CASE REPORT

Systemic Corticosteroid Hypersensitivity in Children

N Gaspar de Sousa, C Santa-Marta, M Morais-Almeida

Immunoallergy Department, CUF-Descobertas Hospital, Lisbon, Portugal

Abstract

We describe 5 cases of immediate-type reactions to systemic corticosteroids observed during the last 2 decades in boys aged 2, 4, 8, 9, and 10 years. Symptoms ranged from generalized urticaria and angioedema to anaphylactic shock immediately after administration. Oral betamethasone was implicated in 2 cases, oral prednisolone in 2 cases, and intravenous prednisolone in 1 case. The parents of patient 5 refused the skin tests. The remaining patients underwent skin prick tests with the following undiluted corticosteroids: parenteral prednisolone, oral prednisolone, parenteral methylprednisolone, parenteral dexamethasone, parenteral hydrocortisone, and oral betamethasone. If the results were negative, intradermal tests were performed with the same drugs at increasing concentrations. Skin test results were positive for all suspect corticosteroids, thus indicating an immunoglobulin E–mediated mechanism. Two patients had positive skin test results to other corticosteroids, suggesting cross-reactivity. An oral challenge test was performed with deflazacort in 4 cases and with betamethasone in 1 case; the results were negative.

Key words: Systemic corticosteroids. Hypersensitivity. Immediate reactions. Children. Skin tests.

Resumen

Se describen 5 casos de reacciones inmediatas a corticoesteroides sistémicos observados durante las dos últimas décadas en niños de 2, 4, 8, 9 y 10 años de edad. Los síntomas incluyeron desde urticaria generalizada y angioedema hasta choque anafiláctico inmediatamente después de la administración. La betametasona oral estuvo implicada en 2 casos, la prednisolona oral en otros 2 casos y la prednisolona intravenosa en 1 caso. El quinto paciente rechazó someterse a pruebas cutáneas. El resto de pacientes se sometieron a pruebas de punción cutánea con los corticoesteroides no diluidos siguientes: prednisolona parenteral, prednisolona oral, metilprednisolona parenteral, dexametasona parenteral, hidrocortisona parenteral y betametasona oral. Si los resultados eran negativos, debían realizarse pruebas intradérmicas con los mismos fármacos a concentraciones crecientes. Los resultados de las pruebas cutáneas fueron positivos para todos los corticoesteroides sospechosos, lo que indica un mecanismo mediado por la inmunoglobulina E. Dos pacientes obtuvieron resultados positivos en las pruebas cutáneas para otros corticoesteroides, lo que indica reactividad cruzada. Se realizó una prueba de provocación oral con deflazacort en 4 casos y con betametasona en 1 caso; los resultados fueron negativos.

Palabras clave: Corticoesteroides sistémicos. Hipersensibilidad. Reacciones inmediatas. Niños. Pruebas cutáneas.

Introduction

Corticosteroids have been used since the late 1940s for their anti-inflammatory and immunomodulatory effects [1]. They are still used today in patients of all ages with a range of diseases (allergic, cutaneous, respiratory, rheumatologic, renal) and even in transplant recipients. This broad spectrum means that several specialties use these agents on a daily basis in settings ranging from the private office to the emergency room. Hypersensitivity most commonly presents with topical corticosteroids, and the incidence of delayed-type hypersensitivity is between 0.2% and 5% [2-4].

Immediate-type, anaphylactic reactions to systemic corticosteroids are very uncommon, but can prove fatal. Little is known regarding their incidence, although some authors have estimated it to be 0.1% to 0.3% [4-6]. Most of the reports describe individual cases or small series [7,8] and mainly involve adults. The number of cases in pediatric patients is also small [9-11], despite widespread use of corticosteroids in this population. We report the only 5 cases of immediate-type hypersensitivity to systemic corticosteroids in children observed and studied by the authors in the last 2 decades.

Case Description

Case 1

A 9-year-old boy with no known history of allergic disease and no previous prescription of corticosteroids received prednisolone succinate intravenously for a large local reaction after an insect bite. After 5 to 10 minutes he developed urticaria, rhinoconjunctivitis, dyspnea, and hypotension, which promptly resolved with intramuscular adrenaline and antihistamines.

Case 2

A 10-year-old boy with a history of allergic rhinitis and asthma experienced 2 separate yet similar episodes of acute urticaria, angioedema, and vomiting immediately after taking oral prednisolone prescribed for an asthma exacerbation. These episodes were self-limiting and did not require treatment.

Case 3

An 8-year-old boy with a history of allergic rhinitis and asthma complained of oral angioedema and facial urticaria that rapidly generalized and was accompanied by sudoresis and a feeling of impending doom 5-10 minutes after taking 70 drops of betamethasone prescribed for an asthma exacerbation. He was medicated in the emergency room with antihistamines and an unknown corticosteroid. His symptoms resolved.

