CASE REPORT

‘Empty sella syndrome’: a case of a patient with sodium succinate hydrocortisone allergy

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Abstract

Objective: We present the case of a woman with ‘empty sella syndrome’ who experienced generalized urticaria after the administration of sodium succinate hydrocortisone in two episodes.

Methods: The patient underwent an allergological evaluation (prick, intradermal, and patch tests) with hydrocortisone sodium succinate, hydrocortisone acetate, hydrocortisone, hydrocortisone sodium phosphate, methylprednisolone hemisuccinate, methylprednisolone, and preservatives held in the formulation of sodium succinate hydrocortisone (sodium phosphate and methyl-*p*-oxybenzoate). The basophil activation test (BAT) was also performed with hydrocortisone. The single-blind i.m. challenge test was performed with hydrocortisone sodium phosphate in 4 days.

Results: Skin test with hydrocortisone sodium succinate and methylprednisolone hemisuccinate was positive. On the contrary, allergological tests performed with other formulations of the same steroids and preservatives were negative. These results showed an immediate-type allergy to succinate ester. BAT was not helpful to improve our diagnostic work-up because our patient was a ‘nonresponder.’ Therefore, the patient underwent successfully to a challenge test with hydrocortisone sodium phosphate.

Conclusions: Patients with succinate ester allergy can tolerate alternative corticosteroids without ester.

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Introduction

Since the 1950s, corticosteroids have been used extensively for pharmacotherapy in atopic, autoimmune, endocrinologic, and inflammatory diseases; they are also important tools for treating allergic reactions and this property seems to contradict their capacity to induce allergic symptoms, a condition that could be a problem of clinical and therapeutic importance. Corticosteroids may cause allergic contact dermatitis in about 0.5–5% of patients following topical therapy (1), but systemic allergy is rare (0.3%) (2).

Sometimes the corticosteroids adverse events seem to be related to esters conjugated to them. Actually, as corticosteroids are poorly soluble in saline solution, they are coupled with esters such as phosphate and succinate ester, which make them water soluble for i.v. administration.

Case report

We present a case of a 45-year-old woman suffering from ‘empty sella syndrome,’ treated with daily oral

hydrocortisone (25 mg/day), daily s.c. somatotropin 4 days/week, and i.m. injection of hydrocortisone in case of surgical procedures to prevent surrenal failure. Before the surgery, she was treated with i.m. sodium succinate hydrocortisone (100 mg) (Flebocortid Richter; Sanofi-Aventis, Milan, Italy) and, after 15 min, she developed generalized urticaria that disappeared after i.m. administration of 4 mg betamethasone. The next day she again had urticaria and was treated with oral betamethasone. The following year she experienced a new episode of generalized urticaria after i.m. sodium succinate hydrocortisone injection and was treated with i.v. betamethasone.

Thus, the patient underwent an allergological evaluation (prick, intradermal, and patch tests) with hydrocortisone sodium succinate, hydrocortisone acetate, hydrocortisone, hydrocortisone sodium phosphate, methylprednisolone hemisuccinate, methylprednisolone, and preservatives held in the formulation of sodium succinate hydrocortisone (Table 1).

The results of the skin tests were recorded after 20 min and compared with negative (saline solutions) and positive controls (histamine 10 mg/ml).

Table 1 Results of allergological evaluation.

	Skin prick test (undiluted solution)	Intradermal test (1:1000 and 1:100 dilution)	Patch test (undiluted solution)	Challenge
Corticosteroids drugs				
Hydrocortisone-21-sodium succinate (50 mg/ml)	Positive (3 mm)	Positive (7 mm)	Negative	NP
Hydrocortisone (10 mg)	Negative	NP	Negative	Negative
Hydrocortisone acetate (25 mg/ml)	Negative	NP	Negative	NP
Hydrocortisone sodium phosphate (100 mg/ml)	Negative	Negative	Negative	Negative
Methylprednisolone hemisuccinate (40 mg/ml)	Positive (3 mm)	Positive (9 mm)	Negative	NP
Methylprednisolone (4 mg)	Negative	NP	Negative	Negative
Preservatives				
Sodium-phosphate	Negative	NP	Negative	Negative
Methyl- <i>p</i> -oxybenzoate	Negative	NP	Negative	Negative

NP, not performed.

