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

Galán C[1], Arrien de Lecea A[1], Bartolomé Zavala B[2], Pérez Escalera M[1], Sánchez de Vicente J[1]

[1]Servicio de Alergia, Hospital Universitario Cruces, Barakaldo, Spain

[2]Departamento I+D Roxall, Parque Científico y Tecnológico de Bizkaia, Zamudio, Spain

Corresponding Author

Javier Sánchez de Vicente

Servicio de Alergia

Hospital Universitario Cruces

48903 Barakaldo, Spain

E-mail: javier.sanchezdevicente@osakidetza.eus

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0938

Keywords: Carmellose. Corticosteroids. Drug allergy.

Palabras clave: Carmelosa. Corticoides. Alergia medicamentosa.

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).

doi: 10.18176/jiaci.0938

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): polyethhylenglicol 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).

doi: 10.18176/jiaci.0938

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

doi: 10.18176/jiaci.0938

positive skin tests to both Trigon Depot® and carmellose. However (and even though IgE to carmellose might be found in up to 9% of the population [9]) we could only detect in vitro specific IgE against carmellose in a single patient. Nevertheless, we confirmed corticosteroid tolerance in the five patients by challenge tests with other corticosteroids including depot compounds without carmellose 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. Carmellose 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 carmellose should be warned and provided, if possible, with a list of drugs and agents that include CMC in their formulation.

Funding

None.

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 Immunol Pract. 2021;9:2968-82.

doi: 10.18176/jiaci.0938

2. Li PH, Wagner A, Thomas I, Watts TJ, Rutkowski R, Rutkowski K. Steroid allergy: clinical features and the importance of excipient testing in a diagnostic algorithm. J Allergy Clin Immunol Pract. 2018;6:1655-61.

3. Venturini M, Lobera T. Del Pozo MD, González I, Blasco A. Immediate hypersensitivity to corticosteroids. J Investig Allergol Clin Immunol. 2006;16:51-6.

4. Niwa Y, Hayama K, Tagui T, Ito-Wanabe M, Endo T, Fujita H, et al. Case of anaphylaxis due to carmellose sodium. J Dermatol. 2020; 47:e15-e17.

5. Bigliardi PL, Izakovic J, Weber JM, Bircher AJ. Anaphylaxis to the carbohydrate carboxymethylcellulose in parenteral corticosteroid preparations. Dermatology. 2003;207:100-3.

6. Field S, Falvey E, Barry J, Bourke J. Type 1 hypersensitivity reaction to carboxymethylcellulose following intra-articular triamcinolone injection. Contact Dermatitis. 2009;61:302-3.

7. Laing ME, Fallis B, Murphy GM. Anaphylactic reaction to intralesional corticosteroid injection. Contact Dermatitis. 2017;57:132-3.

8. Brockow K, Bauerdorf F, Kugler C, Darsow U, Biedermann T. “Idiopathic” anaphylaxis caused by carboxymethylcellulose in ice cream. J Allergy Clin Immunol Pract. 2021; 9: 555-7.

9. Muroi N, Mori S, Ono S, Takahashi HK, Fujii T, Hosoi S, et al. M. Allergy to carboxymethylcellulose. Allergy. 2002;57:1212-3.

TABLE 1

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

CASE	1	2	3	4	5
SKIN TESTS					
TRIGON DEPOT	+ (IDT); - (Prick)	+ (IDT); - (Prick)	+ (IDT);- (Prick)	+ (IDT); -(Prick)	+ (IDT); - (Prick)

doi: 10.18176/jiaci.0938

CARMELLOSE	+ (IDT); - (Prick)	+ (IDT); - (Prick)	+ (IDT); -(Prick)	+ (Prick); ND IDT	+ (IDT); - (Prick)
POLYETHYLENGLYCOL 1500 AND 4000	-	-	-	-	-
POLYSORBATE	-	-	-	-	-
METHYLPREDNISOLONE	-	-	-	-	-
BETAMETHASONE	-	-	-	-	-
DEXAMETHASONE	-	-	-	-	-
TRIAMCINOLONE	-	-	-	-	-
BENZYL ALCOHOL	-	-	-	-	-
ROPIVACAINE	ND	-	-	ND	ND
MEPIVACAINE	-	ND	-	-	-
BUPIVACAINE	ND	ND	-	ND	ND
CHALLENGE TEST					
METHYLPREDNISOLONE	TOL	TOL	TOL	TOL	TOL
BETAMETHASONE	ND	TOL	TOL	TOL	TOL
DEXAMETHASONE	TOL	TOL	TOL	TOL	TOL
ROPIVACAINE	ND	TOL	TOL	ND	TOL
MEPIVACAINE	TOL	ND	TOL	TOL	TOL
DOT BLOT					
CARMELLOSE	+	-	-	-	-

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

doi: 10.18176/jiaci.0938