Case 4

A 4-year-old boy who had received oral betamethasone for an asthma exacerbation experienced immediate-type generalized urticaria and angioedema and lost consciousness 5 minutes after ingestion. His symptoms resolved after administration of adrenaline and an unknown corticosteroid in the emergency room. The patient had a history of anaphylaxis

Table 1. Characteristics of Study Subjects and Healthy Volunteers[a]

Patient	Culprit Corticosteroid	SPT	IDT	Oral Challenge Test
1	Intravenous prednisolone succinate	Positive for PSG, prednisolone succinate, and methylprednisolone, Negative for dexamethasone, hydrocortisone succinate, and betamethasone	Negative	Negative for betamethasone
2	Oral prednisolone	Positive for PSG. Negative for prednisolone succinate, methylprednisolone succinate, dexamethasone, hydrocortisone succinate, and betamethasone	Positive for prednisolone succinate (1:100). Negative for methylprednisolone succinate, dexamethasone, hydrocortisone succinate, Testing for PSG was not performed	Negative for deflazacort
3	Oral betamethasone	Negative	Positive for betamethasone (1/100). Negative for PSG, prednisolone succinate, methylprednisolone succinate, dexamethasone, hydrocortisone succinate, and betamethasone	Negative for deflazacort
4	Oral betamethasone	Negative	Positive for betamethasone (1/10). Negative for PSG, prednisolone succinate, methylprednisolone succinate, dexamethasone, hydrocortisone succinate, and betamethasone	Negative for deflazacort
5	Oral prednisolone	ND	ND	Negative for deflazacort

Abbreviations: IDT, intradermal test; ND, not done; PSG, prednisolone stearoyl glycolate; SPT, skin prick test.

to snail. The parents reported another 2 self-limiting episodes of immediate-type facial urticaria and angioedema after the ingestion of the same drug 3 months earlier.

Case 5

A 2-year-old nonatopic boy experienced generalized urticaria and angioedema less than 15 minutes after taking the third dose of oral prednisolone for nephrotic syndrome. His symptoms resolved with systemic antihistamines. After the second dose, 8 hours earlier, the parents referred mild facial urticaria that resolved spontaneously in 2 hours.

Informed consent was obtained from the parents of patients 1 to 4 to perform skin prick tests (SPT), intradermal tests (IDT), and oral challenge tests with alternative corticosteroids. The parents of patient 5 refused the skin tests, but agreed to the oral challenge test. SPTs were performed with the following undiluted corticosteroids: intravenous prednisolone sodium succinate, 10 mg/mL; oral prednisolone stearoyl glycolate, 20 mg/mL; intravenous methylprednisolone sodium succinate, 40 mg/mL; intravenous dexamethasone sodium phosphate, 5 mg/mL; intravenous hydrocortisone sodium succinate, 50 mg/mL; and oral betamethasone, 0.5 mg/mL. IDTs with the same corticosteroids were performed in 10-fold increasing concentrations (1:1000 to 1:10) only if the SPTs were negative. Skin tests to deflazacort were not performed because hypersensitivity reactions to this drug have never been reported, and, to our knowledge no other authors perform them. We applied the positivity criteria suggested in the European Academy of Allergy and Clinical Immunology position paper on skin tests in the diagnosis of drug hypersensitivity [12]. These results are summarized in the Table. The same SPTs and IDTs were performed in 10 adult atopic volunteers and were all negative.

All patients had a positive skin test result to at least 1 corticosteroid. Single-blind placebo-controlled oral challenge with an alternative systemic corticosteroid was performed in all cases: betamethasone in patient 1 and deflazacort in the remainder. Deflazacort was not used in patient 1 because it was not commercially available when the child was studied. The methodology used for the challenge tests was as follows: the daily dose of corticosteroid was determined according to current weight and progressively administered at 20-minute intervals (10%, 20%, 30%, and finally 40% of the total daily dose). The challenge test results were invariably negative.

Discussion

The mechanism of action of this type of immediate-type reaction to systemic corticosteroids has been much debated. Some authors have suggested an immunoglobulin (Ig) E–mediated reaction [13]. In our case, skin test results with the suspect drug were positive in all patients tested, strongly indicating an IgE-mediated reaction. An irritant effect at higher corticosteroid concentrations can be virtually ruled out, as none of the atopic controls had positive skin test results. All patients had previously been exposed to one or more systemic corticosteroids, except patient 1. It is therefore difficult to explain the presumably IgE-mediated reaction, although neonatal administration or administration during the first years of life cannot be totally ruled out, as this was solely based on the parents' testimony. Patients 1 and 2 also had positive skin test results to at least one other corticosteroid, thus raising the possibility of cross-reactivity, which is consistent with the results of some authors [7,13] and contradicts those of others [8]. In this regard, cross-reactivity has mainly been reported between hydrocortisone, prednisolone and methylprednisolone [7,13].

These 3 corticosteroids have also been the most frequently associated with immediate-type reactions [7-9]. In our population, prednisolone was implicated in 3 cases and betamethasone in 2, although the latter has very rarely been linked with this type of hypersensitivity. Prescription habits can account at least partially for these differences. In Portugal, prednisolone, betamethasone, and deflazacort are by far the most commonly prescribed systemic corticosteroids for children.

Deflazacort, dexamethasone, and betamethasone are usually considered safe systemic alternatives in immediate-type allergy [7,8,10]. This observation is consistent with our results, as 4 patients tolerated deflazacort and 1 tolerated betamethasone. The safety profile of these agents is particularly relevant, as 3 of our patients were asthmatic and could thus have required systemic corticosteroids as rescue medication.

The main limitation of our study is that we did not perform challenge tests with the suspect drug. However, the high risk involved, the patients' clinical histories, and the positive skin test results render such a procedure ethically questionable, especially in children.

To our knowledge, this is the largest published series of pediatric patients with well-characterized immediate-type reactions to systemic corticosteroids. Immediate-type reaction to corticosteroids is probably underdiagnosed, because symptoms can mimic a worsening of the underlying disease. Emergency room staff in particular must be aware of this type of hypersensitivity reaction and take it into consideration in the differential diagnosis of a patient who has received a systemic corticosteroid.

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Nuno Alexandre Gaspar de Sousa

Immunoallergy Department
CUF-Descobertas Hospital
Rua Mário Botas
1998-018 Lisbon, Portugal
E-mail: nunogasparsousa@gmail.com