Non-Immediate Hypersensitivity Reaction to Rifaximin Confirmed With a Drug Challenge Test

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Palabras clave: Exantema maculopapular. Hipersensibilidad a medicamentos. Prueba de provocación con medicamentos. Reacción no inmediata. Rifamicina. Rifaximina.

To our knowledge, we present the first case of a non-immediate hypersensitivity reaction to rifaximin, a broad-spectrum antibiotic increasingly used to treat a variety of gastrointestinal infections over the last decades, confirmed with a drug challenge test (DCT).

Rifaximin is a broad-spectrum antibiotic used against enteric pathogens including gram-positive, gram-negative, aerobic and anaerobic bacteria such as enterotoxigenic and enteroaggregative *Escherichia coli, Salmonella, Shigella, Campylobacter, Plesiomonas,* and *Aeromonas species[*1, 2].It belongs to the rifamycin family, a group of antibiotics synthesized either naturally by the bacterium *Amycolatopsisrifamycinica* or artificially, that include rifampicin (rifampin), rifabutin, rifapentine, rifalazil and rifaximin[3].Unlike other rifamycins, rifamixincontains an additional pyridoimidazole ring, which minimizes systemic absorption and, results in high gastrointestinal concentrations of the drug[3, 4].In the last decades, due to its excellent safety profile, minimal drug interactions and negligible impact on the intestinal microbiome, rifaximin has become more widely used to treat intestinal infections, irritable bowel syndrome (IBS) with small bowel bacterial overgrowth, hepatic encephalopathy in patients with chronic liver disease, and to treat and prevent uncomplicated diverticular disease[4, 5].Despite rifaximin being increasingly used, hypersensitivity reactions to rifaximin

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have been rarely described. To the best of our knowledge we report the first case of a non-immediate hypersensitivity reaction to rifaximin confirmed with a DCT.

We report a case of a 67 year-old female with a medical history of anxiety and depression, chronic diarrhea, IBS with small bowel bacterial overgrowth, two previous episodes of acute diverticulitis, a past papillary thyroid carcinoma treated with surgery and radioactive iodine and mild asthma who was referred to our allergy service for evaluation of an adverse event related to a treatment with rifaximin. After being diagnosed with acute diverticulitis, the patient was prescribed a course of rifaximin400mg every 8 hours. Three hours after the first dose of rifaximin, the patient experienced nausea, vomiting and increasing numbers of diarrheic stools. Despite these symptoms, she continued the rifaximin treatment normally and, on day 4, developed a maculopapular erythematous and pruritic rash over her thorax, abdomen, back and extremities. The patient did not develop fever, blisters, pustules, mucosal involvement, skin hyperpigmentation or desquamation. After discontinuing rifaximin, her skin lesions completely disappeared spontaneous lyin 7 days.

After obtaining the patient´s written informed consent, an allergological work-up including a skin prick test (SPT) and a graded DCT with rifaximin, was carried out. A SPT was performed with rifaximinat 1mg/ml concentration on the volar part of her forearm which had a negative result[6]. On the same day, the patient underwent a DCT, consisting of a graded oral challenge starting at 50mg followed by 150mg 30 minutes later, up to a final dose of 200mg rifaximin. One hour after the DCT, she felt nauseous and presented one diarrheic stool that spontaneously resolved without requiring medication. The DCT was considered inconclusive and repeated 24 hours later. Three

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hours after finishing the second rifaximin DCT, the patient experienced again diarrheic stools and, after 10 hours, developed a maculopapular erythematous and pruritic skin rash on her abdomen and left arm (Figure 1). She was treated with oral prednisone0.5mg/kg/day for 3 days and loratadine 10mg/day for 7 days until the skin lesions completely disappeared without desquamation or leaving any residual lesions.

