P. Dumond[1], P. Franck[2], M. Morisset[1], J. Sainte Laudy[3], G. Kanny[1], D.A. Moneret-Vautrin[1]

Pre-lethal anaphylaxis to carboxymethylcellulose confirmed by identification of specific IgE – review of the literature

[1] Department of Internal Medicine, Clinical Immunology and Allergology University Hospital, 29 avenue du Maréchal de Lattre de Tassigny, 54035 Nancy Cedex
[2] Laboratory of Biochemistry - University Hospital, 29 avenue du Maréchal de Lattre de Tassigny, 54035 Nancy Cedex
[3] Laboratory of Immunology CHU Limoges

Key words

Carboxymethylcellulose, Anaphylaxis, Barium suspension, IgE

Summary

Background: *Carboxymethylcellulose (CMC) is used extensively in the pharmaceutical and food industries on account of its various properties. Anaphylactic reactions are rare. It has been reported principally after intra-articular infiltration of sustained-release corticosteroids containing CMC and, very rarely, after barium enema.* ***Methods:*** *A case of pre-lethal anaphylactic shock after barium enema was studied by prick-test, intra-dermal reaction (IDR), leukocyte histamine release test (LHRT), basophil activation test (BAT), cystein-leukotriene release test (CAST) and dot-blot analysis.* ***Results:*** *IDR to CMC was positive at a concentration of 10 µg/ml. BAT and CAST were positive. Specific IgE were identified using dot-blot analysis.* ***Discussion:*** *This is the third report of CMC-specific IgE and the second of anaphylaxis to CMC associated with a barium suspension in contact with GI tract mucosa. CMC as an excipient in medicinal products may therefore be a risk factor for severe anaphylaxis after injection or following contact with GI tract mucosa. Sensitization and allergic reactions by CMC in food additives have to be considered.*

Introduction

Carboxymethylcellulose (CMC) is used in the pharmaceutical and food industries. It is a vegetable cellulose derivative obtained by the action of chloracetic acid on cellulose in an alkaline medium, whereby hydroxyl functions are substituted by carboxymethyl groups. The basic structure is a (1-4) D glucopyranosyl polymer. The degree of substitution varies according to preparation, but is usually between 0.6 and 0.95. The molecular weight may range from 90 000 to 700 0000 kDa. Anaphylaxis to CMC is known, but is rare.

Specific IgEs against CMC were first identified by Patterson in 1995 (1) using immunoblot analysis, then by Muroi using ELISA (2). We have confirmed the existence of CMC-specific IgE using a dot –blot analysis.

Material and methods

Case report

In March 2003, a 62 year-old man underwent barium enema with Micropaque Colon® during follow-up for

colonic polyposis. He suffered from long-standing asthma, complicated by chronic obstructive pulmonary disease (COPD). There was no personal or family history of atopy. Micropaque Colon®, a barium sulfate suspension, was used as an enema. Thirty minutes later, the patient presented with generalized urticaria, severe bronchospasm, cardiovascular collapse and respiratory arrest. Immediate management of shock consisted of intubation, intravenous epinephrine and vascular filling. He recovered completely after 24 hours.

Allergological testing was performed two months later. The interview revealed two episodes of malaise after intra-articular infiltrations with sustained-release corticosteroids containing CMC for arthrosis-related joint pain. Micropaque Colon® also contains 2.77% CMC. The amount injected by enema was estimated at 2.7 g.

Prick-tests were performed on a skin reactive to codeine. They were positive to Micropaque Colon® (2.5 mm). CMC powder from Coopérative Pharmaceutique Française (Melun 77000 France) was diluted in 5/°° phenolated saline at 1mg/ml, then diluted for skin tests. The prick-test to CMC was negative but the intra-dermal test (IDT) to CMC was positive at 10 µg/ml (8 mm edema, 15 mm erythema, 15 mn after a 4 mm injection papule). In 6 controls, IDT was negative to 10 µg/ml, 100 µg/ml and 1 mg/ml. The basophil activation test (BAT) by flow cytometry was positive to CMC with 15% activation (0.5% spontaneous activation, positive control to anti-IgE: 17 %). The cystein-leukotriene release test (CAST) to CMC was positive: 1,700 pg/ml (control test to anti-IgE: 3,000 pg/ml). Leukocyte histamine release test (LHRT) to CMC was negative. Serum tryptase assay was normal: 5.9 µg/l.

A diagnosis of anaphylaxis to CMC was made. The patient was given a list of injectable medicinal products containing CMC.

