

Hypersensitivity Reaction to Mizolastine: Study of Cross Reactions

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Abstract. A 26-year-old male suffering from acute rhinitis took the first dose of Zolistan (mizolastine, 10 mg), orally, and 15 minutes later he developed intense generalized pruritus, cutaneous rash, oropharyngeal pruritus, edema on his face, difficulty in swallowing, and mild dyspnea. He was treated with methylprednisolone and epinephrine and improved within 30 minutes. The patient had not taken mizolastine before and he has avoided it since the reaction. Cutaneous tests with Zolistan and its excipients proved negative. Simple-blind oral challenge tests with the excipients and then with Zolistan were positive only with Zolistan. In order to confirm the absence of cross-reactivity between mizolastine and other benzimidazoles, we tested omeprazole, domperidone and mebendazole, all of which yielded negative results.

To our knowledge, this is the second case of immediate hypersensitivity to mizolastine documented to date. In our case, the clinical history, physical examination and provocation tests allow us to establish the diagnosis of hypersensitivity to mizolastine and exclude the cross reactivity with other benzimidazole derivatives.

Key words: Antihistamines. Benzimidazole derivatives. Cross-reactivity. Hypersensitivity. Mizolastine.

Resumen. Varón de 26 años que consulta por haber presentado a los 15 minutos de tomar un comprimido de Zolistan (mizolastina, 10 mg), para tratar una rinitis aguda, prurito intenso generalizado, rash cutáneo, prurito orofaríngeo, edema facial, disfagia y leve disnea. Fue tratado con metilprednisolona y adrenalina y mejoró en 30 minutos. El paciente no había tomado mizolastina anteriormente y la ha evitado después. Las pruebas cutáneas con Zolistan y sus excipientes fueron negativas. Los excipientes se administraron por vía oral con buena tolerancia, pero la administración de Zolistan fue positiva. Con el fin de descartar reacciones cruzadas se probaron otros derivados benzimidazólicos (omeprazol, domperidona y mebendazol) sin reacción alguna.

Presentamos el segundo caso de hipersensibilidad inmediata por mizolastina. La historia clínica, la exploración física y las pruebas de administración controlada nos han permitido establecer el diagnóstico y excluir la reactividad cruzada con otros derivados benzimidazólicos.

Palabras clave: Antihistamínicos. Benzimidazólicos, derivados. Hipersensibilidad. Mizolastina. Reacciones cruzadas.

Introduction

Mizolastine is a potent and selective histamine H1-receptor antagonist. Its efficacy and safety in the treatment of allergic rhinoconjunctivitis and urticaria has been demonstrated in controlled clinical trials [1,2]. It belongs to the heterogeneous group of benzimidazole derivatives, which includes antihelminthic (mebendazole, albendazole, thiabendazole), antihistamine (astemizole), antiemetic (domperidone), neuroleptic (droperidol) and proton pump inhibitor agents (omeprazole), among others [1].

Case report

A 26-year-old male was referred to our department because 6 months previously he had taken the first dose of Zolistan (mizolastine, 10 mg) orally, and 15 minutes later he developed intense generalized pruritus, cutaneous rash, oropharyngeal pruritus, edema on his face, difficulty in swallowing and mild dyspnea. He was treated with methylprednisolone and epinephrine (i.m.) and improved within 30 minutes. The patient suffered from acute rhinitis at that moment. He had not taken mizolastine before and he

has avoided it since the reaction. He denied any previous history of drug or food allergies. Other antihistamines, such as loratadine and cetirizine, have subsequently been tolerated by the patient. The patient had been diagnosed 2 years previously with intermittent nonallergic rhinitis.

We investigated the ingredients of Zolistan, and most had been administered to the patient after the reaction without any problems. In addition to mizolastine, the ingredients under suspicion were tartaric acid, and polyoxyethylated castor oil. After obtaining written informed consent, we began the allergologic study in the hospital. Prick (10 mg/ml) and intradermal tests (dilutions from 1:1000 to 1:10) with these excipients (obtained as pure products from the trade name dealers) proved negative [3]. Unfortunately, mizolastine was not provided by the manufacturers. For prick testing, the tablets well diluted with 0.9% NaCl at 10 mg/ml yielded a negative result. Simple-blind oral challenge tests were performed with the excipients and then with Zolistan (only one drug per day). A full therapeutic dose of each drug was administered divided in four parts with an interval of 30 minutes between administrations. Only Zolistan proved positive: 30 minutes after the administration of 2.5 mg, our patient developed generalized pruritus, conjunctival hyperaemia and angioedema of his left eyelid, oropharyngeal pruritus, wheals on his trunk, and cutaneous erythema. Heart rate and blood pressure were normal. He recovered in 2 hours after prompt administration of intramuscular epinephrine, methylprednisolone and chlorpheniramine.

These findings point to mizolastine as the cause of the reaction suffered by our patient. The immediate clinical symptoms suggested a hypersensitivity reaction, but the route of sensitization was unclear. The possibility of a previous administration of some drug belonging to the imidazole derivative group could be the explanation for the sensitization. Furthermore, as confirmation of the absence of cross reactivity between mizolastine and other benzimidazoles was essential for the future management of the patient, we completed the study by testing omeprazole, domperidone and mebendazole. Prick tests and simple-blind oral challenge tests with all of these agents (as previously described) were negative.

Discussion

Mizolastine is usually well tolerated. The most common adverse effects are tiredness, asthenia, and occasionally, headache, increased appetite, somnolence, and dry mouth. Isolated cases of anaphylaxis [4], hypotension, anxiety and depression, neutropenia, minor changes in blood sugar and electrolytes [1,2], and raised liver enzymes [5] have been reported in rare cases.

To our knowledge, this is the second case of immediate hypersensitivity to mizolastine documented to date. In the previous report, skin prick tests with two commercial suspensions including mizolastine proved positive (however, no information about the results in

control patients or a description of positive criteria were provided), and the controlled administration of the drug led to an anaphylactic reaction, but mizolastine-specific IgE was not detectable with the available laboratory techniques [4]. In our case, we highlight the rapid presentation of the symptoms and the small dose of the drug necessary to trigger the reaction after reexposure, suggesting a previous sensitization. Because of this, we consider that our negative prick test does not exclude the responsibility of the drug or an IgE mediated mechanism. The negative predictive value of immediate hypersensitivity skin tests varies depending upon the agent being tested. In fact, tests for small molecular weight drugs (such as mizolastine) have unknown negative predictive values. In addition, the agent responsible might be a drug metabolite that was not formed in the skin or it may be that some other immunologic mechanism was involved in the reaction [6]. Since the patient denies the previous intake of mizolastine, and tolerates other drugs of the same group, the possible sensitization via remains unclear, as in the case of Weidinger [4] (in any case, we have to trust the information provided by the patient). Thus, the possibility of pseudoallergic or anaphylactoid reactions should be considered. These are caused by direct release of mediators from mast cells and basophils. Direct mediator release occurs without evidence of a prior sensitization period, specific IgE antibodies or antigen-antibody bridging on mast cells/basophil cell membranes. This non-immune reaction is immediate, often severe and, because it is not immunologic, may occur the first time that the host is exposed to a particular agent.

In summary, in our case, the clinical history, physical examination and provocation tests allow us to establish the diagnosis of hypersensitivity to mizolastine and exclude the cross reactivity with other benzimidazole derivatives. Our findings suggest an immunologic mechanism but the underlying mechanisms of the reaction have yet to be fully elucidated.

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