

Contact Dermatitis Caused by Efinaconazole and Luliconazole

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We report a case of contact dermatitis caused by both efinaconazole, a topical triazole antifungal drug, and luliconazole, a topical imidazole antifungal drug. Positive patch test reactions were observed with efinaconazole and luliconazole. A patch test with lanoconazole also elicited a positive reaction. We hypothesized that structural similarity between luliconazole and lanoconazole led to cross-reaction, and that the dithiolane ring common to both drugs or the structure of the vinyl imidazole with a dithiolane ring could be the antigenic determinant.

Since efinaconazole and luliconazole have no common structures, patients could be sensitized to both drugs separately. The antigenic determinant of efinaconazole is unknown. However, the chemical formula of ravuconazole, an oral triazole antifungal drug, is similar to that of efinaconazole. Clinicians should carefully consider potential cross-reactivity between these drugs.

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Key words: triazole, efinaconazole, luliconazole, contact dermatitis, cross-reaction

Introduction

Efinaconazole topical nail solution, launched in 2014, is Japan's first triazole topical drug for treating tinea unguium. However, oral antifungal agents can have serious side effects, such as liver dysfunction, and they can interact with other drugs, thus limiting their use. Efinaconazole exhibits strong antifungal activity against dermatophytes and excellent penetration to the nail plate; thus, a good therapeutic effect can be obtained by simply applying it to the nail surface. Although efinaconazole is widely used for these reasons, reports of contact dermatitis following its use are rare. Luliconazole, a topical antifungal drug launched in 2005, exhibits the strongest antifungal activity among currently available imidazole topical antifungal agents.

We report a rare case of contact dermatitis resulting from the use of both drugs.

Case Report

A 75-year-old Japanese man applied the efinaconazole solution to his right four toes but they became red and swollen. He then applied white zinc ointment, but visited

our hospital because the eruption did not improve. At the first interview, erythema and scales on his right toes were seen, but microscopic examination for fungus was negative. Contact dermatitis caused by the efinaconazole solution was suspected, and he was treated with topical corticosteroids.

Two months after the first visit, the patient applied the ketoconazole cream and the luliconazole cream to the groin area and the liranaftate cream to both feet. Due to redness and swelling in his left groin area, he stopped application of the ketoconazole cream and the luliconazole cream and revisited our hospital. At that time, he had extensive erythematous papules in the groin, and excoriations, erosions, and bloody exudates were observed on his left thigh and scrotum (**Fig. 1**). Allergic contact dermatitis caused by the ketoconazole cream and the luliconazole cream was suspected. The patient stopped use of both drugs, and his symptoms resolved with topical corticosteroids and oral anti-allergy drugs.

Methods and Results

Contact dermatitis caused by the topical antifungal drugs

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used by the patient was suspected, and, therefore, patch tests were conducted. The antifungal drugs were applied to 'Torii' patchtester, which were then applied to the patient's back for 2 days. Results were checked on Day 2 (D2), D3, and D7 according to the International Contact Dermatitis Research Group (ICDRG) standard. Patch tests of the efinaconazole solution (as is), a triazole topical antifungal drug, and the luliconazole cream (as is), an imidazole topical antifungal drug, were positive (Table 1,



Fig. 1

Clinical appearance of the skin eruptions on the left thigh and scrotum

Fig. 2). Patch tests of the ketoconazole cream (as is) and the liranafate cream (as is) were negative. To confirm cross-reactivity, patch tests with antifungal drugs that the patient had never used were conducted. The patch test with lanoconazole was positive, whereas tests of other topical antifungal agents and antifungal oral medications were negative (Table 1, Fig. 2).

Patch tests of the components of the efinaconazole, luliconazole, and lanoconazole formulations were also conducted, and in each case, the primary ingredient was positive. The patch test results for the other ingredients in each formulation were negative (Table 2).

Discussion

Of the topical imidazole antifungal drugs used by the patient, the patch test was positive for luliconazole, but negative for ketoconazole. Both drugs have no common structure other than the imidazole ring (Fig. 3). Of the topical imidazole antifungal drugs that the patient had not used, the patch test for lanoconazole was positive, whereas other topical imidazole antifungal drugs were negative. Therefore, it appears that the imidazole ring was not the antigenic determinant.