Identification of specific IgE

Samples

Several solutions were prepared from sodium CMC (Pharmaceutical Cooperation, Melun, France): a 5 mg/mL aqueous solution of bovine serum albumin (BSA), a 5 µg/µL sodium CMC solution obtained from a 20µg/µL aqueous mother solution of sodium CMC in a phosphate buffer.

A CMC-HCl solution was made by diluting the 20µg/µL sodium CMC solution 1:4 in an acid solution (1N HCl). The mixture was put into a water bath at 37°C for 3 hours.

A CMC-BSA solution was made by mixing equal volumes of the CMC-HCl solution and the 5mg/mL BSA solution. The mixture was kept at boiling point for 10 minutes.

Dot-blot

PVDF (Sequi-Blot™ PVDF membrane for protein sequencing 0.2 µm BIO-RAD) membranes were soaked in a methanol bath for 1 minute, then rinsed with distilled water for 2 to 3 minutes.

One micro-liter of each solution was placed on the PVDF membrane. After drying in air for 15 minutes, the membrane was saturated for 1 hour in a 5% BSA solution and 0.05% Tween in phosphate buffer (PBS). It was then rinsed for 2 minutes in PBS and 0.05% Tween. The membrane was then incubated overnight at +4°C in the serum diluted 1:5 in a 1% BSA solution, PBS and 0.05% Tween. The control membrane was incubated in a 1% BSA solution, PBS and 0.05% Tween. The membrane was rinsed 4 times in PBS buffer and 0.05% Tween, then incubated for 1 hour at room temperature in a 1:1500 dilution of human IgE secondary antibodies labelled with peroxidase (Dako). The membrane was rinsed 4 times, then immersed in luminol in the presence of H2O2 directly on the image analyzer (Kodak digital Science 1 Digital Science 1D image analyzer). Image acquisition was performed after an exposure time of 6.6 minutes (20 uptakes).

The dot-blots showed binding of specific IgE to CMC and CMC-HCl samples. Binding was lower to the CMC-BSA mixture. There was no binding of specific IgE to BSA alone. The control membrane did not show non-specific binding to secondary antibodies (Figure 1).

Discussion

CMC (also known as carmellose or E466) is physiologically inert. It is a white to off-white, odorless powder and is slightly hygroscopic. It is soluble in water at all temperatures but practically insoluble in organic solvents. It has several properties: it is a stabilizing, emulsifying, thickening, binding, hydrophilic agent that retains water and can form a protective film. It increases viscosity when dissolved or dispersed in water. It helps form suspensions (from fluids to gels). In the pharmaceutical industry, it is used in topical skin products, eye drops, tablets, solutions for injection, such as corticosteroids for intra-articular in-

jection and other injectable hormones (LHRH and somatostatin). In injectable preparations, CMC is used as a suspension agent for poorly hydrosoluble components. It is a component of barium preparations, hydrocolloidal dressings (because of its absorbent properties) and also adhesive stoma bags. It is also used extensively in the food industry: ice creams, cakes, etc… (table 1) (3). CMC was long thought to lack toxicity and have only laxative effects after oral administration to animals. As a food additive, CMC is considered to be safe in quantities up to 25mg/kg/day since it is inert and not absorbed. Despite its wide spread use, allergy to CMC is rare (table 2). A case of contact dermatitis to CMC was described by Hamada in 1978 in a baker who used CMC to make cakes (4). CMC was also incriminated in the onset of chronic urticaria after using hydrocolloidal dressings (5). A case of reaction to CMC in a lidocaine gel used to lubricate a gastroscope to facilitate its passage has also been described (6) (Table 2), with onset of upper and lower limb weakness lasting for several hours. A nasal provocation test to CMC triggered ipsilateral nasal congestion and dysesthesia of the tongue and temporal region for 30 minutes.

Anaphylactic shock to CMC was first documented with veterinary products in cattle (penicillin, vaccines, steroids) (7)(8)(9). In 1972, De Weck drew attention to the potential risk of accidents in man due to CMC in medicinal products (10). Anaphylaxis was later described after intra-articular injections of sustained-release corticosteroids containing CMC (11-21) (Table 2). Reactions generally consist of pruritus and urticaria followed by hypotension and anaphylactic shock.

