Immediate hypersensitivity to parenteral corticosteroids caused by IgE-mediated allergy to carmellose

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Drug excipients are rare causative agents of drug hypersensitivity reactions. Among them, polyethylene glycol, gelatin, polysorbate, cremophor or carmellose (carboxymethylcellulose) are able to cause immediate reactions [1]. Furthermore, it has been suggested that these excipients might be responsible for most of the presumed immediate hypersensitivity reactions to corticosteroids [2].

We report five cases of immediate hypersensitivity reactions after the administration of different local anesthetics and the steroid compound Trigon Depot®, in all of which we demonstrated IgE-mediated sensitization to carboxymethylcellulose as the underlying cause.

Case 1
A 78-year-old woman consulted for having suffered eight years before, 30 minutes after a joint infiltration of the knee, generalized pruritus and disseminated wheals, palpebral and lingual edema, irritative cough and dyspnea. Joint infiltration was performed with Scandinibsa® (mepivacaine hydrochloride, epinephrine tartrate, sodium metabisulfite, methyl parahydroxybenzoate. Inibsa, Lliçà de Vall, Spain) and Trigon Depot® (triamcinolone acetonide, benzyl alcohol, carboxymethylcellulose sodium, polysorbate 80, Bristol-Myers Squibb. Madrid, Spain).
Case 2

A 63-year-old man was submitted to a caudal block with Ropivacaine Inibsa® (Ropivacaine hydrochloride, Inibsa, Lliçà de Vall, Spain) and Trigon depot®. After ten minutes, he suffered from eyelid and lingual angioedema, generalized, pruritic hives and dizziness.

Case 3

Six months before his consultation, a 48-year-old man had an immediate reaction: facial erythema, nasal congestion and generalized wheals, after performing a caudal block with Trigon Depot® and an undetermined local anesthetic.

Case 4

A 41-year-old man had, three weeks before the consultation, an immediate reaction with generalized wheals, lingual and palatal angioedema, following an elbow infiltration with Trigon Depot® and Mepivacaine Normon 1% (Normon. Madrid. Spain).

Case 5

Five months before the consultation, a 55-year-old man had an immediate clinical picture of pruritus and generalized urticaria following administration of Trigon Depot® and Mepivacaine Normon 1% for a joint infiltration in his hand.

In all cases their adverse reaction subsided with methylprednisolone and dexchlorpheniramine IV.

Skin tests were performed on the five patients with the following drug or excipient dilutions (prick and intradermal tests): polyethyleneglicol 1500 and 4000 (10 and 0.1 mg/ml), polysorbate 80 (4 and 0.04 mg/ml), betamethasone and dexamethasone (4 and 0.4 mg/ml), methylprednisolone and triamcinolone (40 and 4 mg/ml), benzyl alcohol (10 and 1 mg/ml), mepivacaine (20 and 2 mg/ml), ropivacaine (2 and 0.2 mg/ml), carmellose (5 and 0.05 mg/ml), Trigon Depot® (as is and 1/100).
Table 1 shows the results of the skin tests, *in vitro* specific IgE and challenge test for all cases. Informed consent was obtained from all patients. All five patients showed positive skin tests with carmellose; and negative skin and challenge tests with corticosteroids and local anesthetics.

Immediate hypersensitivity reactions to corticosteroids have a very low incidence [2]. In some reported small series, immediate hypersensitivity reactions to parenteral corticosteroids were mostly due not to the steroid itself, but to one of the excipients used in its formulation, such as carmellose and PEG, essentially [2-7]. Carmellose is also part of different pharmacological preparations such as laxatives, radiological contrast agents, hydrocolloid dressings, hormones, moisturizing eye drops, and others.

Carmellose or carboxymethylcellulose (CMC) is an organic compound derived from cellulose. It is a carbohydrate often presented as a salt, i.e., as sodium carboxymethylcellulose, or carmellose sodium. It is used as a treatment to relieve eye irritation and dryness, and as a solubilizer in injectable medications for agents with poor water solubility, such as corticosteroids.

CMC is also present in some foods (as E466), and has been occasionally reported as an allergen in ice creams and other processed foods [8]. CMC oral sensitization is rare (given its large molecular size and low absorption rate through the intestinal mucosa); but when it happens, allergic reactions can occur with minimal doses of oral antigen [8]. On the contrary, in the case of primary parenteral sensitization, much higher oral doses are necessary for eliciting an allergic response. Consequently, oral administration of CMC in food or tablets is generally tolerated in allergic people to carmellose-containing parenteral corticosteroids [5-8].

We report five cases of immediate hypersensitivity reactions after treatment with Trigon Depot® together with a local anesthetic of the amide group, in which the sensitization to carmellose, and not the corticosteroid or anesthetics, turned out to be the trigger agent. All of them had
positive skin tests to both Trigon Depot® and carmelllose. However (and even though IgE to
carmelllose might be found in up to 9% of the population [9]) we could only detect in vitro
specific IgE against carmelllose in a single patient. Nevertheless, we confirmed corticosteroid
tolerance in the five patients by challenge tests with other corticosteroids including depot
compounds without carmelllose such as Celestone Cronodose® (betamethasone phosphate and
acetate 6 mg. Organon Salud, Madrid, Spain). We verified tolerance to the local anesthetic used
in each proceeding as well.

Even though infrequent, we must investigate allergy to excipients in drug formulations,
especially in patients with a negative skin test with the putative causal agent. In particular, when
immediate reactions to corticosteroids are suspected, sensitization to any of the excipients
should be discarded in order to avoid false labelling that compromise the future use of
corticosteroids in these patients. Carmelllose has been reported before as an eventual cause of
immediate allergic reactions to parenteral corticosteroids [2-7]. CMC is also part of different
pharmacological preparations. Patients allergic to carmelllose should be warned and provided,
if possible, with a list of drugs and agents that include CMC in their formulation.

**Funding**
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**Conflict of Interest**
None.

**REFERENCES**

1. Caballero ML, Krantz MS, Quirce S Phillips EJ, Stone CA. Hidden dangers: recognizing
excipients as potential causes of drug and vaccine hypersensitivity reactions. J Allergy Clin


TABLE 1

Results of skin test, challenge test and Dot blot test in the four patients

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IDT: Intradermal test. ND: Not Done. TOL: Tolerated.