

Case report

Cutaneous-mucosal allergic contact reaction due to topical corticosteroids

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We report the case of a 41-year-old nonatopic woman with a previous history of eczematous reaction due to hydrocortisone who suffered worsening of her perennial rhinitis in association with perinasal dermatitis from the use of budesonide in nasal spray form, and stomatitis and pharyngitis due to budesonide in a bronchial inhaler. Patch tests with a series of 25 corticosteroids, some of them at different concentrations and in different vehicles, were positive to tixocortol pivalate, hydrocortisone, budesonide, prednisolone, hydrocortisone butyrate propionate, triamcinolone acetonide, and fluocinolone acetonide. For some of them, a 1% solution in ethanol gave a positive reaction when a 20% mixture in petrolatum did not. Like other authors, we suggest that some multiple positives may represent sensitization to several steroids independently, true cross-reactions, or both, and that ethanol is a better vehicle than petrolatum.

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Although steroid-induced contact dermatitis is now recognized with greater frequency, the appropriate corticosteroid (CS) concentrations and vehicles for skin tests have not yet been standardized, and the patterns of cross-reactivity among the various CS are not well established. Furthermore, there is a need for markers of CS allergy, as it is impractical to test all patients with a complete CS series (6, 10, 11, 33, 41). Hypersensitivity has mainly been reported with CS applied to the skin (2, 5, 14, 16, 17, 19, 29, 30, 32, 37, 38), but reactions may also occur on mucosal surfaces (13, 15, 20–23, 26, 27, 31, 36), and after systemic administration (2, 6, 10, 11, 24, 28, 33, 34, 41).

Budesonide (Bd) was introduced in Spain in 1990 by Astra-Ifesa SA as an aerosol for topically treating rhinitis and bronchial asthma. Recently, it has been supplied as cream and ointment. In spite of its wide use, only a few cases of sensitization have been reported (Medline database from 1966 to 1994, both inclusive) after the use of nasal inhalers (15, 21–23, 31, 36) (most of them by Spanish doctors) and only two with oral inhalers (20, 26).

Case report

A 41-year-old woman with perennial nonallergic rhinitis was treated with Bd nasal spray (Rhinocort[®], Astra-Ifesa SA, Barcelona, Spain), at a dose of 50 µg twice a day. She had not used it before. Forty-eight hours later, she developed worsening of her rhinitis, nasal burning and pruritus, and pruritic erythematous edematous plaques with vesiculation on the upper lip, perinasal area, and cheeks. After stopping Bd, the clinical symptoms completely disappeared in 1 week with no treatment. One month later, Bd was reintroduced in an oral inhaler (Olfex[®], Ifidesa-Aristegui, Bilbao, Spain) by mistake. The patient applied into her mouth 400 µg twice daily. Twelve hours after the second application, she experienced pharyngeal dryness and pruritus with intense erythema and edema of the oral mucosa and odynophagia. At the same time, an erythematous vesiculous papular eruption on her cheeks and peribuccal area was noted. Administration of Bd was discontinued and a progressive improvement of lesions was observed in 1 week without treatment.

The patient had a previous history (2 years before) of eczematous reactions (not well documented) related to the application of a topical cream containing hydrocortisone for a burn and, 1 year later, for treating chloasma.

First, epicutaneous tests were carried out with the standard European panel (Martí Tor SA, Barcelona, Spain) and a second panel including the components of Rhinocort® and Olfex® oral inhaler. Two weeks later, tests were done with a battery of 25 CS in petrolatum (pet) at different concentrations and, finally (2 weeks after that), the same CS in ethanol (eth) (Table 1). Drugs used in test preparations were obtained from the trade name dealers in Spain. Patch tests were performed on the back (clinically normal skin) with Leukotest® (Beiersdorf AG, Hamburg, Germany) covered by Mefix® (Mölnlycke Health Care AB, Sweden). As controls, pet and 94% eth were similarly applied. The patch test readings were conducted according to ICDRG guidelines at 2 and 4 days, and, in the case of CS, the patient was also examined at day 7.

CS were selected, among those marketed in Spain, for their known contact allergenic properties, their potential role as a marker for the detection of CS allergies, or their inclusion in studies of cross-sensitivity patterns. Vehicles and concentrations were established according to other references, and when it was not available a concentration in pet 10 times more than the commercial preparation was used. Whenever possible, a 20% CS concentration in pet and a 1% concentration in eth were tested (in the latter case, always fresh solutions, no more than 1 month old) (1–3, 8, 10, 11, 25, 41).

Results

Results of the standard European panel, ingredients of Rhinocort® and Olfex® oral inhaler (Freon and sorbitan trioleate), and vehicles were negative. In our CS series, seven of them proved strongly positive (Table 1). Since then, the site of them has remained heavily pigmented after resolution. A 1% solution in eth gave a positive reaction for hydrocortisone, prednisolone, triamcinolone acetonide, and fluocinolone acetonide when a 20% mixture in pet did not. Tests with tixocortol pivalate 20% pet and 1% eth proved more intensely positive and faster than 1% pet, but the latest was unquestionably positive too. No noticeable differences were detected between hydrocortisone results 1% and 10% in eth.

