

Hypersensitivity reactions to metronidazole

Isabel García-Rubio, Consuelo Martínez-Cócer, Sara Santos Magadán, Beatriz Rodríguez-Jiménez and Sonia Vázquez-Cortés

Allergy Department. Hospital Clínico San Carlos. Madrid. Spain.

ABSTRACT

Background: Hypersensitivity reactions to metronidazole are infrequently described. However, we believe that such reactions are increasing due to growing use of the drug for the treatment of amebiasis and anaerobe infections combined with other antibiotics. The present study assesses the need for oral provocation in patients with probable hypersensitivity reactions to metronidazole.

Methods: We performed cutaneous prick tests with spiramycin and metronidazole as well as epicutaneous tests with metronidazole at different concentrations in four patients with cutaneous reactions to Rhodogil® (metronidazole plus spiramycin). Controlled oral challenges were then carried out with placebo using erythromycin, spiramycin and metronidazole except in the last patient due to a positive prick test.

Results: Only one patient showed a positive metronidazole prick test. The epicutaneous tests were negative. All patients tolerated erythromycin and spiramycin up to therapeutic doses. Oral provocation with metronidazole proved positive, the first patient presenting a delayed exanthema and the other two early erythema and itching.

Conclusions: We present four cases of cutaneous exanthemas caused by metronidazole (two early and two delayed) and probably mediated by an immune

mechanism which we have only been able to demonstrate in one case. Taking into account the low sensitivity of the cutaneous tests (prick tests and epicutaneous tests), oral provocation must be considered the "gold standard" for establishing the diagnosis in many cases of hypersensitivity reactions to metronidazole.

Key words: Cutaneous exanthema. Metronidazole. Prick test. Oral provocation. Epicutaneous tests.

INTRODUCTION

Metronidazole is a 5-Nitroimidazol compound introduced in 1959 to treat *Trichomonas vaginalis* infections. It is also used in application to amebiasis and anaerobic infections combined with other antibiotics such as aminoglycosides. It is generally well tolerated despite its wide usage. The most frequent side effects are gastrointestinal disorders (nausea, vomiting, diarrhea and, exceptionally, reversible pancreatitis). Reversible haematological alterations have also been described along with disorders of the central nervous system. More exceptionally there can be cutaneous hypersensitivity reactions for all fixed exanthemas. We present four cases of cutaneous exanthemas due to metronidazole.

MATERIAL AND METHODS

We present four patients with an average age of forty who developed cutaneous itching exanthemas (two early and two delayed) after taking Rhodogil® (125 mg metronidazole and 750.000 IU spiramycin) for mouth infections. Two of them also had facial an-

Correspondence:

Dr. I. García-Rubio
Profesor Martín Lagos, s/n
28040 Madrid. Spain
E-mail: mmartinez.hcsc@salud.madrid.org
igrubio@hotmail.com

gioedema. The symptoms disappeared in all cases with the administration of corticoids and/or antihistamines. None of these patients had consumed alcohol beforehand.

The average time elapsed between the reaction and consultation was seven months with the average accumulated dose of two tablets (table I).

Cutaneous prick tests were carried out with spiramycin and metronidazole at a concentration of 250 mg/ml and 125 mg/ml respectively together with epicutaneous tests with metronidazole at 0.5 %, 5 % and 10 % (readings at 48 and 96 hours). For both tests the ten negative controls were patients with supposed adverse drug reaction, symptoms which were later not confirmed by oral provocation (OP). Simple blind oral provocations were then carried out with placebo according to the established Department protocol with erythromycin, spiramycin and metronidazole at up to therapeutic doses. The last patient was not given OP with metronidazole due a positive prick test.

RESULTS

The prick test for spiramycin and the epicutaneous tests with metronidazole were negative. The prick test with metronidazole was only positive in the last case. All patients tolerated both erythromycin and spiramycin. Oral provocation with metronidazole proved positive in the first patient who developed delayed exanthema while the other two showed erythema and early itching (table II).

Oral provocation with metronidazole proved positive with a total accumulated dose of 250 mg in the first two cases and 500 mg in the third. The first patient presented generalized exanthema after seven hours, with intense itching that improved after twenty-four hours with antihistamines. The second developed facial itching an hour later, in the occipital zone and on the arms, becoming facial erythema and exanthema in the occipital zone. These manifestations disappeared after administering corticoids and antihistamines. The third patient, forty-five minutes later, developed erythema on the chest, cheeks and forehead with intense itching of the palate. These manifestations subsided within one hour after administration of intravenous corticoids and antihistamines. At examination, we observed a discreet swelling of the soft palate.