Allergic reactions after oral administration of CMC are not documented(Table 2). One team carried out oral challenge tests in 3 patients, demonstrating tolerance up to 136 - 250 mg (18). Two oral challenges to 62 mg were negative (22). The rectal administration of a barium enema containing CMC has elicited an anaphylactic shock (23); the adverse accident occurred after insufflation. In our case, mastocytosis was excluded and the anaphylactic shock could be related to the amount of CMC in the Micropaque Colon® introduced into the intestine: 2.7 g (estimated at 3 g in the case reported by Muroi), whereas intra-articular infiltration usually contains about 15 to 30 mg. Similarly, the reaction could be potentiated by insufflation, which may increase passage into the blood by rupturing tight inter-cellular junctions so that the product enters the sub-epithelial space (24). Gastro-enterological examinations with barium are frequent, and the incidence of anaphylactic reactions occurring during these examinations is estimated at 1 in several thousand. However, the true number may be higher. (2).

The immunological nature of these reactions has been shown by skin tests (prick-tests, IDR, patch-tests and occasionally scratch-tests) (Table 2), by leukocyte histamine release test (LHRT) to CMC (12, 22), and also by lymphocyte stimulation tests (LST) (6). When the concentration of CMC for positive intradermal tests was specified in the published cases, the range was from 0.075 to

Figure 1 - Dot-blot: One micro-liter of each solution was placed on a PVDF membrane: (1) CMC (5µg/µl), (2) CMC-HCl, (3) CMC-BSA, (4) BSA. After drying and saturation in BSA, the membrane was incubated with (A) the test serum (1:5), or (B) a BSA solution for one night. The IgE bound to CMC was revealed by a human IgE secondary antibody labelled with peroxidase. Chemoluminescence was read directly on an image analyzer (Kodak).

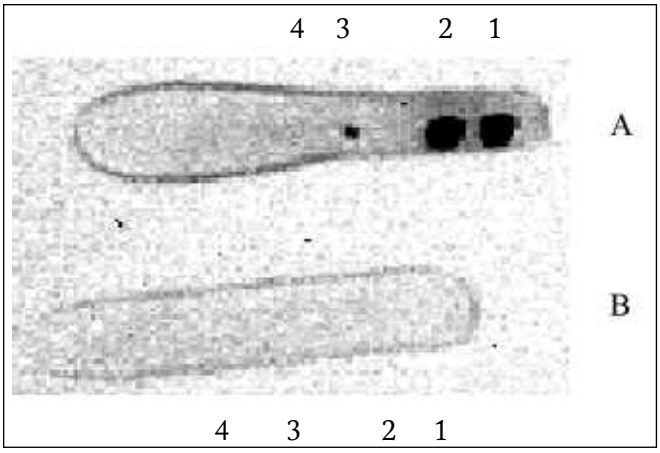

Table 1 - Typical products containing CMC (3)

Packed cheesecake and cake mixes	Ice cream
Icings	Milk shake
Bakery fillings	Frozen mousse
Fruit bar filling	Tomato sauces
Meringues	Salad dressings
Dips and spreads	Frozen chips
Tinned potato salad	Frozen fish sticks
Tinned cream soups	Batter coatings
Frozen whipped toppings	Low–calorie orange squash
Whipped topping basis	Low–calorie orange squash
Sterilized whipping cream	Cottage cheese

Table 2 - Allergy to CMC: cases described in the literature.

