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Severe skin reaction due to excipients of an oral iron treatment

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Key words: drug hypersensitivity; iron; excipients.

Iron deficiency is the most common cause of anaemia, at least in women and the administration of supplemental iron is the preferred approach to raise haemoglobin levels. Iron prepara-

Sunset yellow colorant as cause of hypersensitivity to iron replacement therapy.

tions (both oral and intravenous) have not an optimal tolerability profile, due to frequent local and systemic side effects, some of them also defined as hypersensitivity reactions (1). In this regard, it has been shown that, at least in part, drug reactions may be due to the excipients rather than to the active compound. In that case, patients are erroneously considered 'allergic' to the drug (2, 3) and do not receive the treatment. Colorants, which are commonly used as excipients in many drug formulations, are capable of evoking allergic reactions (4).

A 43-year-old female was referred to our clinic with the putative diagnosis of adverse reaction to iron oral treatment. The patient had a persistent iron deficiency anaemia and she had been on oral iron therapy with ferric propionate (Ferrofolin®; Farmades S.p.A, Rome, Italy) for at least 15 years, without significant problems. In April 2006, the GP replaced that drug with another preparation (ferrous sulphate, Ferrograd®, Abbott Italy S.p.A, Latina, Italy) that was considered more effective. Twenty-four hours after beginning this treatment, the patient developed a severe facial erythema with itching and skin oedema. The treatment was immediately stopped and systemic corticosteroid and antihistamines were given, this leading to disappearance of the lesions within 5 days. No episodes attributable to food or drug allergy was present in the clinical history, but on extensive questioning we ascertained that 10 years before she had to change her occupation (hairdresser) because of contact dermatitis. Nonetheless, no specific diagnostic test had been carried on in the past. We noticed that the two iron formulations had not only a different active principle but also a different excipient content. The ferrous sulphate is prepared as tablets containing Sunset Yellow FC&C No.6 (E110), Erithrosine (E127), Titanium Dioxide (E171), and methylmethacrylate as excipients. On the contrary, the previously tolerated ferric propionate is liquid, azodyes-free, and contains none of the mentioned excipients. When the patient was symptom-free, 2 weeks after discontinuation of steroids and antihistamines, a patch test was carried out with the European standard series of substances. The results were graded according to European

Society of Contact Dermatitis guidelines. Of note, an intense itching immediately appeared at the site of the patch and the patient reported the onset of slight facial erythema 6 h after the application. The test proved positive after 48 h for orange disperse 3 (3+), para-phenylenediamine (3+), and after 72 h for thimerosal (2+), gentamicin (3+), nickel sulphate (3+). Of these, only orange disperse was present in the iron formulation (as Sunset Yellow).

A single-blind, placebo-controlled oral challenge was then made, with ferrous sulphate eliciting facial itching and erythema and no reaction with ferric propionate. After the diagnosis of adverse reaction to orange disperse (Sunset Yellow) was established, the treatment with ferric propionate was resumed and the patient was advised to carefully check in the future the presence of the colorant in foods or drugs or cosmetic product.

The patient described was sensitized to some of the most common contact allergens and it is likely that she had become sensitized to these substances during her former occupation as a hairdresser. In fact, hairdressers and allied workers invariably handle cosmetics that contain colorants and preservatives (mainly para-phenylenediamine). In addition, in the past she had used gentamicin-containing ointments to treat her contact dermatitis. It has been shown that simultaneous patch positivity to paraphenylenediamine and disperse orange 3-like colorants is quite frequent (5), and studies reported a cross-reactivity between azo-dyes and paraphenylenediamine (6). The orange disperse colorants as Sunset Yellow are metabolized by the intestinal flora, with the production of sulfanilic acid (4-amino-benzene sulfonic acid) and 1-amino-2-naphthol-6-sulfonic acid. In turn, sulfanilic acid cross-reacts with para-phenylenediamine (7). This cross-reactivity is probably due to the production of common or similar oxidation products, particularly aromatic chemicals with an amino constituent in the para position.

The present case report highlights the importance of carefully studying the role of all components of a drug treatment, before diagnosing the patient as having hypersensitivity to the active principle.

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Food-exercise-induced anaphylaxis in a boy successfully desensitized to cow milk

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Key words: anaphylaxis; cow milk allergy; desensitization; exercise.

It is well known that exercise can induce systemic reactions, even anaphylactic shock, in some patients suffering from food allergy. Typically, exercise-induced anaphylaxis occurs on exercise immediately after the ingestion of a specific food. Nonetheless, it can occur also in the postprandial state without the certain identification of a specific causative food. In addition, the occurrence of anaphylaxis when the responsible food is ingested immediately after the exercise has been described (1). Food-dependent exercise-induced anaphylaxis has been variously associated with cereals, seafood, peanuts, tree nuts, eggs, milk and vegetables. We describe herein a severe anaphylactic reaction after exercise and milk ingestion in a child who previously underwent a successful desensitization protocol for cow milk (CM) allergy.

The patient was a 9-year-old boy who was diagnosed as having CM allergy at the age of 8 months. The clinical presentations of his CM allergy were urticaria, angioedema and wheezing. The diagnosis had been supported by skin prick test, CAP-RAST assay, and double blind, placebo-controlled food challenge (DBPCFC). Skin test was carried out on the anterior forearm surface with the prick by prick technique using undiluted CM. A negative control (saline solution) and a positive control (histamine 10 mg/ml) were also used (2). The patient showed an 8-mm-positive prick by prick test. The RAST assay (CAP system; Pharmacia, Uppsala, Sweden) gave a

Exercise after milk ingestion provoked anaphylaxis in a boy with induced tolerance to milk.

value of 4.80 KU/l for CM-specific IgE (normal value <0.35 KaU/l). The DBPCFC with CM and soy formula as placebo, performed at the clinic with full facilities for resuscitation, confirmed the diagnosis of allergy to CM. After the diagnosis was established, the patient began strict allergen avoidance and underwent a new food challenge every subsequent year, in order to verify if a remission had occurred. In fact, CM allergy usually remits or attenuates after 3 years of age. In our case, because of the persistence of symptoms confirmed by a stably positive food challenge, we decided to attempt a desensitization (tolerance induction), with slowly increasing doses of CM. The desensitization lasted 180 days, starting with two drops of cow's milk diluted 1:25 and progressively increasing, until a dose of 200 ml of milk (3) could be tolerated.

The protocol of oral desensitization was completed with limited side effects including: localized urticaria, stomach-ache and oral itching. These side effects were mild and self-resolving and required no treatment; but one episode of urticaria was easily controlled with oral antihistamines. At the end of the desensitization, the oral food challenge was negative and the boy could drink regularly about 300 ml of milk daily for breakfast. On one occasion, the boy participated in a football match just 30 min after having breakfast with the usual dose of milk. At the beginning of the second run, he suddenly developed generalized urticaria, angioedema, wheezing and dyspnoea. He was immediately treated on the field by the sports physician with intramuscular adrenaline, diphenhydramine and beta-metasone. He was then admitted at the EC unit, where he gradually recovered. Two months later, he was admitted to the emergency department with a similar major episode, which occurred again during strenuous exercise following ingestion of cow's milk.

After these episodes, we ascertained that the patient could freely drink milk, without subsequent physical exercise, and that physical exercise (full football match) without previous ingestion of milk did not provoke symptoms. The parents were then informed about the possible association of milk ingestion and exercise and were advised to get the boy