

Angioedema and dysphagia caused by contact allergy to inhaled budesonide

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Inhaled corticosteroids may cause various adverse effects ranging from irritation to severe anaphylactic reactions and systemic contact dermatitis. We report a 43-year-old woman who developed sore throat, swelling of the lips and oral cavity and dysphagia, 2 weeks after the use of budesonide spray (Budefat®) for treatment of bronchial asthma. The symptoms occurred with a delay of 3–4 h after the treatment $\times 2$ daily. There were no immediate reactions on prick and intracutaneous testing with the commercial product used by the patient. However, marked pruritic infiltration developed within 24 h, progressing to coalescing eczematous lesions over the following 2 days. In addition, severe oedema of the right upper eyelid was observed. On patch testing, budesonide was strongly positive at day 2 and 3 in a concentration ranging from 1% to 10 p.p.m. (in petrolatum). Other corticosteroids of group A, B, C and D were completely negative. Repeated open application tests with amcinonide and triamcinolone acetonide cream on the ventral aspect of the upper arm were negative. Bronchial exposure to alternative sprays containing beclomethasone dipropionate (group D), fluticasone-17- propionate (D) and dexamethasone-21-isonicotinate (C) was well tolerated. In conclusion, this case is instructive, because the symptoms which developed after a short period of corticosteroid inhalation suggested a type I allergy. Testing proved a severe type IV contact allergy restricted to budesonide (group B), without cross-reactions to major corticosteroids of other groups.

Key words: angioedema; budesonide; corticosteroids; lack of cross-sensitivity; medicaments; patch testing; prick testing. © Blackwell Munksgaard, 2003.

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Corticosteroids are widely used in the treatment of asthma, allergic disorders and other immunological diseases for their anti-inflammatory and immunosuppressive properties. But they may also cause various adverse effects, ranging from local irritation to severe anaphylactic reactions and systemic contact dermatitis (1–3).

We present a patient with symptoms suggesting a type I allergy after inhaling a corticosteroid, whereas testing proved a type IV allergy.

Case Report

A 43-year-old woman developed sore throat, swelling of the lips and oral cavity and dysphagia, 2 weeks after the daily use of budesonide spray (Budefat®, Fatol, Schiffweiler, Germany). This was her first treatment with a corticosteroid for bronchial asthma. The symptoms occurred with a delay of 3–4 h after inhalation $\times 2$ daily.

Prick and intracutaneous testing were performed with Budefat® as is. Readings were performed after 20 min, 24 h and 48 h. There were no immediate reactions on prick or intracutaneous testing with the commercial product used by the patient. However, marked pruritic infiltrations developed within 24 h, progressing to coalescing eczematous lesions over the following 2 days. In addition, severe oedema of the right upper eyelid was observed.

She was patch tested to a corticosteroid series (Hermal, Reinbek, Germany; Chemotechnique, Tygelsjö, Sweden) (Table 1). The patch test reactions were scored according to the criteria of the German Contact Dermatitis Research Group. Budesonide was strongly positive on day 2 and 3 in a concentration ranging from 1% to 10 p.p.m. in petrolatum. Other corticosteroids of group A, B and D were completely negative. On prick testing, there were no immediate reactions after 20 min (Table 1).

Table 1. Patch test results with corticosteroids

Substance (corticosteroid group)	Concentration (in pet.)	Manufacturer	20 min	48 h	72 h
Amcinonide (B)	0.10%	Hermal, Reinbek, Germany	—	—	—
Hydrocortisone (A)	1.0%	Hermal	—	—	—
Triamcinolone acetonide (B)	0.10%	Hermal	—	—	—
Clobetasone-17-propionate (D)	0.25%	Hermal	—	—	—
Hydrocortisone-17-butyrate (D)	0.10%	Hermal	—	—	—
Bethamethasone-17-valerate (D)	0.12%	Hermal	—	—	—
Tixocortol pivalate (A)	1.0%	Chemotechnique, Tygelsjö, Sweden	—	—	—
Budesonide (B)	1.0%	Chemotechnique	—	++	++
	0.10%		—	++	++
	100 p.p.m.		—	++	++
	10 p.p.m.		—	++	++

A repeated open application test with amcinonide and triamcinolone acetonide (group B) commercial creams (Amciderm Creme[®], Hermal, Reinbek, Germany; Volon A Creme[®], Bristol-Myers Squibb, Munich, Germany) was performed over a period of 2 weeks $\times$ 2 a day on the ventral aspect of the upper arm. There was no reaction to either product.

Bronchial exposure tests were performed with the following therapeutic alternatives: fluticasone propionate (group D), beclomethasone dipropionate (group D) and dexamethasone-21-isonicotinate (group C) containing sprays (Flutide[®], GlaxoSmithKline/Cascan, Bühl, Germany; Bronchocort[®], Fujisawa, Munich, Germany; Auxilison[®], Boehringer Ingelheim, Ingelheim, Germany). They were all well tolerated without adverse effects (Table 2).

