

Severe vulvovaginal allergic contact dermatitis due to clotrimazole contained in multiple topical products

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Running head: allergic contact dermatitis due to clotrimazole

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Imidazoles are fungistatic drugs which inhibit the biosynthesis of ergosterol; they are used worldwide in topical and systemic preparations. We report a case of vulvovaginal contact dermatitis due to multiple exposure to clotrimazole.

Case report

A 56-year-old woman underwent gynecological examination for burning and vaginal discharge; suspecting a mycotic infection, topical medicaments were prescribed. At first she applied Gynocanesten cream (containing clotrimazole) which caused a worsening of the vulvovaginal discomfort, then Meclon cream (clotrimazole plus metronidazole) in association with the use of Meclon vaginal solution, containing the same active ingredients, in two different bottles, to be mixed before use. After three days she developed a severe erythematous, edematous and itching vulvovaginitis. She denied having used tampons, sanitary napkins, condoms and other topical ointments.

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Patch tests with the SIDAPA (Società Italiana Dermatologia Allergologica Professionale Ambientale) baseline series (F.I.R.M.A., Florence, Italy), personal topical products, clotrimazole 1% pet. and also miconazole 2% pet. were performed. As metronidazole was not available as standardized allergen, the patient was patch tested with metronidazole pill powder 30% pet.¹. Patch test chambers (Van der Bend, Brielle, The Netherlands) were applied in occlusion on the patient's back for 2 days. Readings were performed at day (D) 2 and D3 following the Italian guidelines in patch testing². The patient showed positive reactions to *p*-phenylenediamine 1% (-/++), benzocaine 5% (-/+), *Myroxylon pereirae* resin 25% (-/+), and textile dye mix 6.6% (-/+), all in pet. Results of patch test reaction to the patient's topical products and the three imidazoles are shown in Table 1. Vulvovaginal allergic contact dermatitis to clotrimazole was diagnosed.

Discussion

Allergic contact dermatitis due to imidazoles is regarded infrequent considering their high prescription rates. Among the imidazoles, miconazole, a phenethyl imidazole, is the most frequent contact sensitizer³. Clotrimazole is a synthetic, broad-spectrum, phenmethyl imidazole. Since the first report in 1978,⁴ only a few cases of contact allergy to clotrimazole have been reported, sometimes involving the anogenital area^{5,6}.

As in our case, in the majority of published cases clotrimazole does not cross-react with other imidazoles and this is due to their different chemical structure. Cross-reactions between clotrimazole and miconazole were observed in only 3 out of 105 reviewed cases⁵. In our patient no positive reactions were observed to metronidazole (a nitroimidazole), a component of the vaginal solution used by the patient. Izu et al reported cross-reactions between metronidazole and two other imidazoles (bifonazole and tioconazole)⁷, however Madsen et al described a case of allergic contact dermatitis to metronidazole without cross-reactions with other azoles.⁸

Recently some cases of positive patch test reactions to both imidazoles and isothiazolinones have been reported; a possible cross-reaction between the two molecules has been hypothesized⁹. In our patient, in spite of multiple positive reactions to different allergens, isothiazolinones did not elicit positive reactions. We emphasize the importance of performing patch tests with different imidazoles in patients with a demonstrated sensitization to any derivative in order to define an appropriate, alternative, topical treatment.

References

1. Barbaud A, Gonçalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis*. 2001; 45:321-328.
2. Stingeni L, Bianchi L, Hansel K et al. Italian Guidelines in Patch Testing - adapted from the European Society of Contact Dermatitis (ESCD). *G Ital Dermatol Venereol*. 2019; 154:227-253.
3. Abhinav C, Mahajan VK, Mehta KS, Chauhan PS. Allergic contact dermatitis due to clotrimazole with cross-reaction to miconazole. *Indian J Dermatol Venereol Leprol*. 2015; 81:80-82.
4. Roller JA. Contact allergy to clotrimazole. *Br Med J*. 1978; 2:737
5. Dooms-Goossens A, Matura M, Drieghe J, Degreef H. Contact allergy to imidazoles used as antimycotic agents. *Contact Dermatitis*. 1995;33:73-77
6. Pullen KS, Warshaw EM. Vulvar allergic contact dermatitis from clotrimazole. *Dermatitis*. 2010; 21:59-61
7. Izu R, Aguirre A, González M, Díaz-Pérez JL. Contact dermatitis from tioconazole with cross-sensitivity to other imidazoles. *Contact Dermatitis*. 1992; 26:130-131.
8. Madsen JT, Thormann J, Kerre S, Andersen KE, Goossens A. Allergic contact dermatitis to topical metronidazole - 3 cases. *Contact Dermatitis*. 2007; 56:364-366.
9. Stingeni L, Rigano L, Lionetti N et al. Sensitivity to imidazoles/nitroimidazoles in subjects sensitized to methylchloroisothiazolinone/methylisothiazolinone: a simple coincidence? *Contact Dermatitis*. 2019; 80:181-183

Table 1. Patch test results on day 2 and day 3 to the patient's topical products and imidazole allergens.

| Patient's own products, tested "as is" | patch test results |
|---|---------------------------|
| Gynocanesten cream | ++/+++ |
| Meclon cream | -/++ |
| Meclon vaginal solution containing metronidazole (bottle 1) | -/- |
| Meclon vaginal solution containing clotrimazole (bottle 2) | + /+++ |
| Meclon vaginal solution prepared according to instruction for use, mixing 1 and 2 | + /++ |
| Imidazole allergens | patch test results |
| Clotrimazole 1% pet. | + /+ |
| Miconazole 2% pet. | - /- |
| Metronidazole 30% pet. | - /- |