The rationale to perform an allergological study with rifaximin on the patient, was due to the fact that she had a long history of gastrointestinal infections, where rifaximin is an effective and a first-line therapy. Although reactions to rifamycins, such as fever, rash, flu-like syndrome, acute renal failure, hemolyticanemia, thrombocytopenia and anaphylaxis, have been described in literature[7], few reactions to rifaximin have been reported since it was approved[3, 4].Our patient initially presented gastrointestinal symptoms three hours after receiving the first dose of rifaximin, described as a non-immune adverse effect to rifaximin. She continued the treatment, developing on day 4 a mild maculopapular rash without dangers signs, suggesting a hypersensitivity reaction. However, due to the patient continuing rifaximin treatment through day 4, the drug latency period could not be determined. As a result, the allergological study began with a SPT instead of patch tests because initially the underlying immunological mechanism of the reaction was unclear. The graded rifaximin challenge elicited cutaneous symptoms compatible with the case history; however, an IgE-mediated mechanism could not be demonstrated with skin testing. Antonicelli *et al*. published a case of a patient with IgE-mediated allergies to rifaximin and rifamycin SV in a 64 year-old male that presented two anaphylaxis, one after oral administration of rifaximin and a second after topical use of with rifamycin SV, with a positive serum-specific IgE to rifampicin, rifabutin and rifapentin(8).Patel *et al*. presented a 62 year-old female admitted to the

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hospital with an hepatic encephalopathy episode, and presented a possible toxic epidermal necrolysis (TEN) to rifaximin, but the patient received other possible culprit drugs during admission and a skin biopsy could not be performed to confirm the diagnosis[4].Additionally, Fritz *et al*. described a 42-year-old female with Stevens-Johnson syndrome (SJS)/TEN confirmed with a skin biopsy, most likely due to rifaximin. However, the patient also received other possible culprit drugs such as spironolactone and an allergological work-out to determine the culprit drug was not performed. In this case, skin lesions improved after the patient discontinued both rifaximin and spironolactone [9]. Yang *et al.* aimed to identify possible culprit drugs for SJSand TEN in a nationwide database in South Korea, finding one suspected case with rifaximin[10].

Despite rifaximin being an antibiotic widely used for certain gastrointestinal infections, hypersensitivity reactions have been rarely described. To our knowledge, we present the first case of a non-immediate hypersensitivity reaction to rifaximin confirmed with a DCT, where an IgE-mediated mechanism could not be demonstrated with an allergological study. Due to the similar structure between rifaximin and other rifamycins, if a diagnosis of immediate or non-immediate allergy to rifaximin is made, the avoidance of rifamycin family should be recommended unless specifically ruled out by individual tests.

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Conflict of Interest

The authors have no conflicts of interest to report.

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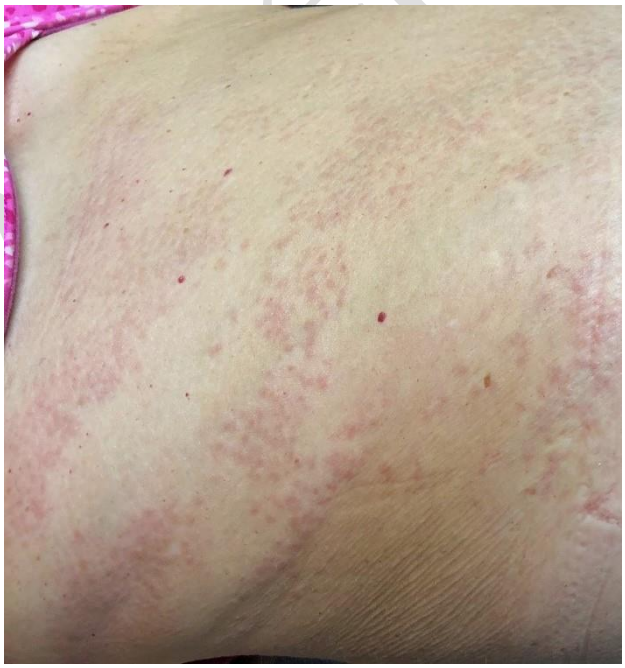
Tables and figures

Figure 1: Maculopapular erythematous and pruritic rash over the patient´s abdomen caused by a rifaximin DCT.



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