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Skin permeation and penetration of crisaborole when coapplied with emollients

To the Editor: Atopic dermatitis (AD), a chronic inflammatory skin disease characterized by eczematous lesions and pruritus, is prevalent worldwide.[1] Crisaborole ointment 2% is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild to moderate AD.[2] Although moisturizers are often used in combination with topical therapies to reduce xerosis and aid in skin barrier repair,[3] their effect on topical drug permeation and penetration when coapplied is not well understood. The objective of this study was to assess the effect of over-the-counter (OTC) cream and ointment moisturizers on the permeation and penetration of crisaborole.

Crisaborole was applied (10 mg/cm^2) to ex vivo healthy abdominal human skin (3 donors, 4 replicates, sliced to a thickness of 500 ± 50 μm with a dermatome) either alone, 15 minutes before, immediately after, or 15 minutes after application of OTC cream (Cetaphil; Galderma Inc, Baie d'Urfé, Montréal, Canada) or OTC ointment (Aquaphor; Beiersdorf Inc, Wilton, CT). The skin was mounted in a flow-through diffusion cell, and the receptor solution (phosphate-buffered saline) was collected at 2-hour intervals up to 24 hours. The amount of crisaborole delivered into the skin and through the skin into the receptor solution was determined by liquid chromatography–tandem mass spectrometry.

When crisaborole was applied 15 minutes before either OTC cream or ointment, there were no statistical differences in the concentration of crisaborole in the receptor solution or the dermis (Figs 1 and 2). However, when crisaborole was applied immediately after OTC cream, the concentration of crisaborole was significantly decreased by approximately 3-fold in the receptor solution (Fig 1, *A*) and 2-fold in the dermis (Fig 2, *A*) compared with crisaborole alone ($P < .05$ for both). Similar results were observed for the epidermis. Application of crisaborole 15 minutes after OTC cream resulted in no statistical difference in the concentration of crisaborole in the receptor solution (Fig 1, *A*) or in the epidermis and dermis (Fig 2, *A*). When crisaborole was applied immediately after OTC ointment, there was no statistical difference in the concentration of crisaborole in the receptor solution (Fig 1, *B*) or in the epidermis and dermis (Fig 2, *B*). However, when crisaborole was applied 15 minutes after OTC ointment, the concentration of crisaborole decreased by approximately 2-fold in both the receptor solution (Fig 1, *B*) and the epidermis (Fig 2, *B*) ($P < .05$ for both).

There are limited data regarding the effect of coapplication of moisturizers and topical treatments.[4,5] Here, we show, using an ex vivo model, that the time between applications can affect drug penetration and permeation. The current findings in an ex vivo model suggest that crisaborole should be applied at least 15 minutes before OTC ointments and creams to minimize the impact on dermal absorption of crisaborole. The current study was limited by the use of ex vivo skin from patients without AD, although this approach is a suitable tool for demonstrating the bioequivalence of topical dosage forms.[6,7] The relationship between the results in this ex vivo study and clinical efficacy, as well as the applicability to other OTC moisturizer formulations, requires further investigation.

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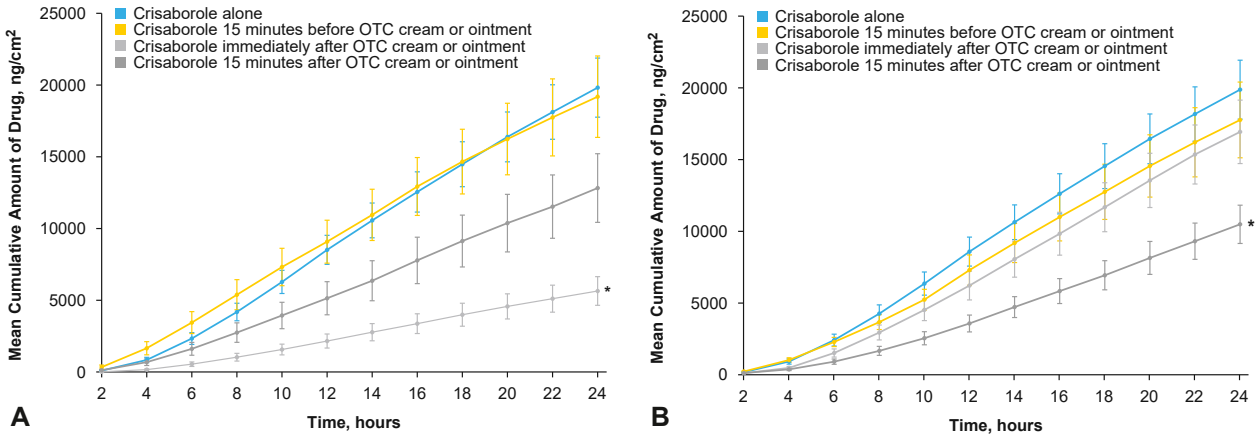

Fig 1. Cumulative amount of crisaborole in receptor solution 24 hours after application alone, 15 minutes before, immediately after, and 15 minutes after application of (**A**) OTC cream and (**B**) OTC ointment. *$P < .05$ versus crisaborole alone. *OTC*, Over the counter.