Reference	Patient	Pathology	Medication	Administration route	Time to reaction	Type of reaction	Prick test, IDT, HLRT, BAT, CAST, LTT and NPT
Müller et al. 1973	Man 29 y.o.	Shoulder Arthralgia	Volon® (triamcinolone acetonide)	Infiltration	Immediate	Anaphylactic reaction	- Prick-test Volon® - - Scratch-test Volon® - - IDT Volon® + - IDT CMC (7.5mg/ml) + and 0.75mg/l +
Bourgeois et al. 1989	Woman 51 y.o.	Carpal tunnel syndrome	Altim® (cortivazol)	Infiltration	30 min	-Localized and then generalized urticaria Treatment with antihistame and corticosteroids	- Prick test Altim® (1:10) +: localized urticaria spreading to the arm and the hemi-thorax - Prick test CMC (10-7) +: localized urticaria with spreading to the arm
					Several hours	-Anaphylactic reaction	
Beaudouin et al. 1992	Woman 49 y.o.	Sciatalgia	Hydrocortancyl® (hydrocortisone)	Infiltration	2 min	Anaphylactic reaction	- IDT Hydrocortancyl+ (10µg/ml) (13 mm) - IDT CMC+ (10µg/ml) (9 mm) - LHRT + hydrocortancyl® and CMC
Beaudouin et al. 1992	Woman	Epicondylitis	Altim® (cortivazol)			Anaphylactic reaction	- Prick and IDT Altim®+ (1µg/ml) -IDT CMC + (1µg/ml) - BAT CMC- LHRT CMC-
Murietta-Aguttes et al. 1991	Woman 30 y.o.	Nonallergic Rhinitis	Kenalog® (triamcinolone acetonide)	Injection	5 min	Cough, localized and then generalized urticaria	- IDT CMC (1µg/ml) + (wheal 11 mm / flare 30 mm)
Patterson et al. 1995	Man 26 y.o.	Sturge-Weber skin lesion of the face	Kenalog® (triamcinolone acetonide)	Injection	15 min	Anaphylactic reaction	-Skin testing Kenalog® (1µg/l) + (>10mm) -Skin testing CMC (0,1µg/ml) + (>10mm) -Immunoblot +
Muroi et al. 1997	Woman 63 y.o.		Balgin S Solution number 3® (Suspension of barium sulphate)	Double-contrast upper gastrointest. Examination	30 min	Anaphylactic reaction	-Skin testing barium sulphate suspension + (wheal 25 by 20 mm/flare 57 by 50mm) -Skin testing CMC + (wheal 21 by 21 mm/ flare 57 by 50 mm) - LHRT by CMC +
Johnsson et al. 1999	Woman 77 y.o.	Chronic leg ulcer	Comfeel® (hydrocolloidal dressing)	Topical treatment	30 min 2 hours	-Itching in the ulcer area -Generalized urticarial rash and slight nausea	-1x1cm piece of the hydrocolloid dressing applied to her forearm for 20 min: stinging at the test site -Scratch test with the dressing: itchy weal and flare reaction -Prick test CMC (100µg/ml) +
Kakuyama et al. 1999	Woman 69 y.o.		Lidocaine jelly	For local anesthesic and lubrifiant in gastroscopic examination		Paresia of the limbs lasting several hours	-IDT lidocaine and CMC - -NPT lidocaine- -NPT CMC + (ipsilateral nasal congestion and dysthesia of the tongue and the ipsilateral temporal region during 30 min - LTT CMC +
Caduff et al. 2000	Man 41 y.o.	Lumbago	Kenacort® (triamcinolone acetonide)	Infiltration		Anaphylactic reaction	-Prick test CMC - -IDT CMC +
Caduff et al. 2000	Woman 53 y.o.	Calcaneodynia	Kenatocort® (triamcinolone acetonide)	Infiltration	2-3 hours	Anaphylactic reaction	-Scratch test CMC+

