# Hypersensitivity to Repaglinide

P Rojas, L Sánchez, A Santos, MP Gómez, H Blanco, JJ Laguna

Allergy Unit, Hospital Central de la Cruz Roja, Madrid, Spain

**Abstract**

Meglitinides (repaglinide and nateglinide) are insulin secretagogues used to treat diabetes mellitus. We present a case of hypersensitivity reaction to repaglinide in a 61-year-old man who developed a maculopapular rash 5 days after treatment.
Skin prick tests including repaglinide (0.5 μg/mL) and patch tests (0.05% in pet and saline) were performed, and the results were negative. A blind oral challenge test with repaglinide was performed and the therapeutic dose was subsequently taken at home every 24 hours for 7 days.
The result was positive with a delayed reaction at day 3. A punch biopsy of the skin lesions revealed drug-induced exanthema.
The clinical manifestations, the latency period, the reappearance of cutaneous lesions after rechallenge, and the histopathology report of the skin biopsy suggest a type IV mechanism.

Key words: Oral antidiabetic drugs. Exanthema. Meglitinides. Repaglinide.

**Resumen**

Meglitinidas (repaglinida y nateglinida) son antidiabéticos orales del grupo de los secretores de insulina aprobados para el tratamiento de la Diabetes Mellitus (DM). Presentamos un caso de hipersensibilidad a repaglinida en un varón de 61 años de edad, que desarrolló un rash máculo-papular 5 días después de iniciar tratamiento con este fármaco.
El estudio alergológico incluyó pruebas cutáneas en prick test con repaglinida (0.5 mgs/ml) y pruebas epicutáneas en parche (0.05%) con repaglinida en vaselina y suero fisiológico. Todas las pruebas cutáneas fueron negativas.
Así mismo realizamos pruebas de provocación con repaglinida y posterior tratamiento domiciliario cada 24 horas por 7 días. El resultado fue positivo con una reacción tardía al tercer día. La biopsia cutánea de las lesiones fue diagnóstica de exantema medicamentoso.
Las manifestaciones clínicas, el tiempo de latencia, la reaparición de las lesiones tras la reprovocación y los cambios histopatológicos de la biopsia cutánea sugieren un mecanismo de hipersensibilidad tipo IV.

Palabras clave: Antidiabéticos orales. Exantema. Meglitinidas. Repaglinida.

## Introduction

Changes in lifestyle that promote obesity and physical inactivity have led to a global increase in the prevalence of diabetes, especially type 2 diabetes mellitus (T2DM), which is one of the most challenging health problems in the 21st century. Several studies suggest that the diabetes epidemic will continue, even if levels of obesity remain constant. The prevalence of diabetes for all age groups worldwide is estimated to reach 4.4% by 2030 [1].

New therapeutic approaches in T2DM have emerged in the last 50 years [2].

The American Diabetes Association (ADA) and the European Association for the study of Diabetes (EASD) consensus in 2006 and in subsequent updates propose a new therapeutic algorithm [3].

Repaglinide, which is a member of a new class of insulin secretagogues, the meglitinides (also including nateglinide), was approved for clinical use in 1997. Repaglinide is a carbamoylmethyl benzoic acid derivative and nateglinide a derivative of phenylalanine.

Repaglinide is absorbed rapidly, metabolized by the liver, and eliminated mainly in bile. It is licensed for use as monotherapy in patients whose diabetes is not controlled by diet and exercise, or in combination with metformin in those patients whose disease is inadequately controlled with metformin in monotherapy [4].

Repaglinide is safe, although there have been reports of

 

adverse events, namely, hypoglycemia (the most frequent), nausea, vomiting, diarrhea, dyspepsia, and headache [5].

We present a case of hypersensitivity reaction to repaglinide.

## Case Description

A 61-year-old man with a 5-year history of T2DM treated with metformin was referred to our Unit. Three months previously, he had begun to experience hyperglycemia, and his endocrinologist added repaglinide to his habitual treatment with metformin.

After 5 days of combination therapy, he developed a maculopapular rash on the face and upper thorax that was particularly profuse on the neck. Repaglinide was discontinued, he started treatment with systemic corticosteroids and antihistamines for 2-3 days, and the reaction disappeared with no residual lesions. The endocrinologist prescribed glimepiride with metformin. After 3 days, the lesions reappeared, although they were less intense. Glimepiride was discontinued and replaced by vildagliptin, although the patient reported the same reaction 2 days later. The episode resolved without treatment after 3 days and the patient continued monotherapy with metformin, which he tolerated well.

We performed a skin prick test with a delayed reading at 24 hours with repaglinide (0.5 μg/mL), glimepride (2 μg/mL), and vildagliptin (50 μg/mL) using the commercialized preparation of the drugs. The pills were crushed and the amounts weighed (using a precision scale in our pharmacy).

