Allergic Contact Dermatitis from Luliconazole: Implication of the Dithioacetal Structure

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Sir,

Allergic contact dermatitis caused by topically applied agents is a problem that physicians seek to avoid during the treatment of skin diseases. In this report, we present a case of allergic contact dermatitis caused by luliconazole, an imidazole anti-fungal drug. Patch testing suggested that luliconazole sensitivity might have been attributable to its dithioacetal structure and revealed that lanoconazole-sensitive individuals have a high risk of luliconazole sensitivity.

CASE REPORT

A 65-year-old woman had been diagnosed with chromomycosis due to *Phialophora verrucosa* at the age of 14 years. She had been treated with a variety of systemic anti-mycotic drugs, such as fluconazole, itraconazole, amphotericin B and voriconazole. Her skin lesions had partially improved, but complete remission could not be obtained. In addition to the systemic treatment, the patient was therefore started on a regimen of topical luliconazole cream (Lulicon® cream 1%, Kayaku Co., Ltd). Two days after starting luliconazole, itchy erythema and papules appeared at the application site (Fig. 1A).

Patch testing showed a positive reaction to luliconazole at 2 and 3 days after application. Since the patient also reported a history of contact dermatitis from lanoconazole cream used for the treatment of tinea pedis, we attempted to evaluate the antigenic epitope causing the allergic reaction. Patch testing with a panel of anti-fungal agents revealed a positive reaction for luliconazole and lanoconazole only (Fig. 1B, Table I). Other ingredients of the luliconazole cream (dibutyl hydroxytoluene, stearic acid, cetostearyl alcohol, propylene glycol, benzyl alcohol, polysorbate 60, isopropyl myristate, methyl p-hydroxybenzoate and petrolatum) had negative results on patch testing (data not shown). Because luliconazole and lanoconazole have a similar chemical structure (Fig. 2), the patient was considered to have been sensitized with lanoconazole and to have cross-reacted with luliconazole, resulting in the allergic contact dermatitis.

DISCUSSION

Luliconazole is a recently developed imidazole anti-fungal agent. Although allergic contact dermatitis due to imidazole anti-fungal agents is not uncommon, no reports concerning luliconazole-induced contact dermatitis have been published. The patient presented herein exhibited allergic reactions to both luliconazole and lanoconazole. Patch testing with a panel of anti-fungal drugs revealed no cross-reaction with imidazole anti-fungal drugs that had a β-substituted 1-phenethyl imidazole (β-SPI) structure, which is known to be one of the important determinants of imidazole-induced allergic contact dermatitis (1). In addition, it was unlikely that a vinyl base was an antigenic determinant, as the

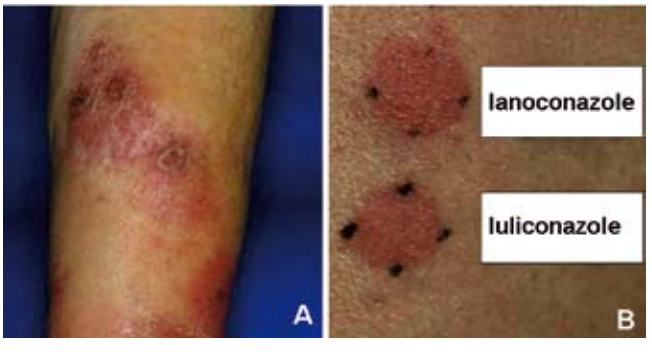

Fig. 1. Clinical manifestations and cross-reactivity of luliconazole and lanoconazole. (A) Severe erythema and small papules were observed around ulcerated nodules of chromomycosis on the forearm. (B) Patch testing with 1% luliconazole and 1% lanoconazole. Control patch testing with petrolatum was negative.

Table I. *Patch test results*

Drug tested	Classification	Day2	Day3
Luliconazole (1% pet.)	vinyl imidazole	++	++
Lanoconazole (10% pet.)	vinyl imidazole	++	++
(1% pet.)	vinyl imidazole	++	++
Neticonazole cream	vinyl imidazole	–	–
Ketoconazole cream	β-SPI	–	–
Miconazole cream	β-SPI	–	–
Sulconazole cream	β-SPI	–	–
Bifonazole cream	other imidazole	–	–
Clotrimazole cream	other imidazole	–	–
Butenafine cream	benzylamine	–	–
Terbinafine cream	allylamine	–	–
Liranaftate cream	thiocarbamate	–	–
Petrolatum	–	–	–

Patch tests were performed with Finn chambers and results were evaluated according to ICDRG standards. Petrolatum was used as negative control. β-SPI: β-substituted 1-phenethyl imidazole.

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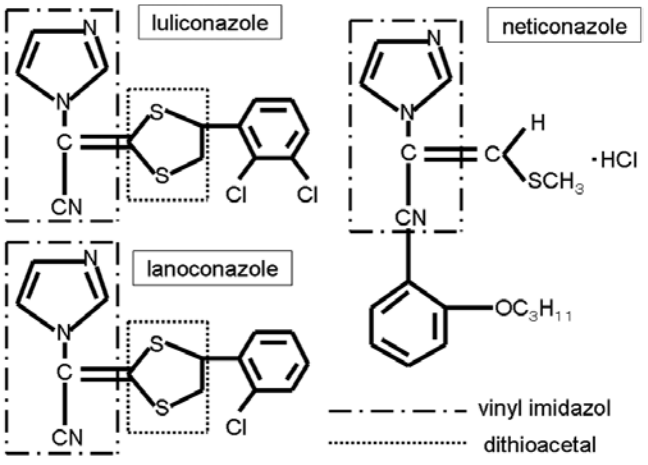

Fig. 2. Similarity in the chemical structure of the vinyl imidazole agents.

present patient did not cross-react with the vinyl imidazole agent neticonazole (Fig. 2, Table I). Consistent with the present case, lanoconazole-sensitive patients have rarely cross-reacted with neticonazole in prior reports (2, 3). It was intriguing to note that luliconazole and lanoconazole have the same dithioacetal chemical structure, which is not present in other imidazole agents (Fig. 2). Although antigenic epitopes of lanoconazole-induced contact dermatitis have not been well defined (4, 5), the present case suggests that the dithioacetal structure is essential for inducing contact dermatitis caused by luliconazole and/or lanoconazole. Hence, at least two major reasons for sensitivity to imidazole anti-fungal drugs should be recognized: β-SPI sensitivity and dithioacetal structure sensitivity, although a requirement of the vinyl base for the latter is uncertain. Luliconazole cream might frequently induce allergic contact dermatitis in individuals who are sensitive to lanoconazole cream, but not to neticonazole cream, due to the dithioacetal structure of the former drug.

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