

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. Those able to cause immediate reactions include polyethylene glycol, gelatin, polysorbate, Cremophor, and carmellose (carboxymethylcellulose) [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 5 cases of immediate hypersensitivity reactions after the administration of local anesthetics and the corticosteroid compound Trigon Depot. We demonstrated IgE-mediated sensitization to carboxymethylcellulose as the underlying cause in all 5 cases.

Case 1

A 78-year-old woman developed generalized pruritus, disseminated wheals, palpebral and lingual edema, irritative cough, and dyspnea 30 minutes after an infiltration of the knee 8 years earlier. The infiltration was performed with Scandinibsa (mepivacaine hydrochloride, epinephrine tartrate, sodium metabisulfite, methyl parahydroxybenzoate [Inibsa]) and Trigon Depot (triamcinolone acetonide, benzyl alcohol, carboxymethylcellulose sodium, polysorbate 80 [Bristol-Myers Squibb]).

Case 2

A 63-year-old man underwent caudal block with Ropivacaine Inibsa (ropivacaine hydrochloride [Inibsa]) and Trigon depot. After 10 minutes, he developed palpebral and lingual angioedema, generalized pruritic hives, and dizziness.

Case 3

Six months before consulting, a 48-year-old man experienced an immediate reaction comprising facial erythema, nasal congestion, and generalized wheals during caudal block with Trigon Depot and an undetermined local anesthetic.

Case 4

Three weeks before the consultation, a 41-year-old man developed an immediate reaction comprising generalized wheals and lingual and palatal angioedema following an infiltration of the elbow with Trigon Depot and Mepivacaine Normon 1% (Normon).

Case 5

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

In all cases, the adverse reaction subsided with intravenous methylprednisolone and dexchlorpheniramine.

The 5 patients underwent skin testing with the following drug or excipient dilutions (prick and intradermal tests): polyethylene glycol 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), and Trigon Depot (as is and 1/100).

The Table shows the results of the skin tests, in vitro specific IgE, and challenge tests for the 5 cases.

The patients gave their informed consent for performance of this study. All 5 patients had positive skin test results with carmellose and negative skin and challenge test results with corticosteroids and local anesthetics.

The incidence of immediate hypersensitivity reactions to corticosteroids is very low [2]. In some small series, immediate hypersensitivity reactions to parenteral corticosteroids were mostly due not to the drug itself, but to an excipient, mainly carmellose or polyethylene glycol [2-7]. Carmellose is also a component of various pharmacological preparations such as laxatives, radiological contrast agents, hydrocolloid dressings, hormones, and moisturizing eye drops.

Carmellose, or carboxymethylcellulose, is an organic compound derived from cellulose. It is a carbohydrate that is often formulated as a salt, eg, sodium carboxymethylcellulose or carmellose sodium. It is used to relieve eye irritation and dryness and as a solubilizer in injectable medications for agents with poor water solubility, such as corticosteroids.

Carmellose is also present in some foods as E466 and has occasionally been reported as an allergen in ice cream and other processed foods [8]. Oral sensitization to carmellose is rare owing to its large molecular size and low rate of absorption through the intestinal mucosa. However, when recorded, the allergic reactions occur with minimal doses of oral antigen [8]. In contrast, in the case of primary parenteral sensitization, much higher oral doses are necessary to elicit an allergic response. Consequently, oral administration of carmellose in food or tablets is generally tolerated by individuals who are allergic to carmellose-containing parenteral corticosteroids [5-8].

We report 5 cases of immediate hypersensitivity reactions after treatment with Trigon Depot, together with a local anesthetic of the amide group, in which sensitization to carmellose—not the corticosteroid or anesthetics—proved

Table. Results of Skin Test, Challenge Test, and Dot Blot Test in 5 Patients.

Patient	1	2	3	4	5
Skin tests					
Trigon Depot	+ (IDT); – (Prick)	+ (IDT); – (Prick)	+ (IDT); – (Prick)	+ (IDT); – (Prick)	+ (IDT); – (Prick)
Carmellose	+ (IDT); – (Prick)	+ (IDT); – (Prick)	+ (IDT); – (Prick)	+ (Prick); ND IDT	+ (IDT); – (Prick)
Polyethylene glycol 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	+	–	–	–	–

Abbreviations: IDT, intradermal test; ND, not done; TOL, tolerated

to be the trigger. All 5 patients had positive skin test results with both Trigon Depot and carmellose. However, we only detected specific IgE to carmellose in vitro in a single patient, even though IgE to carmellose might be found in up to 9% of the population [9]. We confirmed corticosteroid tolerance in all 5 patients by challenge tests with other corticosteroids, including depot compounds without carmellose such as Celestone Cronodose (betamethasone phosphate and acetate 6 mg [Organon Salud]). We also verified tolerance to the local anesthetic used in each procedure.

Although allergy to excipients is infrequent, it should be investigated, especially in patients whose skin test result with the putative causal agent is negative. When immediate reactions to corticosteroids are suspected, sensitization to the excipients should be ruled out in order to avoid false labeling and compromising the future use of corticosteroids in affected patients. Carmellose has previously been reported as an eventual cause of immediate allergic reactions to parenteral corticosteroids [2-7]. It is also a component of various pharmacological preparations. Patients allergic to carmellose should be warned and provided, if possible, with a list of drugs and agents that include it in their formulation.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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.
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.

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