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Percutaneous absorption risks in atopic dermatitis

DOI: 10.1111/bjd.15439

Linked Article: Halling-Overgaard et al. *Br J Dermatol* 2017; **177**:84–106.

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that occurs most frequently in childhood.¹ Skin barrier impairment is observed in both lesional and nonlesional skin in patients with AD.¹ Application of petrolatum-based topicals has been shown to induce expression of key barrier differentiation markers (filaggrin and loricrin), upregulate antimicrobial peptides, reduce T-cell infiltrates and increase stratum corneum thickness, in 'normal-appearing' nonlesional AD skin.² Barrier deficits improve with topical emollients in conjunction with agents to decrease inflammation [e.g. topical corticosteroids (TCS) and calcineurin inhibitors], which has led to the routine use and subsequently increased opportunity for systemic absorption of these topicals.

The data shown in this study demonstrate enhanced penetration of surfactants into the skin in patients with AD, with specific mention of sodium lauryl sulfate. Notably, surfactant-containing formulations perturb skin barrier function proportional to penetration and permeation.³ Furthermore, inflamed skin enhances sensitization of less potent allergens⁴ such as cocamidopropylbetaine and cocamide diethanolamine, which are reported to cause allergic sensitization in AD.^{5–7}

Halling-Overgaard et al.¹ systematically evaluated studies that investigated skin absorption of various penetrants, including medicaments and emollient-based chemicals, in patients with AD. Of the 40 articles that met inclusion criteria, there were 11 human studies examining model penetrants and 26 human studies examining AD pharmacological agents. In particular,

the investigators reviewed the potential systemic effects of long-term and high-potency TCS and noted that patients with severe AD and the very young (< 18 months) appeared to have increased absorption compared with mild–moderate AD and older patients. Furthermore, there was not only a positive association with adrenal insufficiency, but an increasing association between TCS and new-onset type-2 diabetes with duration of use.⁸ The authors proceed to conclude that patients with AD have nearly two-fold increased skin absorption when compared with healthy controls.

Furthermore, as Juhlin et al.⁹ noted, the eutectic mixture of prilocaine and lidocaine had over five times the skin absorption in lesional skin of AD when compared with normal controls. They found that 1–2 h after application on a skin test site of 25–100 cm², the plasma concentrations in the general circulation were 50–450 ng mL^{−1} in patients with AD vs. nondetectable in healthy controls (< 10 ng mL^{−1}). While the plasma levels in the general circulation were 100 times lower than those associated with toxicity, it is important to note that this was after a single 1–2-h monitored application. The 'over-the-counter' availability of topical lidocaine in the U.S.A. in products marketed for itch control presents a significant consideration for patients with AD, especially for children, with their higher skin surface-to-volume ratio.

A crucial message is that given two-fold higher absorption, patients with AD are at higher risk of toxicity from topical products. This study highlights the need for future experimental studies to examine the risk from cumulative exposures. It is possible that chronic exposure to irritants may lead to a hardening that mitigates the increased absorption shown in studies with acute exposure. More studies are needed regarding the topical use of toxic or endocrine-disrupting chemicals in patients with AD.

Acknowledgment

The author would like to express gratitude to Dr Susan Nedorost for her academic discourse and important comments.

Conflicts of interest

None to declare.

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A new potential option for topical treatment of basal cell carcinoma?

DOI: 10.1111/bjd.15652

Linked Article: Gilbert et al. *Br J Dermatol* 2017; **177**:117–124.

Basal cell carcinoma (BCC) is the most common cancer in light-skinned people.¹ With its incidence increasing, BCC imposes a major burden on affected populations in terms of years lost to disability and cost to healthcare systems.¹ Treatment is guided by factors related to the tumour and patient.² Limited topical treatment options exist for BCC, harnessing blunt, nonspecific mechanisms of action, causing substantial local adverse effects (AEs) and reliably clearing small, relatively superficial lesions only.^{3,4}

In this issue of the *BJD*, Gilbert et al. report on a multicentre, open-label, phase 1 clinical trial involving a novel 10% ointment, BIL010t, composed of polyclonal, animal-derived IgG antibodies to nfP2X₇, a receptor expressed by several cancers including melanoma and BCC.⁵ P2X₇ forms a nonselective cation channel in response to sustained concentrations of adenosine triphosphate (ATP), ultimately resulting in apoptosis. Affected tumour cells express a nonfunctional variant of the receptor (nfP2X₇) and a corresponding epitope (E200) absent on nontumour cells. E200 represents the precise target of BIL010t.

In the trial, 21 patients with primary nodular or superficial BCC ≤ 2 cm in diameter for which Mohs surgery was not indicated and for which diagnosis was made with biopsy removing ≤ 25% of the lesion were enrolled. Affected sites included trunk, upper extremities, neck and face. After a biopsy-healing period of 3–4 weeks, participants applied BIL010t to tumour and surrounding skin twice daily for

28 days, at which point all lesions were excised and evaluated microscopically.

Of the 20 participants completing the trial (one lost to follow-up), 11 reported mostly mild local AEs at the application site, including erythema (10 participants – three reported severe erythema), dryness (seven participants), pruritus (five participants) and pain (three participants). Minimal systemic absorption of BIL010t was detected.

After 28 days of treatment with BIL010t, 65% of BCCs decreased in gross size, while 20% showed no change and 15% increased in size. Histological examination of the excision specimens revealed no tumour in three cases, evidence of partial regression in nine cases, and a peritumour lymphocytic infiltrate in the remaining cases. Interestingly, no apparent relationship existed between change in gross size and histological evidence of regression. The influence of anatomical site or histological type of BCC on response was not formally evaluated.

BIL010t shows some promise as a topical treatment option for BCC. The mechanism of action is more targeted than available topical alternatives, although not entirely specific to BCC, raising the possibility of application to other skin cancers with nfP2X₇ expression. Local AEs, experienced by over 50% of participants, were mostly mild, were likely influenced by a broad area of application (25 cm² around the biopsy site), and compare favourably with topical agents currently available for BCC.

Concerns remain about efficacy: only 65% of BCCs treated with BIL010t showed reduction in gross size. By contrast, imiquimod 5% cream, a well-established topical agent, clears 70–80% of BCCs comparable with those in this trial.³ Further, the clinical relevance of the histological end points used in the trial remains uncertain, given that they did not correspond well with gross changes in tumours. Finally, BCCs with more aggressive histological growth patterns or from higher-risk anatomical sites were excluded. Hopefully, these concerns will be addressed with subsequent trials focusing primarily on efficacy.

Acknowledgments

Suephy Chen MD MS and Travis Blalock MD for thoughtful reviews of this manuscript.

Conflicts of interest

None to declare.

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