

## Metronidazole Hypersensitivity in a Patient with Angioedema and Widespread Rash

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Metronidazole is a 5-nitroimidazol compound introduced in 1959 to treat *Trichomonas vaginalis* infections. It shares a high structural similarity with its derivatives (tinidazole, secnidazole and ornidazole) and is used to treat parasitic infections, alone or in combination with other antibiotics. The drug is usually well tolerated, but may occasionally cause adverse effects: gastrointestinal symptoms, hematological alterations, central nervous system disorders and, rarely, drug rashes [1, 2].

We can also find this drug in face creams or cosmetics and its sensitization may occur after their topical application.

We report herein a case of labial angioedema and widespread erythematous rash in a patient with metronidazole IV-type allergy.

A 45 years-old non-atopic man had an history of labial angioedema and itching widespread erythematous maculopapular rash during metronidazole oral treatment prescribed for a gastrointestinal dysbiosis about ten hours from the third administration. Symptoms disappeared within few hours of administration of intravenously chlorphenamine and methylprednisolone. At the time of the event the patient's blood count was normal without eosinophilia or lymphocytosis;

he did not have any organ involvement, inflammatory markers were normal and he was also afebrile. From that event, he avoided the use of metronidazole in any form.

After three years the patient was admitted to our Allergy Department of Fondazione Policlinico Universitario A. Gemelli IRCCS for an allergological evaluation.

We performed an allergological work-up that included skin prick tests (SPTs) and patch tests with metronidazole according to literature [1, 2]. The SPTs were carried out with metronidazole on the volar area of the forearm at 125 mg/ml in the form of powdered tablets dissolved in saline. Histamine (10 mg/ml) was used as a positive control and saline (0,9%) as a negative control. Patch tests (PTs) were applied to the interscapular region and performed with metronidazole as the one used for prick tests dissolved in petrolatum at a concentration of 0.5 %, 5% and 10% and with the undiluted solution. We also performed both tests in 10 healthy selected patients as controls.

The SPT was negative, while the PTs showed a positive reaction after 72 hours with an erythematous infiltrate of 12 mm at the undiluted solution. All the healthy subjects presented negative results. The same allergological evaluation with other imidazole derivatives (tinidazole, albendazole, mebendazole, tioconazole) showed negative results.

Even if the patient refused to undergo an oral provocation test (OPT), his clinic history and allergy testing results were highly suggestive of a cell-mediated allergy (IV-type reaction) to metronidazole and we recommended the patient to avoid this drug and the other compounds from all the imidazole series for the future.

Hypersensitivity reactions to metronidazole are rare. However they are increasing due to growing use of the drug to treat amebiasis and anaerobe infections combined with other antibiotics.

In literature different cases of hypersensitivity reactions to metronidazole are described: cutaneous adverse reactions such as allergic contact dermatitis [4], fixed drug eruptions [5],

systemic reactions [1-3], respiratory crisis [6, 7], anaphylaxis reactions [2], Stevens-Johnson syndromes/toxic epidermal necrolysis [8], acute generalized exanthematous pustulosis [9] and serum sickness reactions [10].

Most of the systemic reactions described are not confirmed by allergy testing, except for some cases of immediate reactions established by positive SPT [1, 2]. Instead, most reactions to this drug confirmed by positive PTs were essentially allergic contact dermatitis in patients sensitized to topical metronidazole for the treatment of rosaceous acne [4] or fixed drug eruptions [5].

In our case, the patient did not have family or personal history of allergy or contact dermatitis. Since we were not able to establish from the clinical history the timing of the reaction, we decided to perform both SPTs and PT. Based on the different experience described in literature for PT, we used the tablet of metronidazole (Flagyl®) crushed and dispersed initially at 0.5%, 5% and 10% and finally, since the previous negative results, in the pure form. To exclude false positives, we performed the same test in 10 healthy subjects with negative results. In literature, the majority of the positive PTs with metronidazole were obtained from a fixed exanthema residual lesion. In this case we described another form of delayed systemic reaction proved with a positive PT after oral metronidazole administration.

The low sensitivity of SPTs and PTs with metronidazole and their lack of standardization makes it difficult to diagnose a metronidazole allergy. OPT still is essential for the diagnosis of early and delayed hypersensitivity reactions [1], even if it is not always feasible for ethical reasons. In a previous study [1], the authors presented four cases of cutaneous exanthemas (two early and two delayed). Only one patient showed a positive metronidazole SPT (all epicutaneous tests were negative). OPT with metronidazole proved positive in the 3 patients with negative SPT: a delayed exanthema in the first patient and an early erythema and itching in the other two. According to these results, this test could be considered the “gold standard” for establishing the diagnosis of

metronidazole hypersensitivity reactions. In our case the patient denied previous treatment with oral or topical metronidazole but since the reaction was delayed we suppose a possible sensitization during the oral treatment. Furthermore, since cross-reactions with other imidazole derivatives were showed in literature, we can't exclude an indirect sensitization to metronidazole through the use of other cross-reactive molecules. The imidazole derivatives are commonly found in many cosmetics and it is difficult for the patient to remember a possible use of these molecules in the past.

Cross-reactions have been reported between metronidazole and tinidazole [5] and between albendazole and metronidazole by oral challenge. Other authors found a lack of reactivity between metronidazole, tinidazole, tioconazole, albendazole, ketoconazole and mebendazole by epicutaneous tests [2]. In our experience the other imidazole derivatives seem not cross-reactive with metronidazole, but further studies should be performed in order to evaluate their cross-reactivity.

In conclusion, we described a rare case of a different type (angioedema and widespread erythematous maculopapular rash) of delayed systemic reaction to metronidazole after oral administration, without any apparent topical sensitization and confirmed by patch testing.

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### **Conflict of interests**

The authors declare that they have no conflict of interest.

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