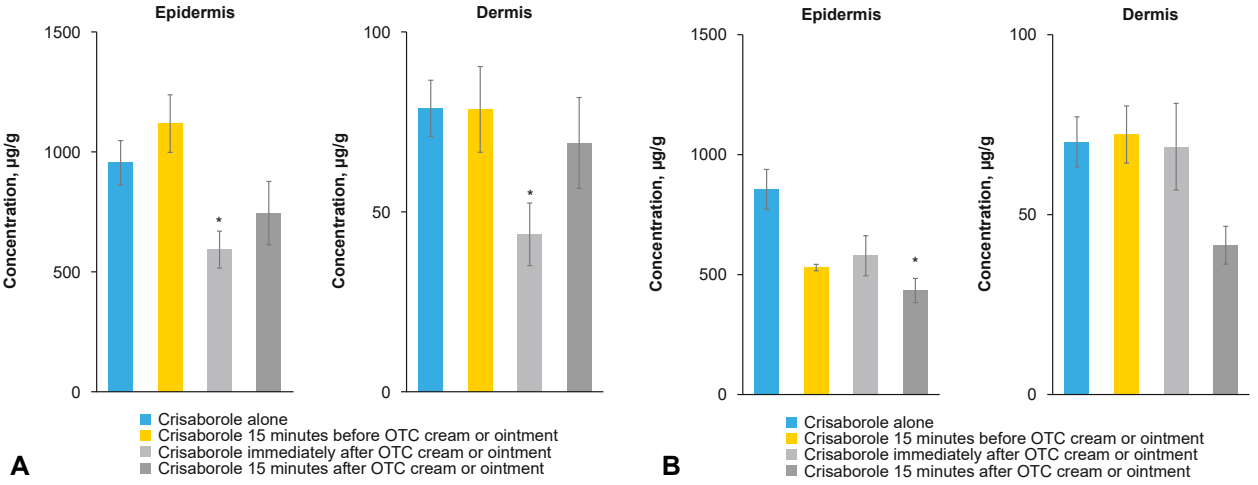

Fig 2. Mean concentration of crisaborole recovered from epidermis and dermis 24 hours after application alone, 15 minutes before, immediately after, and 15 minutes after application of (**A**) OTC cream and (**B**) OTC ointment. *$P < .05$ versus crisaborole alone. *OTC*, Over the counter.

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Mohs micrographic surgery for penile carcinoma with urethral invasion: A multidisciplinary approach

To the Editor: The tumor-node-metastasis classification of penile cancer was first described in the 1988 third edition of the American Joint Committee on Cancer's (AJCC's) *Cancer Staging Manual*. Initially, urethral invasion was considered to be T3 disease and, thus, was often treated with partial or complete penectomy that achieved satisfactory oncologic outcomes but yielded poor cosmetic, functional, and psychological results. With the updates in the eighth edition of the AJCC *Cancer Staging Manual*, first available for comments in 2016, tumor-node-metastasis staging is now independent of urethral involvement.[1] Urethral invasion without involvement of the corpora is defined as a low- or intermediate-risk tumor (Tis, Ta, T1a) and is not associated with a worse prognosis than that of a similar tumor without urethral invasion.[1,2]

The AJCC guidelines now support the use of penile organ-sparing Mohs micrographic surgery (MMS) for Tis, Ta, and T1a tumors with urethral invasion.[3] Currently, however, little is known about the surgical and functional outcomes after MMS for these tumors. We present our experience with 6 patients presenting with low-risk penile cancer and urethral extension treated with MMS followed by urologic reconstruction.

Six patients with penile carcinoma and urethral invasion who received MMS were retrospectively identified (Table I). Before MMS, a Foley catheter was placed to allow for urethral dissection, reconstruction, and healing. All patients received a ventral meatotomy and, if needed, a urethotomy, at the time of the first Mohs layer. In 4 of the 6 patients, the entire tumor, including the urethral invasion, was cleared with 2 or 3 MMS stages. Because of persistent proximal urethral involvement on Mohs frozen sections in 2 patients, a distal urethrectomy was done at the time of urologic reconstruction to achieve a negative margin, which was confirmed on intraoperative frozen sections and with permanent histology. Urologic reconstruction was performed 1 day after MMS and included urethroplasty with neomeatus (n = 5), glansplasty (n = 4), and advancement flap (n = 1). The postoperative care was uncomplicated in all patients. With a median follow-up time of 20.5 months (range: 10-26 months), all patients are recurrence free and have expressed great satisfaction with form and functionality. All but 1 can urinate standing, and all 6 have retained sexual function with the ability for sexual penetration (Fig 1).

Because of the low incidence of penile carcinomas (2120 cases in 2017), no randomized controlled studies have examined MMS for penile tumors.[4] To date, 4 case series have reported on using MMS for penile carcinoma, including Mohs et al (N = 35), Brown et al (N = 20), Shindel et al (N = 30), and Machan et al (N = 42).[5] Within these case series, MMS was attempted in 4 patients with urethral invasion, and in accordance with our findings, no tumor recurrence was reported at 4 to 91 months of follow-up.[5] Similar to the existing literature, the current study is limited by its retrospective design, the small number of patients, the short follow-up time, and the absence of validated instruments for functionality assessments. To our knowledge, our study represents the largest reported cohort of patients, to date, to receive MMS for penile carcinoma with urethral involvement.

In conclusion, MMS completely cleared 4 out of 6 early penile squamous cell carcinomas with urethral invasion. In 2 cases, the entire cutaneous involvement and distal urethral involvement were cleared with MMS, but further proximal urologic urethral resection was needed at the time of urologic reconstruction. Form and function were mostly preserved in all cases. Although small, the study adds to our understating of MMS as an effective, low-morbidity treatment for penile carcinoma and supports the use of MMS for patients with low- and intermediate-risk penile cancer with urethral invasion.

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