Comment

For confirmation of our suspicion that budesonide was the cause of the allergic reaction, other bronchial corticosteroid sprays with similar or even identical vehicles were exposed and well tolerated. We, therefore, concluded that budesonide was responsible for the severe adverse reaction in this patient.

Contact allergy to inhaled budesonide can occur within few days and produce severe symptoms such as stomatitis, perioral eczema, swelling of the lips and eyelids, urticaria, general pruritus

and nasal septum ulceration and perforation (after the use of budesonide-containing sprays) (3). Bircher et al. (4) have reported a 37-year-old man who developed similar symptoms to our patient from inhaled budesonide powder, after only 5 days of use. This patient was also negative on prick testing with budesonide and amcinonide but showed strong delayed reactions on patch testing. In addition, he developed a macular exanthema of the trunk after 2 days. Our patient was highly sensitive to budesonide only, as documented by the strong reactivity in the dilution series down to 10 p.p.m., associated with periorbital oedema.

Angioedema and urticarial reactions to chemicals and drugs are not always immunoglobulin E-mediated or a sign of intolerance but can sometimes be observed in conjunction with type IV allergy. Common examples are angioedema of the face in individuals highly allergic to the hair dye *p*-phenylenediamine (5) or β -lactam antibiotics such as ampicillin. In a series of 101 patients with adverse reactions to this group of antibiotics, 21 patients (20.8%) had a positive patch test, 10 of whom suffered from maculopapular eruption and 9 from urticaria/angioedema (6). Immune complexes may play a pathogenetic role in this subset of patients.

According to their chemical structures, corticosteroids are divided into 4 groups (A–D, (Table 3) (7–9). Recently, the group D was proposed to consist of 2 subdivisions: group D1

Table 2. Constituents of used and tested sprays

Budéfát [®] (Fatol, Schiffweiler, Germany)	Bronchocort [®] (Fujisawa, Munich, Germany)	Auxilison [®] (Boehringer Ingelheim, Ingelheim, Germany)	Flutide [®] (GlaxoSmithKline/Cascan, Bühl, Germany)
Budesonide (group B)	Beclomethasone dipropionate (group D)	Dexamethasone-21- isonicotinate (group C)	Fluticasone-17- propionate (group D)
Trichlorofluoromethane	Trichlorofluoromethane	Trichlorofluoromethane	Norfluorane
Cryofluorane		Cryofluorane	
Dichlorodifluoromethane	Dichlorodifluoromethane	Dichlorodifluoromethane	
Sorbitan trioleate	Sorbitan trioleate	Sorbitan trioleate	

Table 3. Group definition of corticosteroids (7–10)

Group A (Hydrocortisone type)	Group B (Triamcinolone type)	Group C (Betamethasone type)	Group D (Hydrocortisone and clobetasone-17-butyrate type)
Cortisone	Amcinonide	Betamethasone	Clobetasone-17-propionate
Cortisone acetate	Budesonide	Betamethasone sodium phosphate	Clobetasone-17-butyrate
Hydrocortisone	Triamcinolone acetonide	Dexamethasone	Hydrocortisone-17-butyrate
Hydrocortisone acetate	Flucinolone acetonide	Dexamethasone sodium phosphate	Hydrocortisone-17-valerate
Prednisolone	Flucinonide	Dexamethasone acetate	Betamethasone dipropionate
Prednisolone acetate	Halcinonide	Dexamethasone-21-isonicotinate	Fluticasone-17-dipropionate
Methylprednisolone acetate		Fluocortolone pivalate	Betamethasone-17- valerate
Prednisone		Fluprednidene acetate	Alclometasone dipropionate
Tixocortol pivalate		Fluocortolone caproate	Beclomethasone dipropionate

containing C₁₆ methylsubstitution and halogenation on the B ring (e.g. betamethasone dipropionate) and group D2 comprising the labile ester steroids that lack both substitutions (e.g. hydrocortisone-17-butyrate) (10).

Cross-reactions to corticosteroids of the same and of the other groups were not observed in our patient. This is unusual, because patients with a sensitivity to budesonide often react not only to other corticosteroids of group B (4, 11) but also to those of group D (8, 9) and, in some reported cases, also to group A (12).

On the other hand, Cooper and Shaw (13) reported a patient showing contact allergy to inhaled beclomethasone dipropionate (group D) who tolerated alternative therapy with inhaled budesonide (group B).

Therefore, reliable recommendations of safe alternative corticosteroid-containing inhalers in patients allergic to budesonide cannot be given based on the literature only. Such knowledge can serve as a guideline, but tolerance by each individual patient must be evaluated in every case.

Our patient is instructive, because the symptoms which developed after a short period of corticosteroid inhalation suggested a type I allergy. Testing proved a severe type IV contact allergy restricted to budesonide (group B), without cross-reactions to major corticosteroids of the other groups. Inhalational exposure tests with 2 corticosteroids of group D and one of group C identified therapeutic alternatives.

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