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Steroid allergy: report of two cases

Ya-Shang Peng, Shyh-Dar Shyur, Horng-Ying Lin, Cheng-Yu Wang

Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan, ROC

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Corticosteroid preparations have anti-inflammatory and immunosuppressive properties and are widely used in the treatment of asthma and allergic disorders. Steroids themselves, however, can induce hypersensitivity reactions. The number of reports on contact allergy or anaphylactic reactions is increasing. Steroid hypersensitivity should be considered in any patient whose dermatitis becomes worse with topical steroid therapy, or in patients who develop systemic allergic reactions after the use of systemic steroids. The diagnosis can be confirmed by skin testing, *in vitro* evidence of specific IgE, oral or parenteral challenge, or an allergic patch test. The latter may be positive within 20 min, which indicates immediate contact urticaria, or at 72 to 96 h, which indicates delayed contact hypersensitivity. In this article we report two cases of steroid allergy. Case 1 was a 5-year-old asthmatic boy with an anaphylactic reaction to steroids and aspirin. Case 2 was a 2-year-old boy with atopic dermatitis and steroid contact urticaria. Both cases 1 and 2 showed positive results to triamcinolone, dexamethasone, hydrocortisone, and methylprednisolone in the immediate skin allergy test. Case 2 had immediate contact urticaria to hydrocortisone and clobetasone butyrate. Case 1 had a positive systemic allergic reaction to cortisone acetate, prednisolone, and dexamethasone on the oral steroid challenge test, and also had aspirin induced angioedema and urticaria 10 min after challenge with 50 mg aspirin.

Key words: Anaphylaxis, aspirin sensitivity, contact urticaria, steroid allergy

Steroid-induced anaphylactic reactions and contact hypersensitivity caused by hydrocortisone were first reported in the 1950s [1]. These reactions, however, have gained increased attention only until recently. Several reports on "steroid sensitivity" to topical, inhalant, oral, and parenteral steroids have been published. The reported incidence of contact hypersensitivity to topical corticosteroids ranges from 2% to 5% [2], whereas other allergic sensitization reactions are less common. These reactions include urticaria, bronchospasm, anaphylactic reaction, rash, paresthesias, tremor, nausea, vomiting, and angioneurotic edema [3]. Hydrocortisone, prednisolone, and methylprednisolone are the most commonly reported steroids that cause anaphylactic-like reactions. Dooms-Goossens and Morren [4] reported in 1992 that corticosteroids were the seventh most common causative agents for contact hypersensitivity. In 1992, Wilkinson also showed that hydrocortisone was the third commonest allergen in patients with stasis dermatitis, and the eighth commonest allergen in patients with hand dermatitis [2,5]. The results of a multicenter study [6] on contact allergy to corticosteroids showed 2.6% of 7238 patients had contact allergy to one or more steroids, which include budesonide (1.4%), tixocortol pivalate (1.4%), and hydrocortisone-17-butyrate (1%). These results are comparable with the results of a Swiss multicenter study on corticosteroid sensitivity, where an incidence of 2.2% was reported, with 1% of the patients reacting to budesonide, tixocortol pivalate, and hydrocortisone-17-butyrate [7]. We report two cases of steroid allergy in order to remind pediatricians that widely used corticosteroid preparations can cause various allergic reactions.

Corresponding author: Dr. Shyh-Dar Shyur, Department of Pediatrics, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 104, Taiwan, ROC.

Case Reports

Case 1

A 5-year-old boy presented to the Mackay Memorial Hospital with asthma and allergic rhinitis experienced urticaria and angioneurotic edema about 10 min after taking cortisone acetate, prednisolone, dexamethasone, and aspirin (Fig. 1). The symptoms lasted a few days after the use of cortisone acetate, but he had experienced more severe and persistent symptoms for 1 week after taking dexamethasone. The severity of symptoms associated with steroids was directly related to the strength of the preparations with dexamethasone, which caused more severe symptoms than did prednisolone; whereas prednisolone caused more severe symptoms

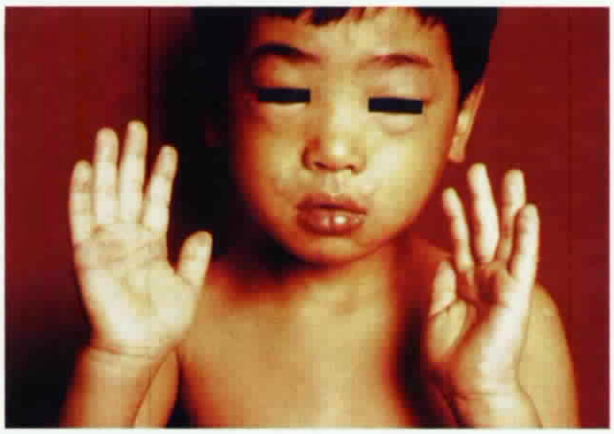

Fig. 1. Case 1 showing obvious angioneurotic edema and urticaria over the face, trunk, and extremities 10 min after taking 50 mg aspirin. Similar, but less severe symptoms appeared after oral steroid challenge testing (dexamethasone > prednisolone > cortisone acetate).

than did cortisone acetate. Beclomethasone inhalation, however, did not produce any reactions or worsen his pulmonary function.