The chemical structures of luliconazole and lanoconazole are very similar, and in many cases, the drugs are cross-sensitizing^{1,2}. In the present case, the patient did not

Table 1 Results of patch tests with antifungal drugs

Group	Allergen (as is)	D2	D3	D7	
triazole	efinaconazole 10% solution*	+?	+?	+	
	itraconazole 50 mg capsule 10% pet.	-	-	-	
	luliconazole	1% cream*	+?	+	++
		1% solution	+	+	++
	ketoconazole	2% cream*	-	-	-
		2% lotion	-	-	-
imidazole	lanoconazole 1% solution	-	+	++	
	neticonazole 1% ointment	-	-	-	
	oxiconazole 1% cream	-	-	-	
	miconazole 1% cream	-	-	-	
	bifonazole 1% cream	-	-	-	
	clotrimazole 1% cream	-	-	-	
thiocarbamate	liranafate 2% cream*	-	-	-	
allylamine	terbinafine 1% cream	-	-	-	
	control (petrolatum)	-	-	-	
	control (aqua)	-	-	-	

*: topical antifungal drugs used by the patients (ICDRG standard)

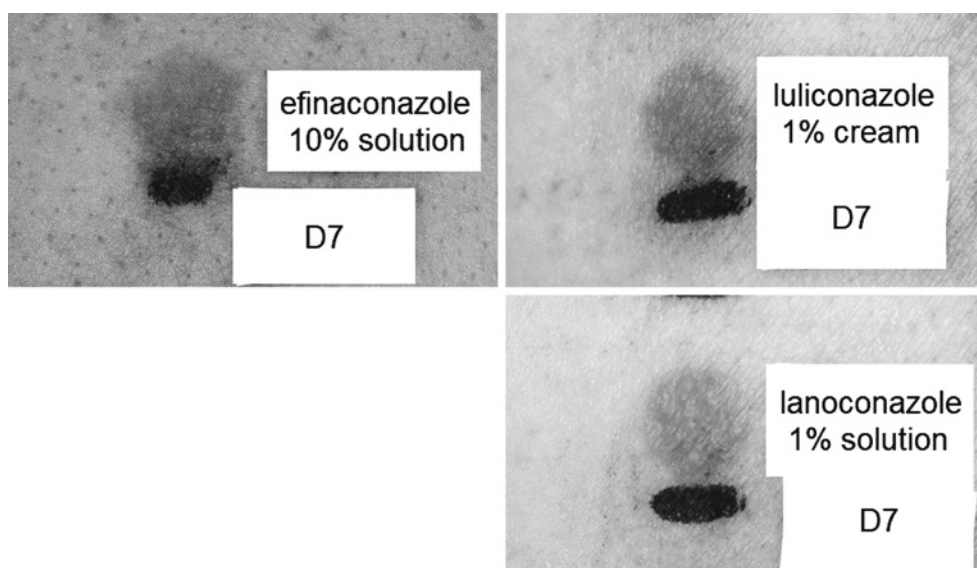


Fig. 2

Positive patch test reactions to the efinaconazole 10% solution (as is), the luliconazole 1% cream (as is), and the lanoconazole 1% solution (as is) on D7

Table 2 Results of patch tests with the components of the efinaconazole, luliconazole, and lanoconazole

Allergen		D2	D4	D8
efinaconazole	10% etoh	-	+?	+
	1% etoh	-	+	+
	0.1% etoh	-	-	-
other ingredients of efinaconazole 10% solution (decamethylcyclopentasiloxane, diisopropyl adipate, emulsified alkyl, dibutyl hydroxytoluene, anhydrous citric acid, sodium edetate hydrate, ethanol)		-	-	-
luliconazole	1% pet.	-	+	+
	0.1% pet.	-	+	+
	0.01% pet.	-	-	-
other ingredients of luliconazole 1% cream (dibutyl hydroxytoluene, sorbitan stearate, cetostearyl alcohol, medium chain fatty acid triglyceride, propylene glycol, benzyl alcohol, polysorbate 60, isopropyl myristate, methyl paraoxybenzoate)		-	-	-
lanoconazole	1% pet.	-	+	+
	0.1% pet.	-	+	+
	0.01% pet.	-	-	-
other ingredients of lanoconazole 1% solution (macrogol 400, methyl ethyl ketone, ethanol)		-	-	-
control (petrolatum)		-	-	-
control (ethanol)		-	-	-

(ICDRG standard)

use lanoconazole, but was suspected of having been cross-sensitized by luliconazole. We hypothesized that the dithiolane ring common to both drugs, or the struc-

ture in which the vinyl imidazole has a dithiolane ring, was the antigenic determinant (Fig. 3)². The structure of neticonazole also contains a vinyl imidazole, but the