Montoro et al. 2000	Man 47 y.o.	Recurrent arthritis in the left shoulder	Trigon Depot® (triamcinolone acetonide)	Infiltration	15 min	Anaphylactic reaction	- Prick Trigon® (40mg/ml) - IDT Trigon® (4mg/ml) + (11 x 12mm) -Prick CMC (8mg/l) - IDT CMC (8mg/l) + (9x8mm)
Schuster et al. 2000	Woman 54 y.o.	Achillodynia	Kenacort® (triamcinolone acetonide)	Infiltration	5 min	Anaphylactic reaction	-Prick Kenacort® (7,5mg/ml)+ (>3mm) -IDT Kenacort ® (1µg/ml)+ (>15mm) and (10µg/ml)+ (>20mm) -Scratch-test CMC (7,5mg/ml)+ (>5mm)
Bigliardi et al. 2003	Woman 76 y.o.	Sciatalgia	Kenacort® (triamcinolone acetonide)	Infiltration	30 min	Anaphylactic reaction	-Prick test Kenacort® - IDT Kenacort® (100µg/ml) + -Prick test CMC (7.5µg/ml)– IDT CMC (0.075µg/ml) + -LHRT CMC - CAST CMC - Immunoblot - OC 136 mg-
Bigliardi et al. .2003	Man 37 y.o.	Shoulder arthralgia	Triamcort- Depot® (triamcinolone acetonide)	Infiltration	30 min	Anaphylactic reaction	-Prick Triamcort®-(10 mg/ml)- IDT Triamcort®(100µg/ml) + -Prick CMC (10ug/ml)- IDT CMC (1ug/ml)+ -CAST CMC + Immunoblot -OC 250 mg –
Bigliardi et al. 2003	Man 59 y.o.	Elbow arthralgia	Diprophos® (bethamethasone)	Infiltration	30 min	Anaphylactic reaction	- Prick test Diprophos® + IDT Diprophos® + -Prick test CMC (7.5µg/ml) equivocal -IDT CMC (0.075µg/ml) + -CAST CMC - -Immunoblot – -OC 250 mg
Garcia-Ortega et al. 2003	Man 48 y.o.		Trigon Depot® (triamcinolone acetonide)	Intra-articular injection	2 hours	Anaphylactic reaction	- Prick test Trigon® + -Prick test CMC (1mg/l)+ wheal-and-flare local reaction with severe forearm itching and erythema lasting 30 min
Bircher et al. 2004	Man 52 y.o.		Kenacort® (Triamcinolone acetonide)	Paravertebral infiltration		Anaphylactic reaction	-Prick-test Kenacort® - -IDT CMC (7.5mg/l, 1:10) +
Opplinger et al. 2004	Woman 20 y.o.	Lichen planus	Kenacort® (triamcinolone acetonide)	Infiltration	1 hour	Generalized urticaria	-Prick test Kenacort® – -Prick test CMC – -IDT Kentocort® (0.1µ/l) + - IDT CMC (0.1µg/l) +
Opplinger et al. 2004	Woman 55 y.o.	Epicondylitis	Diprophos® (bethamethasone)	Infiltration	20 min	Anaphylactic reaction	-Prick test Diprophos® + -Prick test CMC + - IDT Diprophos® and CMC-
Venturini et al. 2006	Woman 69 y.o.		Trigon depot® (triamcinolone acetonide)	Infiltration		Anaphylactic reaction	-Prick test triamcinolone with CMC + -Prick test CMC +
Venturini et al. 2006	Man 38 y.o.		Trigon depot® (triamcinolone acetonide)	Infiltration		Anaphylactic reaction	-Prick test triamcinolone with CMC + -Prick test CMC +
Rival 2008	Man 58 y.o Woman	Fibrotic nodule Calcaneum osteophytose	Altim® (cortivazol) Altim®	Infiltration infiltration	Unknown <1min	Anaphylaxis anaphylaxis	IDT:+ oral challenge (62 mg):: negative Prick test :++ oral challenge (62 mg):: negative

IDT: intradermal test, BAT: basophil activation test, LHRT: Leucocyte Histamine Release Test, NPT: Nasal Provocation Test, LTT: Lymphocyte Transformation Test, CAST: Cellular Antigen Stimulation Test.

10 microgram/ml. In this study, skin tests with immediate results were negative with up to 1 mg/ml in 6 controls, but positive in our patient at 10 μg/ml. BAT and CAST were also positive to CMC. The presence of specific IgE was first demonstrated by Patterson in 1995 by an immunoblot analysis performed after anaphylactic shock following intra-articular injection of sustained-release corticosteroids (1). Muroi reported finding CMC-specific IgE, using the ELISA technique, in a case of anaphylactic shock following barium enema (2). We present here a third case where CMC-specific IgEs were identified. The identification of specific IgE using a dot-blot analysis shows that CMC is indeed an allergen.

With this technique, the CMC bound non-covalently to the PVDF membrane. Heat-induced binding to a protein gives a weaker result, suggesting that the CMC epitopes are masked by the protein binding. Processing to obtain the free acid form did not modify the allergenicity of CMC.

Muroi et al. searched for specific IgE using ELISA in 387 healthy subjects (25). They showed an incidence of 9%. In their opinion, he combination of CMC-specific IgE and a positive LHRT could identify subjects at high risk of anaphylactic reaction.

In our case, sensitization to CMC probably occurred during intra-articular injections of sustained-release corticosteroids carried out months or years before the barium enema. However, questions remains as to the role of dietary CMC as a long-term sensitizing factor, especially in people with impaired GI tract mucosa. So far allergy to CMC in food has not been reported. Further studies should be however carried out