Case 2

A 2-year-old boy with asthma and atopic dermatitis presented to the Mackey Momorial Hospital. He developed contact urticaria only when using clobetasone butyrate and hydrocortisone topically, whereas oral prednisolone, beclomethasone inhalation, and budesonide nasal aqua were tolerated.

We performed an immediate skin allergy test (Table 1), an allergic patch test (Table 2), and an oral steroid challenge test in cases 1 and 2 and three other atopic children. The skin test was performed using steroids (triamcinolone, dexamethasone, hydrocortisone, and methylprednisolone), *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, histamine (1 mg/mL), and 50% glycerin as a negative control. The substances were applied to the palmar surface of the forearm by puncture method. The concentration of steroids was the same as that used for systemic administration (Table 1). The mean diameters of the wheal-and-flare lesions were recorded at 20 min. A wheal at least 3 mm larger than the wheal of the negative control was considered positive. The patch test was read at 20 min, or at 72 to 96 h. Oral challenge was performed by giving one tablet of prednisolone (5 mg/tablet), cortisone acetate (25 mg/tablet), or dexamethasone (0.5 mg/tablet) at intervals of 7 days. The patients were observed at least 2 h after administration. The challenge test was non-blinded.

Both cases 1 and 2 showed positive results to triamcinolone, dexamethasone, hydrocortisone, and methylprednisolone on the immediate skin allergy test. Only case 2 with contact urticaria had positive results to hydrocortisone and clobetasone butyrate on the allergic patch test at 20 min, but not at 72 to 96 h. Only case 1 had generalized urticaria and angioneurotic edema using cortisone acetate (25 mg/tablet), prednisolone (5 mg/tablet), and dexamethasone (0.5 mg/tablet) on the oral steroid challenge test. He also

Table 1. Immediate skin allergy test

	Case 1	Case 2	Control
Positive control (histamine, 1 mg/mL)	+	+	+
Negative control (glycerin, 50%)	-	-	-
Triamcinolone (group B) (20 mg/mL)	+	+	-
Dexamethasone (group C) (5 mg/mL)	+	+	-
Hydrocortisone (group A) (50 mg/mL)	+	+	-
Methylprednisolone (group A) (40 mg/mL)	+	+	-
DP (10 000 AU)	+	-	+
DF (10 000 AU)	+	-	+

Abbreviations: DP = *Dermatophagoides pteronyssinus*; DF = *Dermatophagoides farinae*

Table 2. Allergic patch test for immediate contact urticaria

	Case 1	Case 2	Control
Betamethasone dipropionate (group D) (0.064%)	-	-	-
Fluocinonide (group B) (0.05%)	-	-	-
Triamcinolone acetonide (group B) (0.1%)	-	-	-
Desoximetasone (group C) (0.25%)	-	-	-
Hydrocortisone (group A) (1%)	-	++	-
Clobetasone butyrate (group D) (0.05%)	-	+	-

experienced aspirin hypersensitivity 10 min after challenge with 50 mg aspirin.

Discussion

Allergy to corticosteroids presents as a systemic allergic reaction after ingestion or injection of corticosteroid, or as contact hypersensitivity following the topical application of corticosteroid preparations.

Four groups of corticosteroids were classified by Coopman *et al* [8] in 1989 according to their substitutions of C_{16} or C_{17} on the D ring and on the C_{20} or C_{21}-side chain as the basis of cross-reactive sensitization patterns (Table 3). The four groups included group A (hydrocortisone type), group B (triamcinolone acetonide type), group C (betamethasone type), and group D (hydrocortisone- and clobetasone-17-butyrate type). The potential for systemic hypersensitivity reactions in allergic individuals is particularly prominent in group A glucocorticosteroids, which are among the bulk of those administered systemically [9, 10]. Of the various corticosteroid preparations available, the most commonly implicated one in producing anaphylactic-like reactions seems to be hydrocortisone [3,11]. Reactions to methylprednisolone sodium succinate and oral prednisolone have been also reported. The most common steroids that cause contact hypersensitivity include tixocortol pivalate (group A), budesonide (group B), and hydrocortisone-17-butyrate (group D) [6,7,12,13]. Amcinonide, clobetasol propionate, triamcinolone acetonide, hydrocortisone acetate, and hydrocortisone alcohol are also common offenders [12].

