twice a week on the mice skin following UVB-irradiation (200mJ/cm2). The number of UVB-induced skin papillomas was counted at the indicated time.

Results: Papillomas were induced at 12 weeks on the UVB-irradiated mouse skin. The number of papilloma was significantly decreased on active vitamin D3 ointment-treated mice skin. However, the anti-tumor effect was not observed on corticosteroids or tacrolimus ointment-treated skin.

Conclusion: Active vitamin D3 ointments show potent anti-tumor effect on UVB-treated mouse skin. The active vitamin D3 ointments might decrease the risk of UVB-induced skin tumors under phototherapy.

INTRODUCTION

Ultraviolet irradiation (UV) has long been used for various skin disorders. However, long term phototherapy might induce skin tumors. Furthermore, tacrolimus ointment, which suppresses skin immune system, might augment UV-induced skin carcinogenesis. Although tacrolimus ointment is useful for facial atopic dermatitis, the risk of UV-induced carcinogenesis should not be ignored.

Using mouse skin model, Chida et al., showed that topical application of 1-α,25-(OH)2D3 inhibits skin tumor promotion by 12-α-tetradecanoylphorbol-13-acetate [1]. However, no report exists on the effect of active vitamin D3, tacrolimus, or corticosteroids against UVB-induced skin tumor formation. In the present study, using mouse skin we investigated the effect of active vitamin D3, tacrolimus, and corticosteroids ointments on the UVB irradiation-induced skin papilloma formation.

MATERIALS AND METHODS

Animals

Female hairless mice (HOS:Hr-1) aged 6 weeks were purchased from Shizuoka Laboratory Center (Shizuoka, Japan). They were housed in cages with wire mesh covers, and were fed by autodaved mouse chow and water. All animal experiments were conducted according to the Guidelines for Animal Experimentation at Asahikawa Medical College and National Regulations for Animal Experiments.

Ultraviolet B irradiation

UVB irradiation source was a Toshiba-Eizai Dermaray instrument (DMR-1, Tokyo, Japan) equipped with five fluorescent lamps (FL-20-SE-30, Toshiba, Japan). The UVB source emits an energy spectrum with high fluence in the UVB region (290-320nm) with its peak at 313 nm. In order to block UVC emission a WG-295 long pass filter was used (Schott Glass Technology, Duryea PA). The emitted dose was routinely quantitated by a UVB radiometer photodetector (IL443 and SEE 240, International Light, Newburyport, MA).

Induction of skin tumors and evaluation of the effect of topical treatments in mouse skin papilloma

UVB irradiation (200ml/cm2) was performed for 20
each group mice twice a week. Various corticosteroids (betamethasonevalerate, betamethasonebutyrate propionate, which were purchased from Maruho Co., Ltd (Osalka, Japan)), active vitamin D3(tacalcitol, carcipotriol, maxacalcitol), tacrolimus, or white petrolatum ointments, which were purchased from Torii Co., Ltd (Tokyo, Japan), were applied on the mice skin immediately following the UVB irradiation. The irradiation was done on the back for 6 months. The number of UVB-induced papillomas was counted at the indicated time.

Statistics

Statistical significance of the data obtained was evaluated by Student’s t-test using unpaired analyses.

RESULTS

Mouse skin papillomas were induced by UVB irradiation by 12 weeks and constantly increased in number. Application of betamethasonevalerate, carcipotriol, tacrolimus, or white petrolatum ointments was performed on the UVB-irradiated site. The number of papillomas significantly decreased on calcipotriol treated mice skin (Figure 1). The anti-tumor effect was not observed by betamethasone valerate or by tacrolimus treatment. The anti-tumor effect was also detected by other active vitamin D3 ointments, tacalcitol, and maxicalcitol. There was no significant difference in the anti-tumor effects among the three active vitamin D3 ointments (Figure 2).

DISCUSSION

In the present study, using mouse skin we demonstrated that active vitamin D3 ointments suppressed induction of UVB-induced papillomas. Previous reports indicate that topical application of 1-α, 25-(OH)2D3 inhibits phorbol ester-dependent tumor promotion in mouse skin [1,2]. We for the first time demonstrated that active vitamin D3 ointments in the clinical use inhibit UVB-induced papilloma formation in mice skin. Song et al showed that 1-α,25-(OH)2D3 reduces UV-induced DNA damages such as thymidine dimer formation and 8-oxa-7,8-dihydro-2-deoxyguanosine, which may explain the photoprotective effect of active vitamin D3 [3]. Furthermore, 1-α,25-(OH)2D3 has increased p53 expression and decreases nitric oxide products reducing the thymidine dimer formation [4]. These findings might explain the decreased papilloma formation by active vitamin D3 application on mice skin.

UV irradiation has long been used for psoriasis and combination therapy of UVB irradiation and active vitamin D3 ointments is known to be more potent than each treatment [5]. However, a potential risk exists for the induction of skin tumors in the long term UV irradiation treatment. The present study indicates that the combination of UVB and active vitamin D3 application might be less tumorigenic.

Tacrolimus ointment, a macrolide immunosuppressive agent, is used on sun-exposed facial lesions of atopic dermatitis, which may increase the risk of phocarcinogenesis. Niwa et al., showed tacrolimus ointment increased carcinogenesis in 7, 12-dimethylbenz[a]anthracene (DMBA)-phorbol ester-treated mice skin [6]. In contrast, Mitamura et al., showed that tacrolimus ointment suppressed tumor induction of DMBA-phorbol ester treated mice skin [7]. In the present study, tacrolimus ointment did not increase the UVB-induced skin papilloma formation supporting the latter result.

Application of dexamethasone on DMBA-phorbol ester-treated mice skin reportedly suppresses skin tumorigenesis [8]. In our system, no inhibitory of papilloma induction was detected by corticosteroids treatment. Different tumor induction system and/or different corticosteroid potency might explain the discrepancy.

CONCLUSION

Our study demonstrated that active vitamin D3 ointment decreases UVB-dependent tumor induction. The combination of active vitamin D3 and UV-phototherapy and topical application of sun-exposed area might be recommended in daily dermatological treatments.
REFERENCES