References

1. Patterson DL, Yunginger JW, Dunn WF, Jones RT, Hunt LW. Anaphylaxis induced by the carboxylmethylcellulose component of injectable triamcinolone acetonide suspension (Kenalog). Ann Allergy Asthma Immunol 1995; 74:163-6.
2. Muroi N, Mori S, Ono S, Takahashi HK, Fujii T, Hosoi S, Henmi K, Nishibori M. Allergy to carboxymethylcellulose. Allergy 2002;57:1212-3
3. Hanssen M, Marsden J, Kenton L. Everything one should know about additives in food. 1985; 150.
4. Hamada T, Horiguchi S. A case of allergic contact dermatitis due to sodium carboxymethyl cellulose. Jap J Ind Health 1978; 20: 207-11.
5. Johnsson M, Fiskerstrand EJ. Contact urticaria syndrome due to carboxymethylcellulose in a hydrocolloid dressing. Contact Dermatitis 1999; 41: 344-5.
6. Masahiro Kakuyama, Hiroshi Toda. An adverse effect of carboxymethylcellulose in lidocaine jelly. Anesthesiology 1999; 91:1969
7. Kendall PH. Untoward effects following local hydrocortisone injection. Ann Physical Med 1958; 4:170-5.
8. Leeman W, De Weck AL, Schneider CH. Hypersensitivity to carboxyméthylcellulose as a cause of anaphylactic reactions to drugs in cattle. Nature 1969; 223:621-623.
9. Black L, Menard FJRR, Beadle GG, Pay TWF. Hypersensitivity in cattle after foot-and-mouth disease vaccination: response to hydroxypropyl-methylcellulose. J Hyg 1975; 75:79-86.
10. De Weck AL, Schneider CH. Allergic reactions in man, horse, and cattle due to the presence of carboxymethylcellulose in drug formulations. Proc. Eur Soc Stud Drug Toxicity 1972; 13:203-204.
11. Muller E, Pevny I, Metz G. Hypersensitivity towards carboxymethylcellulose, constituent of a steroid crystal suspension. Der Hautarzt 1973; 24:317-8.
12. Bourgeois M. Choc anaphylactique sévère après infiltration de cortivazol. Allergie au carboxyméthylcellulose. Rev Fr Allergol.1989; 29: 143-144.
13. Beaudouin E, Kanny G, Guéant JL, Moneret-Vautrin DA. Anaphylaxis caused by carboxylmethycellulose: report of 2 cases of shock from injectable corticoids. Allerg Immunol 1992; 24:333-5
14. Murrieta-Aguttes M, Michelen V, Leynadier F, Duarte-Risselin C, Halpern GM, Dry Jean. Systemic allergic reactions to corticosteroids. J Asthma 1991; 28: 329-39.
15. Caduff C, Reinhart WH, Hartmann K, Kuhn M. [Immediate hypersensitivity reactions to parenteral glucocorticoids? Analysis of 14 cases]. Schweiz Med Wochenschr 2000; 130: 977-83.
16. Montoro J, Valero A, Elices A, Rubira N, Serra-Baldrich E, Amat P, Malet A. Anaphylactic shock after intra-articular injection of carboxymethylcellulose. Allergol Immunopathol 2000; 28: 332-3.
17. Schuster C, Wuthrich B, Hartmann K, Kuhn M; Anaphylaxis to E 466. Allergy 2000; 55:303-4
18. Bigliardi PL, Izakovic J, Weber JM, Bircher AJ. Anaphylaxis to the carbohydrate carboxymethylcellulose in parenteral corticosteroid preparations. Dermatology 2003; 207:100-3
19. Garcia-Ortega P, Corominas M, Badia M. Carboxymethylcellulose allergy as a cause of suspected corticosteroid anaphylaxis. Ann Allergy Asthma Immunol 2003; 91:421.
20. Oppliger R, Hauser C. Anaphylaxis after injection of corticosteroid preparations--carboxymethylcellulose as a hidden allergen. J Dtsch Dermatol Ges 2002; 2:928-30.
21. Venturini M., Lobera T, Pozo M.D., Gonzalez I., Blasco A. Immediate hypersensitivity to corticosteroids. J Investig Allergol Clin Immunol 2006; 16:51-56.
22. Rival-Tringali, A. L., N. Gunera-Saad, et al. Tolerability of oral administration of carboxymethylcellulose in two patients presenting anaphylactic reaction after carboxymethylcellulose injection]." Ann Dermatol Venereol 2008 ;135: 402-6.
23. Muroi N, Nishibori M, Fujii T, Yamagata M, Hosoi S, Nakaya N, Saeki K, Henmi K. Anaphylaxis from the carboxylmethylcellulose component of barium sulfate suspension. N Engl J Med 1997; 337:1275-7.
24. Nishibori M, Muroi, N. Anaphylaxis from the carboxymethylcellulose component of barium sulfate suspension. N Engl J Med 1997; 337:1275-7.
25. Mori S, Muroi N, Ono S, Takahashi HK, Nishibori M. Analysis of sensitization to carboxymethylcellulose: identification of high risk group using ELISA and histamine release experiment. Inflamm Res 2004;53:164-9.