Steroid sensitivity is not a single entity but a complex phenomenon in which several mechanisms and factors, such as intolerance, idiosyncrasy, or immunological reactions, interact [3]. Substances with a cyclopentenophenanthrene structure in their molecule, such as hydrocortisone, can act as incomplete antigens or haptens, which become complete antigens when combined with body proteins [4]. The above reactions may involve type I immunological reactions of Gell and Coombs, in which a reaction occurs between antigens and specific antibodies of the immunoglobulin E class. It is known that several steroid structures, such as corticosteroids, are transported and attached to plasma proteins. Thus, it is emphasized that some steroids linked with proteins could produce antisera with steroid specificity [14]. Some steroid anesthetics such as althesin and pancuronium bromide have induced anaphylactic and other reactions during intravenous administration [15,16]. Those reactions to hydrocortisone and hydrocortisone-17-butyrate hypersensitivity are truly immunological and not idiosyncratic, as shown by Lauerma *et al* [17,18]. They demonstrated that the infiltrate in corticosteroid patch test reactions was identical to that in other contact hypersensitivity reactions. An *in vitro* test has shown that Langerhans cells, but not monocytes, are capable of presenting corticosteroids with the induction of a lymphocyte proliferative response. It is possible for a patient to become Addisonian as a result of immunological attack against hydrocortisone in the adrenal gland [9,19]. The antibodies of idiopathic Addison's disease have been demonstrated to react with enzymes in the pathway of hydrocortisone biosynthesis [20].

Aspirin-sensitive asthmatic patients may be particularly predisposed to anaphylactic reactions to intravenous hydrocortisone [21-24]. The mechanisms involved are not clear, although arachidonic acid metabolites have been suspected to have a role because aspirin is known to inhibit cyclooxygenase [22].

The clinical features of steroid hypersensitivity include urticaria, bronchospasm, anaphylactic reaction, maculopapular rash, paresthesias, tremor, nausea, vomiting, angioneurotic edema, and contact dermatitis [3]. The incidence of steroid-induced anaphylactic reactions is very low, but these reactions are more common in aspirin-sensitive asthmatic patients. The clinical features in patients with steroid-induced anaphylaxis include loss of consciousness, hypotension, shock, abdominal cramps, vomiting, diarrhea, hypersecretion of mucus, bronchospasm, angioedema, urticaria, generalized pruritis, and flushing, which are all the same as anaphylactic reactions induced by other agents [3,11,23,24].

The patient in case 1 had angioneurotic edema and urticaria about 10 min after taking cortisone acetate, prednisolone, and dexamethasone. The severity of symptoms was directly related to the strength of the steroids. The patient in case 2 had contact urticaria, an immediate reaction of the skin within minutes to 1 h after contact occurring via an immunological (IgE-mediated) or non-immunological pathway. The reported incidence of contact hyper-sensitivity to topical corticosteroids ranges from 2% to 5% [2]. Resistant eczema and multiple positive patch test reactions to medicaments are typical features in corticosteroid-sensitive patients [2,6,25,26]. Lesions localize mainly on the hands and legs. Patients who develop atopic, allergic, and/or irritant contact der-matitis on the hands, as well as those who experience stasis dermatitis and leg ulceration, are often present with corticosteroid contact allergy [25,26]. Contact hypersensitivity is not limited to the skin; there are several reports of worsening

of perennial rhinitis from budesonide [27,28] and tixocortol pivalate [29,30] with perinasal dermatitis from nasal spray, and a report of conjunctivitis following the ophthalmic use of betamethasone valerate [31]. The cross-reactivity among glucocorticosteroids extends to other non-glucocorticosteroids including sex steroids [32]. Physicians who treat patients with known glu-cocorticosteroid allergy should thus be alert to the possibility of dermatitis related to stress reactions (systemic contact dermatitis to endogenous hydrocortisone) and/or the menstrual cycle (autoimmune progesterone dermatitis) [9,10,32].

The diagnosis of steroid hypersensitivity is aided by obtaining the patients' history, observing clinical manifestations, and performing laboratory tests. Unexpected systemic allergic reaction after systemic use of corticosteroids, particularly in patients with aspirin intolerance, or resistant eczema localized mainly on the hands and legs may suggest steroid hypersensitivity. Skin prick testing and *in vitro* measurement of IgE levels can help in identifying a true IgE-mediated reaction. Patch testing is the diagnostic method of choice for corticosteroid-induced immediate contact urticaria (found at 20 min) or delayed contact hypersensitivity (read at 72 or 96 h). Cases 1 and 2 had positive reactions to steroid in the skin puncture test. Only case 2 had positive findings in the patch test recorded at 20 min. Preservatives in topical steroid preparations may also sensitize the skin, and should be considered as potential allergens. The newer corticosteroids often result in more positive allergy tests [33] because of better skin penetration. This phenomenon is also observed in budesonide and the newer esters. It is important to differentiate steroid hypersensitivity from other causes of systemic allergic reactions and contact dermatitis.

The treatment of corticosteroid hypersensitivity is to avoid the causative drug. Other steroids, particularly those in other groups (group C produces less hypersensitivity), may be tried, but the cross-reactivity between groups is a hazard. There are few reports of cough and bronchospasm caused by inhaled beclomethasone dipropionate [34,35] or budesonide [36], and these should be reversible with prompt administration of oxygen, adrenaline, diphenhydramine, and nebulized β_2-agonists [23,24].

Corticosteroid hypersensitivity, which occurs most frequently among patients with chronic dermatitis or aspirin intolerance, is increasingly recognized. Physicians should be aware of the possibility of an adverse reaction to steroid even when its previous use has been without incident [37].

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