

Cutaneous adverse drug reactions caused by delayed sensitization to carboxymethylcellulose

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Adverse drug reactions can be caused by excipients. Adverse immediate hypersensitivity caused by carboxymethylcellulose is rare, but well known. Three cases of delayed hypersensitivity emphasize that this excipient can also induce delayed systemic symptoms.

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Case Histories

Case 1

In 1996, a 24-year-old man had developed a drug reaction with eosinophilia and systemic symptoms caused by Tegretol® (carbamazepine and carboxymethylcellulose). Positive patch test reactions were obtained with carbamazepine at 10% pet.; carboxymethylcellulose was not tested at the time. Subsequently, the patient experienced eczematous rashes following the intake of pills containing paracetamol and a non-steroidal anti-inflammatory

drug. Patch tests, prick tests with paracetamol and prick tests with non-steroidal anti-inflammatory drugs gave negative results. The intradermal tests with paracetamol and non-steroidal anti-inflammatory drugs without carboxymethylcellulose gave negative results.

Case 2

A 48-year-old man with a history of chronic rheumatism resulting from diffuse idiopathic skeletal hyperostosis (DISH) and photosensitization to ketoprofen developed flexural dermatitis 3 days after an intra-articular injection of betamethasone dipropionate and carboxymethylcellulose. A few months later, he had a maculopapular rash of the trunk 24 hr after taking pills containing piroxicam and carboxymethylcellulose. Intradermal tests gave a delayed positive result with betamethasone (belonging to chemical class C of corticosteroids) diluted at 0.04 mg/ml (15 negative controls), but a negative result with betamethasone dipropionate at 7 mg/ml and corticosteroids belonging to chemical class A or class B. Intradermal tests with piroxicam and other non-steroidal anti-inflammatory drugs not associated with carboxymethylcellulose gave negative results. Oral provocation tests with prednisolone (30 mg) and piroxicam (30 mg) in pills not associated with carboxymethylcellulose were well tolerated.

Case 3

A 40-year-old woman with a history of hypothyroidism and intolerance to a wound dressing containing carboxymethylcellulose for leg ulcers (because of a protein S deficiency) developed a chronic generalized urticaria. Chronologically, the urticaria had appeared when pills containing levothyroxine had been introduced. The generalized urticaria disappeared when pills containing levothyroxine and carboxymethylcellulose were discontinued, and replaced by pills containing levothyroxine and hydroxypropylcellulose.

Investigations

In these 3 patients, carboxymethylcellulose was suspected of being causal, and investigations were performed to demonstrate sensitization to the excipient (Table 1). All of the patients had patch tests and prick tests with undiluted carboxymethylcellulose performed, and if they gave negative results, an intradermal test or an oral provocation test with carboxymethylcellulose was performed. In cases 2 and 3, patch tests with carboxymethylcellulose were also performed at a concentration of 30% in water and pet.

Drug skin tests were performed following the procedures published by the European Society of Contact Dermatitis (1). The intradermal tests were performed by injecting 0.02 ml, and results were considered to be positive when the diameter of the papule read after 20 min was twice that of the injection papule.

The patch tests results were all negative. In 1 case (patient 2), a delayed positive reaction was observed on a prick test performed with pure carboxymethylcellulose, yielding an infiltrated, erythematous reaction after 24 hr (6 negative controls).

In patient 3, the intradermal test performed with sterile carboxymethylcellulose diluted at 1 mg/ml in saline gave positive results on the 20-min reading, but also a delayed infiltrated reaction 10 mm in diameter at 24 hr (3 negative controls).

In patient 1, because all skin test results remained negative, an oral provocation test with a cumulative dose of 1.115 mg of carboxymethylcellulose was performed under hospital surveillance, inducing a generalized eczematous rash on the following day.

To analyse the potential cross-reactions with hydroxypropylcellulose, patch tests and prick tests with hydroxypropylcellulose in pure form were performed, and gave negative results in the 3 cases. In the third case, an intradermal test performed with hydroxypropylcellulose diluted at 1 mg/ml in saline gave a negative result. In cases 2 and 3, the oral provocation test with hydroxypropylcellulose gave a negative result. In case 2, the oral provocation test with microcrystalline cellulose at a cumulative dose of 160 mg also gave a negative result.

Discussion

Carboxymethylcellulose (also called carmellose or croscarmellose, E466) can induce immediate reactions (2–8) or contact allergy (9) (delayed hypersensitivity). This delayed sensitization can mimic multiple sensitizations to different drug classes. On the basis of our results, in delayed reactions to carboxymethylcellulose, prick tests and intradermal tests (1 mg/ml) can have positive results. If the latter are not observed, an oral provocation test with carboxymethylcellulose can be performed under hospital surveillance. In immediate reactions to injectable drugs containing carboxymethylcellulose, it has been reported that oral administration of this excipient is well tolerated, owing to its weak absorption (7, 8). We emphasize that, in cases of delayed hypersensitivity to carboxymethylcellulose, there is no oral tolerance. In our 3 cases with delayed reactions to carboxymethylcellulose, there were no cross-reactions with hydroxypropylcellulose.

Table 1. Clinical features and investigations in 3 patients with delayed reactions to carboxymethylcellulose

	Sex, age (years)	Other history	Clinical features of the AR due to CMC	Patch test	Prick test	Intradermal test	Oral provocation test (1.511 mg)	Cross-reaction with HPC?
Case 1	M, 24	DRESS caused by carbamazepine	Eczematous rash with several pills containing paracetamol or non-steroidal anti-inflammatory drugs, both at 7 mg/ml, and corticosteroids belonging to chemical class A or B. Intradermal tests with CMC	—/—	—	Not done	+ at 24 hr Disseminated eczema	No Negative patch and prick test results with pure HPC
Case 2	M, 48	Photoallergy to topical ketoprofen	Maculopapular rash with betamethasone dipropionate and CMC, and then with piroxicam and CMC	—/—	+ at 24 hr	Not done	Not done	No Negative patch test prick test and oral provocation test results (160 mg)
Case 3	F, 40	Chronic leg ulcers related to a protein S deficiency with a contact allergy to CMC and delayed pressure urticaria	Delayed urticaria and oedema caused by levothyroxine and CMC	+/-/0	—	Diluted at 1 mg/ml, positive at 20 min and infiltrated erythematous reaction (10 mm in diameter) at 24 h	Non done	No Negative prick test result with pure HPC and intradermal test diluted at 1 mg/ml

Patch tests were performed with pure carboxymethylcellulose, and also with carboxymethylcellulose diluted 30% in water and pet. in cases 2 and 3. AR, adverse reaction; CMC, carboxymethylcellulose; DRESS, drug reaction with eosinophilia and systemic symptoms; HPC, hydroxypropylcellulose.

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