Case Report

Skin rash during treatment with generic itraconazole

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ABSTRACT

Generic drugs have the same active substance, the same pharmaceutical form, the same therapeutic indications and a similar bioequivalence with the reference medicinal product (branded). Although a similar efficacy is postulated, some cases of clinical inefficacy during treatment with generic formulations have been reported. In this case, we describe a woman with onychomycosis that developed a skin rash during treatment with a generic formulation of itraconazole. Drug administration and its re-challenge confirmed the association between itraconazole and skin rash. Both Naranjo probability scale and World Health Organization causality assessment scale documented a probable association between generic-itraconazole and skin rash. The switch from generic formulation to brand one induced an improvement of symptoms. Since we are unable to evaluate the role of each excipient in the development of skin rash, we cannot rule out their involvement. However, more data are necessary to better define the similarities or differences between branded and generic formulations.

Key words: Brand-itraconazole, generic-itraconazole, onychomycosis, skin rash

INTRODUCTION

Generic drugs are equivalent to brand formulation if they have the same active substance (with a difference of ± 5%), the same pharmaceutical form and the same therapeutic indications and a similar bioequivalence (±20%) with the reference medicinal product (Law no. 425/1996 in G.U. no. 208 of 05.09.1996. legislative decree no. 219/06).[1] Even if generic drugs contain the same active ingredients as the branded counterparts, they could be different as far as excipients are concerned.[2]

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In addition, it has been estimated that the switch from brand to generic formulation induces benefits in about 30% of the treated patients while about 30% did not experience any benefit, about 10% complained side-effects and about 30% discontinued treatment due to clinical inefficacy or development of side-effects.[3] In agreement recently Paveliu *et al*.[4] documented that the brand-generic switch may be critical in the presence of drugs with narrow therapeutic index.

Three cases of clinical inefficacy after the switch from brand itraconazole to its generic formulation have been reported.[5] In this case we are reporting on a patient that developed a skin rash during treatment with generic itraconazole.

CASE REPORT

A 49-year-old woman (high 155 cm, weight 52 kg), without previous history of drug or alcohol abuse or allergies, had been

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brought to her general practitioner for an infection on her left foot. Clinical and microbiological evaluation documented a "candida" infection, the diagnosis of onychomycosis was performed and an oral treatment with itraconazole (sporanox® 100 mg tablet twice a day for 10 days and then 100 mg/day for 1 month) was prescribed. About 20 days later, the patient returned to her general practitioner for the persistence of onychomycosis and the development of skin rash on the body.

On examination, her blood pressure was 110/70 mm Hg, heart rate 65 beats/min, respiratory rate 18 breaths/min and temperature 36.2°C. No peripheral lymphonodes were observed. Cardiovascular, abdominal and respiratory relieves were normal. Skin rash examination revealed giant hives associated with sudden itching and an increase in local skin temperature in most of the body parts, regions, especially on the trunk and upper limbs, but without regional positive lymphonodes.

Itraconazole was dismissed and betamethasone (4 mg/12 h for 3 days) was started, with a complete remission of skin rash.

About 5 days later, due to the impairment of onychomycosis, the patient takes again itraconazole and develops the skin rash.

History excluded allergic manifestations related to drugs, herbal supplements or contacts with chemical agents. A detailed pharmacological evaluation revealed that the patient chose the generic itraconazole (itraconazole Mylan generics®) on the advice of the pharmacist.

Both the Naranjo Probability Scale[6] and the World Health Organization (WHO) causality assessment scale,[7] used to evaluate the relationship between adverse drug reaction (ADR) and drug, documented a probable association between skin rash and itraconazole.

Therefore, itraconazole Mylan generics® was promptly dismissed and a treatment with sporanox® + betamethasone (4 mg/12 h) was started with an improvement of skin rash in few days.

One month later, during the follow-up, a complete remission of onychomycosis was recorded without the development of side-effects.

DISCUSSION

We are reporting on a case of skin rash occurring during treatment with generic formulation of itraconazole.

In our present case, the general practitioner prescribed a branded drug. In agreement with the Italian law (149/2005), the pharmacist must inform the patient on the availability of a lower price formulation and let the patient choose. In the present case, the pharmacist informed the patient that the lower cost formulation of itraconazole available in pharmacy was "itraconazole Mylan generic®" and the patient has taken it and developed the skin rash.

Several factors may be related to the development of side effects, e.g., dispensing error, diseases or drug-drug interactions;[8-20] in our patient, both history and clinical evaluation suggested to excluded these.

Therefore, we postulated that generic formulation of itraconazole may be involved in the development of skin rash.

In fact, the re-challenge with generic-itraconazole induced the development of skin rash while the re-challenge with brand-itraconazole completely improved the onychomycosis without the development of side-effect.

Using Naranjo probability scale and WHO causality assessment scale, we showed a probable relationship between skin rash and generic-itraconazole.

Controversy remains on whether generic drugs are interchangeable with brand-name drugs as far as efficacy and ADRs are concerned.[21] Probably a role in the development of side-effects could be played by pharmaceutical excipients.

Recently, it has been reported that pharmaceutical excipients are not inert ingredients[22] and we have recently documented the lack of efficacy after the switch from brand to the generic formulation of allopurinol.[23]

Although, we are unable to evaluate the role of each excipient in the development of side-effects, in our patient we cannot rule out their involvement in the development of skin rash [Table 1].

Table 1: Excipients present in brand and generic formulations of itraconazole

Capsule		Capsule shell	
Sporanox®	**Itraconazole Mylan generics®**	**Sporanox®**	**Itraconazole Mylan generics®**
Sugar spheres, hypromellose, macrogol	Sugar spheres (sucrose and maize starch), hypromellose (E464), sorbitan stearate (E491), silica colloidal idrata (E551)	Gelatine, titanium dioxide (E171), erythrosine (E127), indigotin (E132)	Gelatine; titanium dioxide (E171), red iron oxide (E172)

CONCLUSION

This case could represent a first point to define the similarities or differences between branded and generic drugs, even if more data are necessary to validate this observation.

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