
Anaphylaxis to disodium cromoglycate

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Background: Reports about side effects from cromolyn sodium (DSCG) are few and only a minority of them indicate the possibility of an immediate type I hypersensitivity reaction.

Methods: We report an 8-year-old boy with a history of seasonal rhinoconjunctivitis and asthma. The patient reported two immediate episodes of acute asthma following inhalation of a cromolyn sodium (DSCG) capsule with an interval of 6 months. The latter occasion was also associated with conjunctivitis and generalized urticaria, requiring emergency treatment.

Results: An end-point prick test elicited a 4-mm wheal at 10 mg/mL with DSCG solution for inhalation and DSCG eye drops. An end-point intradermal skin test with DSCG solution for inhalation elicited a 12-mm mean diameter wheal at 10 mg/mL. During the intradermal test, the patient developed conjunctivitis and wheezing with a FEV₁ fall of 27% from baseline. Controlled conjunctival and bronchial challenge tests were positive. The bronchial challenge test was repeated 3 years later showing a FEV₁ fall of 22% five minutes after inhalation of 1 mg/mL DSCG during one minute. A leukocyte histamine release test performed by an autoanalysis fluorometric procedure, with several dilutions of DSCG, was negative.

Conclusions: This case of DSCG anaphylaxis satisfies the criteria for an IgE-mediated reaction. We believe that thought should be given more frequently to this mechanism when patients report adverse reactions to DSCG.

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INTRODUCTION

Disodium cromoglycate (DSCG) or cromolyn, available since 1973, has been considered an antiallergic drug, acting principally as a mast cell stabilizer. Reports about side effects from DSCG are few and only in a minority of them do the authors indicate the possibility of an immediate type I hypersensitivity reaction.^{1–3}

CASE REPORT

The patient is an 8-year-old boy with a history of seasonal rhinoconjunctivitis and asthma. Skin prick tests with 16 allergens demonstrated positive reactions to grass and olive pollen. Treatment with an oral antihistamine, DSCG capsules (Intal, Fisons Limited, England) by inhalation, and immuno-

therapy with a pollen extract was prescribed for spring seasonal symptoms. In a follow-up visit 1 year later, the patient reported immediate acute asthma following the first inhalation of a DSCG capsule and, for this reason, discontinued the medication. Six months later, after inhaling one capsule of DSCG (Frenal, Sigma-Tau SA, Spain), he again had immediate acute asthma. This occasion was also associated with conjunctivitis and generalized urticaria, requiring emergency treatment.

TESTS PERFORMED

The following tests were performed 3 months after the second reaction. The patient and his parents received information about possible risks of skin and challenge tests, and prior to each challenge a written informed consent was signed by the parents. As reagents for the skin tests, the DSCG solution for inhalation (Nebulcron, Fisons Limited, England) without any additive and

DSCG eye drops (Cusicrom, Cusí SA, Spain) containing benzalkonium chloride, both diluted in saline solution, were used. An end-point prick test elicited a 4-mm wheal at 10 mg/mL with both reagents. An end-point intradermal skin test with DSCG solution for inhalation elicited a 12-mm mean diameter wheal at 10 mg/mL. During the intradermal test, the patient developed conjunctivitis and wheezing with an FEV₁ fall of 27% from baseline. Prick and intradermal skin tests gave negative results in ten atopic patients previously treated with DSCG.

One drop of DSCG eyedrop solution diluted with saline in increasing concentrations was applied to one of the patient's eyes. As control, a drop of saline was used on the other eye. After 15 minutes, the concentration of 1 mg/mL of DSCG induced conjunctival redness, itching, and slight edema in the challenged eye.

A controlled bronchial challenge test with a 20-mg capsule of DSCG elicited a peak-flow fall of 48% five minutes after inhalation. The patient also had cough, wheezing, conjunctivitis, and a generalized skin rash. The symptoms improved, and the peak-flow values returned to prechallenge levels in 60 minutes without medication. Bronchial challenges with a capsule containing lactose and inhalation of 4 mg sodium nedocromil (Tilad, Fisons Limited, Spain) did not produce any bronchial reaction in the patient. Methacholine PC₂₀ was 14 mg/mL prior to the bronchial challenge test.

Bronchial challenges with a 20-mg capsule of DSCG were negative in six patients who reported cough after inhalation of this drug.

A prick test with DSCG (10 mg/mL) was positive 8 months and 3 years later. Bronchial challenge test repeated 3 years later elicited an FEV₁ fall of 22% five minutes after inhalation of 1

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mg/mL DSCG during one minute. FEV₁ returned to prechallenge levels in 30 minutes without medication.

Total IgE concentration in serum was 1316 IU/mL. A leukocyte histamine release test performed by an autoanalysis fluorometric procedure, with several dilutions of DSCG, was negative.

DISCUSSION

Since being introduced in England in 1968, cromolyn has achieved wide usage, with only occasionally reported adverse reactions. The most common side effects, such as cough, dry mouth, pharyngeal irritation or mild transient bronchospasm, have been attributed by most investigators to local irritative effects of the powder on the hyperreactive airways.⁴ In some cases, inhalation of DSCG has resulted in severe anaphylaxis,⁵ even causing death.⁶ Although in these cases an IgE mechanism was not considered, other authors have demonstrated an IgE-mechanism in patients with reactions to DSCG by skin prick tests,² passive transfer,¹ or detection of serum specific IgE by RAST.³

The failure of DSCG to release histamine in vitro from the patient's ba-

sophils may be due to an inadequate drug protein interaction, permitting cross-linking of receptors on the basophils in vitro, or to the tendency of DSCG to form an insoluble complex with calcium and magnesium ions contained in the buffer system.⁵

In our patient, the positivity of skin tests and conjunctival and bronchial challenges suggest that the mechanism was the result of an IgE-mediated reaction. Although in all reported cases of anaphylaxis to the drug DSCG previously had been well tolerated in our patient, the reaction apparently occurred after inhalation of the first capsule. The hypersensitivity to the drug persisted 3 years later.

In summary, this case of DSCG anaphylaxis satisfies the criteria of an IgE-mediated reaction. We believe that thought should be given more frequently to this mechanism when patients report adverse reactions to DSCG.

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REFERENCES

1. Brown LA, Kaplan RA, Benjamin PA, et al. Immunoglobulin E-mediated

anaphylaxis with inhaled cromolyn sodium. *J Allergy Clin Immunol* 1981; 68:416-20.

2. Skarpaas IJK. An unexpected reaction towards disodium cromoglycate. *Allergy* 1987;42:318-9.
3. Wass U, Plaschke P, Björkander J, Berlin L. Assay of specific IgE antibodies to disodium cromoglycate in serum from patient with an immediate hypersensitivity reaction. *J Allergy Clin Immunol* 1988;81:752-7.
4. Settipane GA, Klein DE, Boyd GK, et al. Adverse Reactions to Cromolyn. *JAMA* 1979;241:811-3.
5. Serup J. Severe asthmatic reaction during long-term treatment with disodium cromoglycate powder inhalations. *Acta Med Scand* 1979;205:447-8.
6. Leynadier F, Pujade-Lauraine, Cornaille G. Death after cromoglycate. *Allergy* 1985;40:540-1.

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