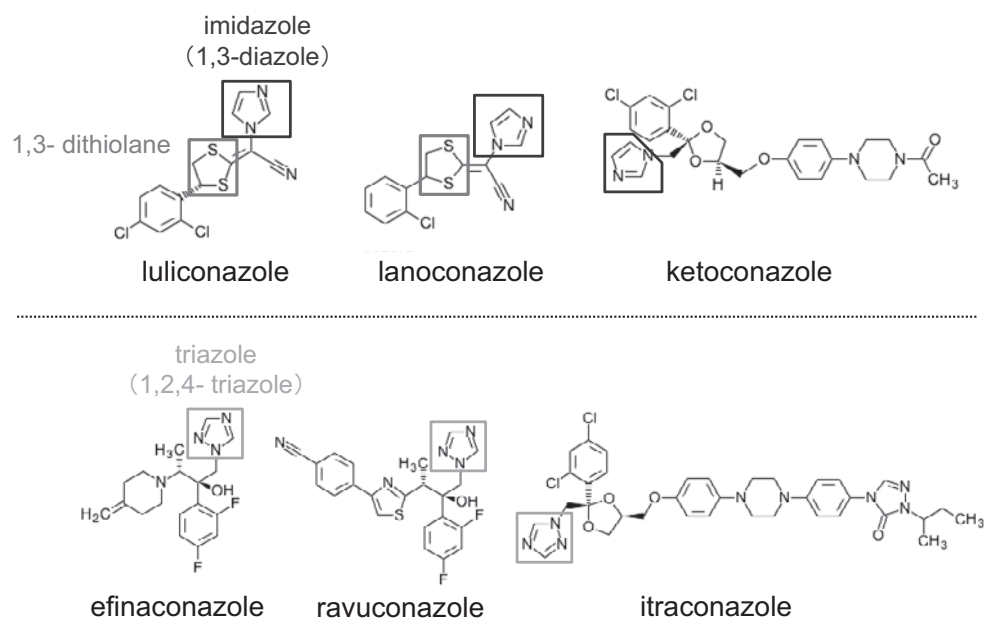


Fig. 3
Chemical structures of imidazole and triazole

Table 3 Cases of contact dermatitis caused by efinaconazole

Author	Age	Sex	The drugs used	Positive patch test	Negative patch test
Hirohata	64	M	efinaconazole ketoconazole	efinaconazole	ketoconazole luliconazole terbinafine
Nishikawa	60	M	efinaconazole	efinaconazole	(not tested)
Yamaguchi	66	M	efinaconazole luliconazole	efinaconazole	luliconazole
Oiso	74	M	efinaconazole bifonazole terbinafine	efinaconazole luliconazole	terbinafine ketoconazole bifonazole liranaftate
Nishioka	57	F	efinaconazole	(unknown)	(unknown)
Our case	75	M	efinaconazole luliconazole ketoconazole liranaftate	efinaconazole luliconazole lanoconazole	(see Table 1)

patch test for this drug was negative.

Only six cases of contact dermatitis caused by efinaconazole use have been reported, including the present one (Table 3)³⁻⁷. Although the main ingredient of the efinaconazole solution is present at a high concentration (10%), it was thought that it is less susceptible to causing sensitization than other antifungal drugs because external application is limited to the periungual area. Luliconazole was used in 2 of the 6 cases of contact dermatitis reported in the literature, but only in the present case was the luliconazole patch test positive. Since there is no chemical structure common to both efinaconazole and

luliconazole (Fig. 3), it was thought that sensitization to the drugs occurred separately. Oiso et al. reported a positive patch test for unused luliconazole⁵. They suggested the possibilities that the patient was hypersensitive or that there was cross-sensitization between efinaconazole and luliconazole. In addition, in the present case, the patch test for itraconazole, the oral triazole antifungal drug that the patient had never used, was negative. Although the antigenic determinant of efinaconazole is unknown, the chemical structure common to efinaconazole and itraconazole is only the triazole ring (Fig. 3), and it was thought that the triazole ring is not an antigenic de-

terminant.

Ravuconazole, a recently launched oral triazole antifungal drug, has a major part of its structural formula in common with efinaconazole. Both drugs have a common structure of {2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol}, which is different from itraconazole (Fig. 3). Therefore, clinicians should carefully consider the possibility of cross-sensitization with these drugs.

Conflict of Interest: The authors declare no conflict of interest.

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