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Immediate-type hypersensitivity reaction to Mannitol as drug excipient (E421): a case report

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KEY WORDS

Mannitol; Urticaria; excipient; Rhinitis; oral challenge test; Paracetamol; olive tree pollen

Summary

Allergic reactions to mannitol have been reported rarely, despite its widespread use as a drug and as a food excipient. This is the first case report in which oral mannitol induces an immediate type hypersensitivity as a drug excipient, in a 42 year old man affected by rhinitis to olive tree pollen. Unusual and undervalued risk factors for mannitol hypersensitivity are examined.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to be the second most common cause of drug-induced hypersensitivity reactions with immunological and/or non immunological mechanisms. When clinical manifestations, particularly urticaria and angioedema, are induced by a single NSAID molecule, the reaction is supposed to be genuinely IgE-mediated, because of its high selectivity (1). However, sometimes hypersensitivity reactions may be induced by an excipient, a preservative or a dye contained in the pharmaceutical preparation. In this case, the diagnostic procedure is much more complex and elaborated. The presumptive diagnosis is fortuitously suspected because, for instance, patient realizes to tolerate the same drug packaged in a different formulation and assumed accidentally (2). We describe the case of a patient with an urticaria-angioedema syndrome after taking effervescent granular

formulation of paracetamol. We demonstrated that the culprit of the adverse reaction was the mannitol added as a sweetener to paracetamol, not the drug itself.

Case report

A 42 year old atopic male patient came to our attention for a severe urticaria and angioedema at the Allergy and Clinical Immunology Service of Civil Hospital Vito Fazzi (Lecce, Italy). Symptoms appeared two hours after having taken 500 mg granular effervescent paracetamol packaged as sachets (Tachipirina® effervescent granules, Angelini Inc., Milan, Italy). Neither respiratory involvement nor hypotension were present, so the patient was promptly treated with corticosteroids and antihistamines orally, until complete remission of symptoms that occurred after three days. Maternal hypersensitivity to NSAIDs was reported in his clinical history, but he had not manifested any previous

adverse reactions to NSAIDs. He was also affected by a seasonal allergic rhinoconjunctivitis to Olive tree pollen (as confirmed by previous skin prick test already performed in another Allergic Service), treated with oral antihistamines during the May-June pollination period, classified as an intermittent severe rhinitis. Based on clinical manifestation and strict correlation between symptoms and drug intake, we considered paracetamol as the culprit agent for the adverse cutaneous reaction, and recommended patient to avoid its assumption. After one month, the patient underwent an oral incremental challenge test with alternative NSAIDs drugs (Nimesulide 100 mg and Etoricoxib 90 mg), which were well tolerated. Eighteen months later, the patient went back to our observation with a diffuse severe urticarial rash and facial angioedema associated to laryngeal stridor and shortness of breath. Symptoms appeared about 45 minutes after the ingestion of a cup of coffee sweetened with an industrial dietetic sugar-like product (Dietor[®], Leaf Italia Inc., Bologna, Italy) that he had never taken before. We treated the patient administering systemic corticosteroids and antihistamines with prompt regression of symptoms. Patient denied assumption of any drug before the last episode. In the light of the new immediate-type hypersensitivity reaction, we decided to reconsider the previous diagnosis to carry out a more careful allergic investigation. Three weeks after the last reaction, skin prick test (SPT) with commercial inhalants extracts (Stallergenes Inc., Milan, Italy) for grass and tree pollens, animal danders, molds and house-dust mite were performed. The SPT confirmed the presence of monosensitization to the pollen of Olive tree previously reported by patient. Examination of Dietor[®] composition (a mix of sorbitol, mannitol and fructose) and Tachipirina[®] 500 mg formulation (Paracetamol 500 mg, NaH₃CO₃, sodium carbonate 103.0 mg, citric acid 800 mg, mannitol 160.6 mg, sodium docusate 0,200 mg, maltitol 180.5 mg and aspartame 13 mg) evidenced the presence of mannitol in both compounds. Furthermore, patient had started again to drink coffee sweetened with normal sugar-cane, thus excluding the responsibility of coffee as an allergen. Then, a skin prick test with mannitol 20% (Isotol, Diaco Biofarmaceutici Industry, Trieste, Italy) was performed with negative result, while an intradermal test to mannitol diluted 1:10 with 0.9% sterile saline gave a positive response, resulting in a wheal with a diameter of 8 mm x 6 mm, while a SPT with histamine chloride 1%, as positive control, gave a wheal of 10 mm x 8 mm. Total serum IgE in addition to inhalants specific IgE were performed using the ImmunoCAP-System radioimmunoassay (Phadia Inc., Thermo Scientific, Uppsala, Sweden). Increased total IgE 154 IU/ml and Olive pollen specific IgE at 1.83 kUAL⁻¹ (cut-off value 0.10 kUAL⁻¹) were found. After having obtained the patient's written informed consent, an oral challenge test (OCT) was performed with Paracetamol 1000 mg tablets, which did not contain man-