DISCUSSION

We have presented four cases of cutaneous exanthemas due to metronidazole (two early and two delayed), probably mediated by an immune mecha-

Table I
Characteristics of patients, dose and time between the reaction and consultation

	Sex	Age	Symptoms	Dose*	Months**
1	H	23	Micropapular exanthema arms and back	3	2
2	M	45	Generalised hives	5	8
3	H	47	Generalised exanthema Facial swelling	1 1	6
4	H	47	Micropapular exanthema on face, neck and thighs with later desquamation Oropharyngeal itching and facial angioedema	4	12

*Tablets.

**Time passed between the reaction and the consultation.

Table II
Oral provocation with metronidazole

	Dose (mg)	Time	Symptoms
1	250	7 hr	Generalised itching exanthema
2	250	1 hr	Occipital exanthema and facial erythema with itching
3	500	45 min	Erythema on thorax, cheeks and forehead with swelling and itching on the soft palate

nism which we have only been able to demonstrate in one case.

There are very few published cases of immediate hypersensitivity to metronidazole¹⁻⁴. Rash and itching type reactions have been described, particularly with topical metronidazole for the treatment of rosaceous acne, one case of exanthema similar to pityriasis rosea and two of acute generalized exanthematic pustulosis^{5,6}. In one of them the epicutaneous test with metronidazole at 0.75 % proved positive after seventy-two hours. Some cases have also been published involving serum disease and toxic epidermal necrolysis/Steven-Johnson Syndrome among philippine workers in Taiwan who received high doses of metronidazole combined with mebendazole⁷. However, the majority are cases of fixed exanthemas linked to medication. In some cases positive epicutaneous tests have been recorded with metronidazole at different concentrations^{8,14,15}.

Initially disulfiram-type reactions had been described (Antabus effect) when alcohol had been con-

sumed concomitantly. It is thought that this is due to blocking of the hepatic dehydrogenase aldehyde enzyme and to later accumulation of acetaldehyde in the blood. Two publications have recently questioned this type of reaction but their authors believe it necessary to conduct new studies to corroborate these results^{9,10}. None of our patients had ingested alcohol.

On many occasions it is not easy to determine from the clinical history whether the reaction is mediated by IgE or is a delayed reaction, since the patients do not remember exactly how much time has passed between taking the medication and manifestation of the reaction when the latter is only cutaneous. Furthermore, at the time of consultation, the cutaneous symptoms have disappeared and the patients are not always able to provide the report from at the first medical visit. Thus, it is necessary to carry out cutaneous tests: prick and/or intradermal and epicutaneous tests.

Cutaneous prick tests have been described with different positive antibiotics, though on many occasions there is a lack of information on the methodology used or the clinical symptoms involved¹¹. Despite their great use in confirming the etiopathogenic mechanism of type I reactions, the sensitivity of these tests is not particularly high. We have found no other cases in the literature of positive prick tests for metronidazole.

Regarding the epicutaneous tests with antibiotics, their performance is not as high as in the cases of contact dermatitis¹². Positive results have been described for ECT particularly with certain drugs such as betalactams, antiepileptics drugs, benzodiazepines and nonsteroidal antiinflammatory drugs¹³ but there is a lack of information on other medications. The majority of the positive epicutaneous tests with metronidazole were obtained from a fixed exanthema residual lesion^{8,14,15}.

Two cases have been described of fixed exanthema from tinidazole with positive oral provocation for metronidazole^{16,17}, though other authors have failed to confirm this¹⁸. On also taking into account the high structural similarity between metronidazole and its derivatives (tinidazole, secnidazole and ornidazole), the possibility of cross-reactivity is seen to be very high. For this reason, and because other therapeutic alternatives are available, the possibility of provoking our patients with these derivatives is not considered.

Taking into account the low sensitivity of cutaneous testing (both prick tests and epicutaneous tests), oral provocation appears to be an essential

tool for the diagnosis of early and delayed hypersensitivity reactions to metronidazole. We believe that in our cases, after oral provocation the symptoms did not reappear in the same way as in the initial reaction possibly because joint administration with spiramycin modifies haptenization of the drug after its hepatic metabolism.

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