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Skin Penetration of Betamethasone and Calcipotriol When Vehiculated in an Ointment or Cutaneous Foam Formulation: A Skin Absorption Study Using a Reconstructed Human Epidermis Model

Massimo Milani* **and Francesca Colombo**

Medical Department Cantabria Labs Difa Cooper; Caronno P. (VA) Italy

***Corresponding author:** Massimo Milani, Medical Department Cantabria Labs Difa Cooper; Caronno P. (VA) Italy, Tel: +39 349 1681636; E-mail: massimo.milani@difacooper.com

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Abstract

Objective: The topical use of corticosteroids and vitamin D derivatives represents the first line treatment of mild or moderate plaque psoriasis. The most studied and used fixed combination of betamethasone (BMS) and calcipotriol (CAL) for the treatment of PS is available in different topical formulations, among which ointment (OIT) and cutaneous foam (CF). For topical products, the type of formulation has great impact in the pharmacokinetic behaviour of active molecules, for examples formulations like ointments, due to their occlusive action, are generally more efficient in enhancing the penetration of active compounds compared to other formulations. However few data comparing the pharmacokinetic characteristics of BMS and CAL in OIT and CF are available. The aim of this study was to evaluate and compared the characteristic of skin penetration of two commonly used topical formulations: ointment and cutaneous foam of BMF (0.5 mg/g) and CAL (50 µg/g).

Methods: To evaluate the penetration potential of the active ingredients contained in the two formulations included in the study the Reconstructed Human Epidermis by Matter (RHEM) model was used. The permeability experiments were performed 4 hours after the application of equal amounts of the two tested formulations. The concentration of BMS and OIT in both acceptor and donor compartments were quantified using ELISA test.

Results: The penetration of active compounds (BMS and CAL) in fixed combination vehiculated in OIT (7.6% ± 1.8% and 5.1% ± 8.6% for BMS and CAL, respectively) or in CF (7.8% ± 2.0% and 2.1% ± 4.7% for BMS and CAL, respectively) in a RHEM model resulted comparable for both the formulations. The OIT showed a slightly, although not significant, greater penetration of the CAL compounds.

Conclusions: The ointment and foam formulations are superimposable, in term of penetration of active compounds through this RHEM model. This data suggested that the ointment formulation still represents a useful topical treatment for the management of mild or moderate plaque psoriasis.

Keywords: ***Plaque psoriasis; Betamethasone; Calcipotriene; Ointment; Cutaneous foam; Reconstructed human epidermis model; Skin penetration***

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1. Introduction

Psoriasis is an immune-mediated chronic skin disease that affects about 1-3% of the Caucasian population [1]. The plaque psoriasis (PS), occurring in more than 80% of affected patients, represent the most common clinical variant [2]. The pathology is characterized by the presence of erythematous scaly plaques that could appear on different parts of the body (scalp, lower back, intergluteal cleft, umbilical area, elbows, and knees). The localized psoriasis is characterised by few lesions while in widespread psoriasis the lesions are several and can affect the whole cutaneous surface [3]. Patients with mild or moderate plaque psoriasis can be treated with topical agents, generally characterized by a high efficacy and safety. Corticosteroids and vitamin D derivatives (such as Calcipotriol), alone or in fixed combinations, are commonly used in PS treatment. Calcipotriene (CAL), a vitamin D analogue, is involved in the production and release of pro-inflammatory cytokines and regulates epidermal cell proliferation and differentiation. Topical corticosteroids, such as betamethasone (BMS), exert different biological effects such as the inhibition of the recruitment and migration of inflammatory cells, modulation of cytokines and chemokine release, and regulation of DNA synthesis [3]. Different studies have reported the efficacy and safety of these compounds, either alone or in combination, in the treatment of mild-to-moderate plaque, scalp and nail psoriasis [4-6].

The most studied and used fixed combination of BMS and CAL for the treatment of PS is available in different topical formulations: ointment, gel, cream, and more recently cutaneous foam. For topical products, the type of formulation has great impact in the pharmacokinetic behaviour of active compounds. Formulations like ointments, due to their occlusive action, are generally more efficient in enhancing the penetration of corticosteroids compare to other formulations [7], influencing positively the clinical efficiency of ointments.

Few data comparing the pharmacokinetic characteristics of BMS and CAL in ointment and cutaneous foam are available. The aim of this study was to evaluate and compared the characteristic of skin penetration in Reconstructed Human Epidermis by Matter model (RHEM) of two commonly used topical formulations: ointment (OIT) and cutaneous foam (CF) of BMF (0.5 mg/g) and CAL (50 µg/g).

2. Materials and Methods

2.1 Topical formulations

Two commercially available formulations used in plaque psoriasis were included in the study: ointment (OIT) and cutaneous foam (CF). Both formulations contained 0.5 mg/g betamethasone (BMS) and 50 µg/g calcipotriol (CAL).

2.2 *In vitro* cellular test

To evaluate the penetration potential of the active ingredients contained in the two formulations included in the study the Reconstructed Human Epidermis by Matter model (RHEM) was used, following the general principles of OECD TG 428 [8].

The suitability of the system was confirmed determining the effective time of exposure required to reduce the viability of treated cultures to 50% of controls (ET-50 value), following exposure to 1% Triton X-100, that resulted in line with the tabulated values (measured ET-50:5.82).

Tissues were take-off from the agarose, cleaned, transferred on fresh medium, and maintained at 37°C, 5% CO_2 until test substances application. For the application test, tissues were transferred on well plates filled with 1 mL of culture medium. 50 mg of each formulation were applied on tissue surface in single application and maintained for 4 hours. At the end of treatments, tissues were rinsed several times with 4 mL PBS. The media underlying the tissues, homogenates and washing solutions were collected for the analysis of active ingredients. The test was performed in triplicate for each formulation.