nitol. Paracetamol was divided in 4 doses (250 mg) and administered orally with one hour intervals between each other. During the OCT, arterial pressure, pulse-oxymetry and FEV1 were monitored (30 minutes and every hour after administering each dose or as soon as any symptoms arose). Patient remained in the hospital under medical supervision for at least two hours after the end of OCT, and then he was asked to contact doctors in the following 24 and 48 hours, in case any delayed reaction appeared. The response to the OCT was considered positive as a cutaneous and/or mucosal (erythema, wheals and/or angioedema) or respiratory (a decrease of at least 20% in the FEV1) manifestations appeared, or in case of hypotension. Emergency resuscitation equipment and personnel were available during the test along. No adverse reaction was observed. A week later another OCT with mannite was performed. Mannite is an oral laxative of 10 grams in weight (Mannite Dufour, Iuppa Industry, Alessandria, Italy) sold as OTC laxative. A galenic preparation was obtained by diluting 100 mg of mannite in 100 ml of sterile water. An initial dose of 1 mg/ml, and after one hour of 3 mg/ml were taken by the patient without any adverse reaction. Finally, 10 mg/ml were administered an hour later, but 45 minutes after this dose (total dose 14 mg/ml) the patient reported a generalized itching with an urticarial rash on the trunk, associated to lips angioedema without any drop in blood pressure. FEV1 decreased 15% from basal. The patient was immediately treated with intravenous methylprednisolone (40 mg) and chlorphenamine maleate (10 mg/ml) in 100 ml of saline, and the adverse reaction faded completely. The patient was addressed to the Laboratory of Allergy and Clinical Immunology Department in Bari University, to perform serum dosages of Olive recombinant allergens by Phadia-Thermo Scientific Inc. and a Basophil Activation Test, but he declined any further investigation. So, patient was correctly informed about his mannitol hypersensitivity and recommended to avoid mannitol present in drugs and in foods as an excipient, and to communicate his particular hypersensitivity in case of hospitalization.

Discussion

Preservatives, excipients and dyes in drug formulations represent a true puzzle for allergists and dermatologists. At a first sight, the active pharmaceutical molecule is usually considered the responsible agent for a hypersensitivity reaction following the drug assumption, but sometimes a more careful investigation is required for the correct identification of the culprit agent (3). Kaliskaner et al. described a 22 year old man treated with rifampicin for a tuberculosis lymphadenitis. After 11 months of treatment, the patient regularly developed skin eruptions showing as recurring, self-limited, macular, itchy rashes, symmetrically placed on the face, ears, buttocks, elbows and knees. The lesions appeared at the same time every