The basophil activation test (BAT) was also performed with hydrocortisone. Briefly, fresh whole blood was incubated with hydrocortisone at different concentrations (0.01, 0.1, and 0.5 mg/ml). Basophil stimulation buffer and anti-IgE (BD Pharmingen, San Jose, CA, USA) were used respectively as negative and positive control. The sample was analyzed on an FACSCanto flow cytometer (BD Biosciences Immunocytometry Systems, San Jose, CA, USA). Data of BAT were expressed as percentage of CD63+ basophils.

The single-blind i.m. challenge test was performed with hydrocortisone sodium phosphate (100 mg/ml) in 4 days. Day 1: three doses of saline solution (placebo). Day 2: 1, 2, 3, and 4 mg. Day 3: 10, 20, 30, and 40 mg. Day 4: 100 mg. Each dose was administered every 30 min.

Prick and intradermal tests with hydrocortisone sodium succinate and methylprednisolone hemisuccinate were positive, while prick, intradermal, patch, and challenge tests performed with the preservatives and other formulations of hydrocortisone and methylprednisolone were negative (Table 1). These tests were also negative in five healthy control patients.

To confirm allergic sensitization to hemisuccinate ester and predict tolerance to hydrocortisone sodium phosphate, we performed BAT with hydrocortisone without the preservatives (3). After *in vitro* stimulation with hydrocortisone for 30 min, we did not observe any stimulation of basophil reactivity with anti-IgE antibody and with allergenic stimulation in our patient. Since the patient was a 'nonresponder' (due to the absence of positive control stimulation) BAT was not helpful to improve our diagnostic work-up.

Moreover, to exclude sensitization to sodium phosphate, we performed a single-blind i.m. challenge test with hydrocortisone sodium phosphate, which the patient tolerated without the side effects.

Discussion

These outcomes suggest an independent immunologic potential of the esters; we could demonstrate in our

patient an immediate-type allergy to succinate ester, which confirmed the data from previous studies (2, 4, 5). Moreover, unlike other studies, we have administered the patient the same corticosteroid that caused reaction, but conjugated with a different ester. In fact, our patient, suffering from 'empty sella syndrome,' needed parenteral hydrocortisone for emergency and despite being allergic to sodium succinate hydrocortisone she tolerated sodium phosphate hydrocortisone without the side effects.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- Goossens A & Matura M. Contact allergy to corticosteroids. *Allergy* 2000 **55** 698–704. (doi:10.1034/j.1398-9995.2000.00121.x)
- Burgdorff T, Venelman L, Vogt T, Landthaler M & Stolz W. IgE-mediated anaphylactic reaction induced by succinate ester of methylprednisolone. *Annals of Allergy, Asthma and Immunology* 2002 **89** 425–428. (doi:10.1016/S1081-1206(10)62046-7)
- Sturm GJ, Kranzelbinder B, Sturm EM, Groselj-Strele A & Aberer W. The basophil activation test in the diagnosis of allergy: technical issues and critical factors. *Allergy* 2009 **64** 1319–1326. (doi:10.1111/j.1398-9995.2009.02004.x)
- Caimmi S, Caimmi P, Bousquet J & Demoly P. Succinate as opposed to glucocorticoid itself allergy. *Allergy* 2008 **63** 1641–1643. (doi:10.1111/j.1398-9995.2008.01894.x)
- Koutsostathis N & Vovolis V. Severe immunoglobulin E-mediated anaphylaxis to intravenous methylprednisolone succinate in a patient who tolerate oral methylprednisolone. *Journal of Investigational Allergology and Clinical Immunology* 2009 **19** 330–331.

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