

Case report

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Allergic reaction to Croscarmellose sodium used as excipient of a generic drug

N. MUMOLI, M. CEI, R. LUSCHI, G. CARMIGNANI and A. CAMAITI

*From the Department of Internal Medicine, Ospedale Civile Livorno, 57100 Livorno, Italy**Address correspondence to Dr N. Mumoli, Department of Internal Medicine, Ospedale Civile Livorno, viale Alfieri 36, 57100 Livorno, Italy. email: nimumoli@tiscali.it**Received 2 September 2010 and in revised form 6 September 2010*

Croscarmellose sodium is a very commonly used pharmaceutical additive approved by the US Food and Drug Administration. It is used in injectable preparations as a suspending agent to promote solubilization of compounds with poor water solubility; it is also present in tablets as binder, glidant and antiadherent, in bulk laxatives as active principle and as an additive in food products. Croscarmellose hypersensitivity is a rarely reported event. We describe a case of a woman who developed allergic reaction to Croscarmellose used as excipient of a generic drug (generic preparation of oral furosemide) during treatment for chronic heart failure.

Case report

A 87-year-old woman was admitted to our hospital in January 2010 for acute pulmonary edema; on physical examination and chest radiograph, we found signs of congestive heart failure with blood pressure 155/80 mmHg; we started treatment with oxygen supplementation; furosemide, morphine and nitrates were administered intravenously. Echocardiography showed an enlarged left ventricle (end diastolic diameter 60 mm), reduced systolic function (ejection fraction 40%) and moderate mitral regurgitation. Blood test results showed high concentration of B-type natriuretic peptide

(1092 pg/ml); all other laboratory test results were normal.

The patient's medical history included hypertension, previous myocardial infarction, chronic heart failure, an episode of hematochezia during aspirin therapy and was remarkable for colonic diverticulosis with, in the past, at least three episodes of acute diverticulitis.

Her medications were furosemide, omeprazole, ticlopidine, carvedilol and ramipril.

On further questioning, the patient reported that in the past she was taking branded furosemide (Lasix 25 mg, Sanofi-Aventis, Milano, Italy); however, when her practitioner shifted her to a generic preparation of furosemide (Furosemide 25 mg, Laboratorio Farmacologico Milanese, Varese, Italy), she developed an erythematous cutaneous rash with diffuse itching that promptly disappeared after drug suspension. After this, she did not resume any furosemide tablet for about 2 years. Recently, having forgotten what had happened, and because of weight gain and mild dyspnea, she resumed the treatment with the generic furosemide, and the rash appeared again. After another suspension of treatment, resulting in the disappearance of the rash, she experienced the aforementioned episode of pulmonary edema.

We then compared the composition of Lasix tablets with that of the generic preparation, and we found that they differed only for the absence of



Figure 1. Lasix and generic furosemide with only one different excipient (arrows).

Croscarmellose sodium in the brand drug (Figure 1); a presumptive diagnosis of Croscarmellose hypersensitivity was made, and we prescribe the brand furosemide for oral therapy. The patient's recovery was uneventful and she was asymptomatic for the last 3 months. Croscarmellose sodium is a carboxymethylcellulose (CMC) that is widely used as an additive in pharmaceutical and non-pharmaceutical industry; in particular, it is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. It has been implicated in IgE-mediated allergic reactions to parenteral administration of depot steroids.^{1,2} Other reports stated that oral administration of CMC is well tolerated in such subjects, because this additive is presumed not to be absorbed through the digestive tract;³ however, CMC anaphylaxis has been reported after contact with gut mucosa during barium enema.⁴ In our case, CMC was the only component of the generic furosemide that was not present in the brand tablet and other drugs, and the timing of the reaction is consistent with CMC allergy. Furthermore, the patient may have been sensitized by the previous exposure to this ubiquitous additive, resulting in hypersensitivity. We hypothesise that if even a small amount of CMC has been absorbed by the gut, this could have led to a typical type 1 hypersensitivity reaction; moreover, we speculate that several episodes of acute diverticulitis may have promoted the increase of the gut permeability and facilitated the CMC absorption. Furthermore, use of the Naranjo ADR Probability Scale⁵ indicated a probable relationship between the Croscarmellose hypersensitivity and generic preparation of furosemide in this patient.

To our knowledge, this may be the first case reporting oral allergy to CMC; therefore, we do suggest that patients with a CMC hypersensitivity should actively check with their pharmacy or prescribing physician to verify that their medications are free of this excipient agent.

Finally, although there is bioequivalence between generic and brand drug, often the ingredients are different; therefore, we recommend that physician continue to exercise caution in the consideration of brand drug with generic drug substitution under certain circumstances.

Conflict of interest: None declared.

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