The patient underwent patch testing on his upper back with the 3 drugs diluted in petrolatum and saline solution as follows: repaglinide 0.05%, glimepiride 0.25%, and vildagliptin 5% (Curatest Nonwoven Patch Test Strip, Lohman & Rauscher International GmbH, Rangsdorf, Germany). Readings were taken at 48 and 96 hours.

The results of patch testing and skin testing were negative. Therefore we decided to perform a single-blind oral challenge test (OCT) with repaglinide (0.125 μg, 0.25 μg, and 0.5 μg), glimepiride (0.5 μg, 1 μg, and 2 μg), and vildagliptin (12.5 μg, 25 μg, and 50 μg). Doses were increased at 1-hour intervals.

Due to the reaction described by the patient, the therapeutic dose was subsequently taken at home every 24 hours for 7 days.

The result with repaglinide was positive, with a delayed reaction at day 3: the patient developed erythematous macules with regular borders on his face and neck (Figure 1).

A punch biopsy of the skin lesions showed a sparse lymphocytic cell infiltrate distributed around the vessels of the superficial plexus. Spongiosis with exocytosis of lymphocytes and minimal parakeratosis was observed in the epidermis. The patient was diagnosed with drug-induced exanthema (Figure 2).

The results of the OCT with glimepiride and vildagliptin were negative.

We proposed an OCT with nateglinide to investigate possible cross-reactivity between repaglinide and nateglinide, but the patient refused. Therefore, we recommended avoidance of the metiglinide group.

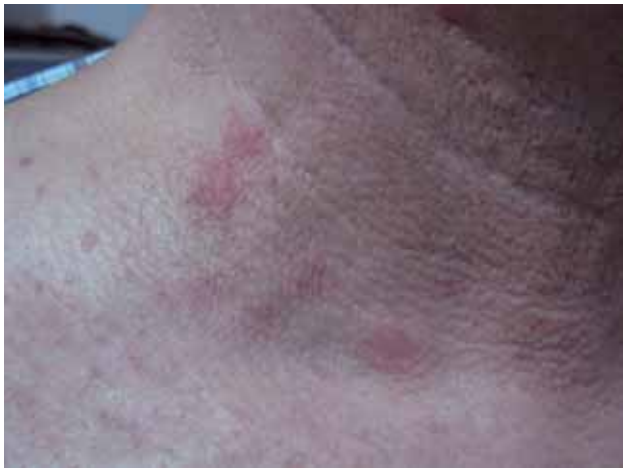

Figure 1. Erythematous maculae on the neck due to repaglinide.

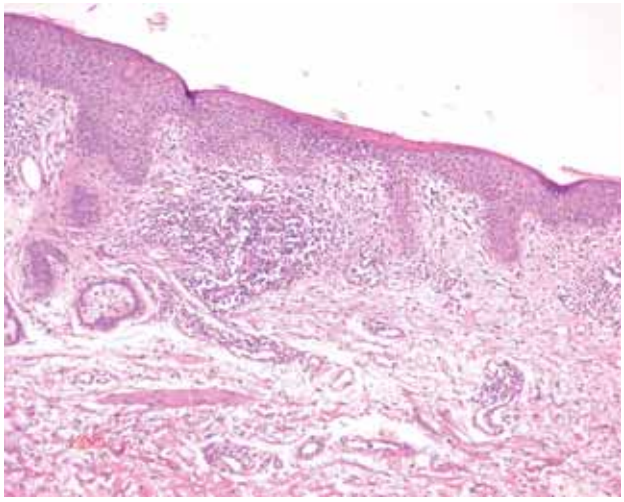

Figure 2. Skin biopsy: Drug exanthema.

## Discussion

Although widely used, oral antidiabetic drugs are not free of side effects; however, to our knowledge there have been no reports of hypersensitivity reaction. In the case of meglitinides, the severity of adverse events is mild to moderate.

Nan et al [6] and Jaiswal et al [7] reported 2 cases of acute hepatotoxicity and Lopez-García et al [8] described a case of cholestatic hepatitis associated with repaglinide and an immune mechanism (eosinophils in the liver inflammatory infiltrate).

Our literature search revealed no reports of hypersensitivity to meglitinides.

The clinical manifestations, the temporal relationship between initiation of therapy and onset of the reaction, the reappearance of cutaneous lesions after rechallenge, and the histopathology results suggests a type IV mechanism.

We suspect that the initial reaction due to repaglinide was

perpetuated by inadequate treatment and that the following reactions were a re-activation of the first one, as was evident in the OCTs with the other 2 drugs involved (glimepiride and vildagliptin), which were both negative.

In the case we report, neither skin prick tests nor intradermal tests were useful for diagnosis.

We present a case of hypersensitivity to repaglinide. To our knowledge, this is the first case reported.

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**Patricia Rojas Pérez-Ezquerra**

Allergy Unit
Hospital Central de la Cruz Roja
Avda. Reina Victoria, 22
28003 Madrid
E-mail: projasperezezquera@seaic.org