2.3 Determination of active ingredients

BM and CAL were quantified in media (containing substances penetrated through the epidermis and released), homogenates (containing substances penetrated through the epidermis and not released) and washing solutions (containing substances not penetrated through the epidermis) using commercially available competitive ELISA kits.

3. Results

TABLE 1 reported the percentage amounts of betamethasone (BMS) and calcipotriol (CAL) penetrated through the epidermis and released (Media), penetrated through the epidermis and not released (homogenates), and not penetrated through the epidermis (washing solutions) when ointment (OIT) and cutaneous foam (CF) were applied on the reconstructed human epidermis (RHE) model. The same data are also presented graphically in FIG. 1.

TABLE 1. **Distribution of BMS and CAL through the reconstructed human epidermis model after the application of OIT and CF. Results are expressed as mean percentage ± standard deviation. (n=3)**

	Media		**Homogenates**		**Washing solutions**	
	BMS % (mean ± SD)	**CAL % (mean ± SD)**	**BMS % (mean ± SD)**	**CAL % (mean ± SD)**	**BMS % (mean ± SD)**	**CAL % (mean ± SD)**
Ointment	7.6 ± 1.8	5.1 ± 8.4	1.8 ± 0.3	8.6 ± 4.2	84.7 ± 6.7	83.2 ± 8.2
Cutaneous foam	7.8 ± 1.9	2.1 ± 5.3	2.0 ± 0.5	4.7 ± 3.8	86.1 ± 7.4	91.8 ± 9.5

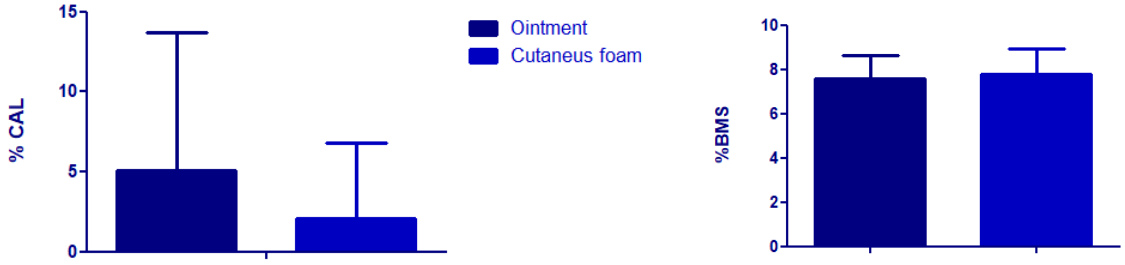

FIG. 1. **Amount of Betamethasone and Calcipotriol absorbed in reconstructed human epidermis model.**

As reported in TABLE 1 and expressed graphically in Figure the penetration of active compounds (BMS and CAL) in fixed combination vehiculated in OIT or in CF in a RHE model shows superimposable absorption characteristic for both the formulations. The OIT showed a slightly, although not significant, greater penetration of the CAL compounds, as observed in media and homogenates results.

4. Discussion

Ointment (OIT) is considered an efficient formulation for topical treatment of various skin disease. Ointment compared to other formulations, such as solution, cream, and low-viscosity cream showed a homogeneous spreading and better spreadability [9]. Although the greasiness of ointment could influence the patients' appreciation, this formulation is typically more effective than creams [10]. Different topical formulations of fixed combination of BMS and CAL for the treatment of PS are available, among them the cutaneous foam (CF) was recently introduced.

Few *in vitro* and *in vivo* studies have compared the fixed combination of BMS and CAL vehiculated in OIT or in CF in terms of penetration of active compounds through the skin and clinical improvement in psoriasis.

In a study conducted by Lind et al. [11] foam application showed minimal crystallisation and an increased skin penetration of CAL and BMS (evaluated using a full-thickness pig ear skin as *in vitro* model) compared to ointment. These data do not agree with the present study, where a comparable absorption of active compounds between the two formulations were observed. This could be correlated with the different *in vitro* models used. In our study a reconstructed human epidermis was selected thanks to its similarities to human tissues in terms of morphology and biochemical composition. This model could be considered suitable for transport experiments of drugs and other compounds across skin and therefore it could be used for permeability studies. In addition, the ointment was found to be more occlusive compared to the foam [11] and it is known that the occlusive proprieties generally positive correlated with the penetration.

An *in vivo* study evaluated the effect of a CAL/BDM foam formulation compared to CAL/BDM ointment (generally used as first-line treatment), observing that the effectiveness of the CAL/BDM foam was higher than that of the CAL/BDM ointment. Indeed, after 4 weeks, mean total clinical score was significantly decreased on test site treated with the foam compared with the ointment, with a difference of -0.75 (CI: -1.46 to -0.04). However, according to the European Medicines Agency (EMEA) guidelines on clinical investigation of new medicinal products for the treatment of psoriasis, in comparative active-controlled trials, it is suggested that at least a 1-point improvement of the monitored primary outcome score should be considered as a meaningful clinical improvement in supporting superiority [12]. Therefore, considering the confidence interval calculated during the trial, it is not possible to exclude that the different clinical efficacy between the two formulations could be marginal.

5. Conclusions

Guidelines recommend the topical use of corticosteroids and vitamin D derivatives at first line treatment of psoriasis. The most used fixed combination of betamethasone calcipotriol are available in different formulations, however few studies have been conducted on the differences, in term of penetration of active compound through the skin, among the different formulations.

In vitro experiments are useful tools to evaluate the skin permeation profile of medicinal products. In this study we demonstrated that the CAL/BDM ointment and the CAL/BDM foam are superimposable, in term of penetration of active compounds through the skin. This data suggested that the ointment formulation still represents a useful topic treatment for the management of mild or moderate plaque psoriasis.

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