day and lasted about 45 min, then disappeared spontaneously without any treatment. After various investigations with oral challenge tests for each anti-tubercular drug assumed by patient, Authors identified the culprit agent in a blue dye, patent blue dye, present in a rifampicin branded formulation. Such dye was substituted by indigotin (indigo blue) in another branded rifampicin formulation which, on the contrary, was tolerated by the patient (2). The whole allergic work-up was rather elaborated and skin tests showed to be not very helpful to the patient in the diagnosis (2). In our case report, it was the assumption of the synthetic sweetener to alert about the necessity to perform a new allergic session, in order to investigate the patient more carefully. Mannitol is a white crystalline sugar also named *mannite* or *manna sugar*. Manna is one of most ancient sweeteners in Europe before the introduction of the sugar cane. Mannitol is an acyclic hexitol sugar derived from the reduction of D-mannose (an aldohexose), which is not metabolized and therefore is excreted unchanged in the urine (4). For its hyperosmotic and diuretic properties, mannitol has been used for prophylaxis against acute renal failure due to toxic causes and to reduce cerebrospinal or intraocular fluid pressure (4). Although not so frequently reported in literature, D-mannitol is known to cause immediate-type hypersensitivity reactions when given intravenously (5-8). Such manifestations are usually attributed to mannitol hyperosmolar properties, able to trigger a non-specific mast-cells or basophils degranulation (8). For that reason, usually this immediate type hypersensitivity reactions are reputed to be non immunologic (6,8). In our case, the patient had assumed mannitol orally, so a hypertonic effect causing a direct mast-cell degranulation seemed to be excluded. On the contrary, Venkatesh and Hegde have proposed D-mannitol can induce a true IgE-mediated reaction (9). In their experience, D-mannitol usually exists as a cyclic form. However, in an aqueous solution, a very small amount of the acyclic form exists. D-mannose acts as a prosensitizer, the Schiff base conjugates with amino groups of proteins, as confirmed by their studies *in vivo* and *in vitro*, acts as a sensitizer, and lastly D-mannitol acts as a non-sensitizing elicitor (9). Moreover, they demonstrated in a patient the presence of circulating mannitol-specific human IgE by enzyme-linked immunosorbent assay (ELISA), using a D-mannitol-protein conjugate as coating antigen, both with affinity-chromatographed serum from the sensitized subject (10), because mannitol-specific IgE could not be detected in the allergic subject serum, probably for the binding of the hydrophilic mannitol (or any other sugar alcohol) to the hydrophobic polystyrene surface of microtiter wells (10). The presence of mast cell-bound mannitol-specific IgE in the patient was shown by positive SPT using D-mannitol-protein conjugates (10). This could explain why SPT gave a negative response in our pa-

tient. Mannitol is widely used in food industry as a sweetener and a dietetic substance, because its uptake is independent of insulin (4); it is thus applicable in diabetic and dietetic food products. Mannitol is also widely utilized in pharmaceuticals as excipient namely E421, according to European directives about food excipients (11). Mannite is the unrefined form of mannitol sold as an over-the-counter oral laxative, packaged like a butter pat. Because of a possible anaphylactic reaction by administering mannitol intravenously (5-8), we preferred to perform an oral challenge test in our patient, considering the oral route less hazardous and more ethical. In that way, we could calculate the administered dose, by stopping the challenge test as soon as patient had shown any symptom of adverse reaction. Recently, Australian researchers reported a 39 year old woman who had 3 anaphylactic reactions following intravenous administration of paracetamol, although the patient tolerated oral paracetamol. Skin tests and Phadia ImmunoCap to 1-amino-1-deoxy-d-mannitol confirmed the responsible agent was mannitol contained in intravenous formulation of paracetamol (12). Mannitol is the most widely distributed sugar alcohol in nature, and it has been reported in more than 100 species of vascular plants of several families, including the Oleaceae (olive, privet, ash tree) and the Apiaceae (celery, carrot, parsley) (13). Moreover, it has caused anaphylactic reactions as food allergen contained in pomegranate (*Punica granata*) (14) and mushrooms (15), as confirmed by skin tests in both the reported clinical cases (14,15). Interestingly, mannite for commercial and pharmaceutical purposes is obtained and collected by *Fraxinus species* trees (ash tree), which belong to the *Oleaceae* family. The amount of mannitol varies during the different seasons in the trees of *Fraxinus species*, while it is constant and always stable in Olive trees during the whole year (16). Alternatively, various purification processes are requested to extract mannitol from Olive leaves and separate it from its stereoisomer, sorbitol (17). Because our patient was afflicted by an Olive tree pollen rhinoconjunctivitis, probably Olive tree pollen allergy should be considered an undervalued risk factor for mannitol hypersensitivity, even in the light of the increased attention given to carbohydrates as allergens (18). A further botanical study investigated the average annual concentrations of starch and soluble sugars, including mannitol, in Olive tree leaves, branches, bark and roots, but unfortunately, not in pollen (19). According to the literature reports, alimentary route seems the most likely pathway able to induce mannitol sensitization, but there is also the possibility that, in our patient, mannitol hypersensitivity had been induced through the inhalant pathway, so, beyond a food allergen, a drug allergen and an excipient allergen, mannitol might even be a respiratory allergen.

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