Discussion

Contact hypersensitivity from topical CS is becoming increasingly recognized (3–5% depending on the studies). In view of this fact and because the clini-

Table 1. Results of corticosteroid patch tests

Substance	Concentration	Vehicle	Results		
			48 h	96 h	7 d
Class A (hydrocortisone type)					
Hydrocortisone	1–10–25%	Petrolatum	–	–	–
	1–10%	Ethanol	+++	+++	+++
Prednisolone	2–20%	Petrolatum	–	–	–
	1%	Ethanol	+++	+++	+++
Prednisolone acetate	5–20%	Petrolatum	–	–	–
	1%	Ethanol	Not soluble		
Tixocortol pivalate	1%	Petrolatum	–	–	+++
	20%	Petrolatum	++++	++++	++++
	1%	Ethanol	++++	++++	++++
Methylprednisolone acetate	20%	Petrolatum	–	–	–
	1%	Ethanol	Not soluble		
Hydrocortisone acetate	10–20%	Petrolatum	–	–	–
	1%	Ethanol	Not soluble		
Cortisone acetate	10–20%	Petrolatum	–	–	–
	1%	Ethanol	Not soluble		
Prednisone	2–20%	Petrolatum	–	–	–
	1%	Ethanol	Not soluble		
Hydrocortisone butyrate propionate	1%	Petrolatum	–	–	–
	20%	Petrolatum	++++	++++	++++
	1%	Ethanol	Not soluble		
Class B (triamcinolone acetonide type)					
Triamcinolone acetonide	20%	Petrolatum	–	–	–
	1%	Ethanol	+++	+++	+++
Fluocinolone acetonide	20%	Petrolatum	–	–	–
	1%	Ethanol	++	++	++
Fluocinonide	20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Halcinonide	20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Budesonide	1%	Petrolatum	++++	++++	++++
	1%	Ethanol	Not done		
Class C (betamethasone type)					
Fluocortolone	20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Dexamethasone	10–20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Beclomethasone salicylate	20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Beclomethasone dipropionate	20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Paramethasone acetate	1–20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Flumethasone	5–20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Desoxymethasone	20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Class D (hydrocortisone-17-butyrate type)					
Clobetasone butyrate	20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Clobetasol propionate	20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–
Betamethasone dipropionate	20%	Petrolatum	–	–	–
	1%	Ethanol	Not soluble		
Betamethasone valerate	20%	Petrolatum	–	–	–
	1%	Ethanol	–	–	–

cal signs of CS allergy are not always obvious, some authors argue that CS should be added to the standard patch test series, and for this effect contact allergy markers should be found (3, 8, 10, 41). The best candidates at present are Bd, tixocortol pivalate, and, perhaps, hydrocortisone (3, 8, 10–12, 33, 41).

Bd is usually included in the CS patch test series and causes a higher rate of positive reactions (3.2–3.6%) than any other steroid except hydrocortisone (3, 8, 10). These results have been observed, even though Bd has never been used before or after a first exposure to it, strongly suggesting cross-reactivity among CS. In fact, our patient suffered a previous eczematous reaction with hydrocortisone. The special reactivity of Bd can be explained by the nature of the acetal function, which allows the molecule to mimic the molecular shape of either the acetonide or the ester group (6, 11, 30, 33). Indeed, Bd is a mixture of two diastereoisomers, the (*R*-) and the (*S*-) isomer. The (*R*-) isomer can be considered a full member of the acetonide group, and the (*S*-) isomer mimics the ester group (10–12, 30, 33).

Most CS patients react to several CS (as in our case). This may represent sensitization to several CS independently, true cross-reactions, or both (3). Coopman et al. (4) hypothesized that cross reactions occur primarily within four groups of CS (Table 1). Most of them happen between CS of the same group; this could justify the positivity of hydrocortisone, prednisolone, hydrocortisone butyrate propionate, and tixocortol pivalate (from the class A), and budesonide, triamcinolone acetonide, and flucinolone acetonide (from the class B). However, cross-reactions also occur between CS of different types, especially between A and D class and, in some cases, between B and D (4, 5, 33, 35).

Bd is therapeutically applied topically to the skin and mucous membranes. Contact hypersensitivity is not limited to the skin after cutaneous administration (2, 5, 14, 16, 17, 19, 29, 30, 32, 37, 38). There are several reports of worsening of rhinitis (13, 15, 21–23, 27, 31, 36) and rare cases of oral mucosa inflammation after nasal (21) or oral administration (20, 26). Interestingly, both features occurred in this case.

Groups at risk of developing CS hypersensitivity are patients with stasis dermatitis and leg ulceration, irritant and/or allergic dermatitis, perianal or vulval disease, etc (3, 7, 8, 39). Our patient had none of these disorders, but it is possible that the burn she suffered facilitated the initial sensitization to CS.

Patch testing conditions for CS have not been standardized. In general, higher concentrations than in the commercial products are required although they might inhibit the reaction in view of their anti-inflammatory effect. With regard to the vehicles, the

main problems are the solubility of the CS in them and their bioavailability. Eth 94% seems to be suitable for most CS; however, degradation reactions have to be taken into account. In other cases, pet seems to be satisfactory. Alternative vehicles (e.g., dimethylsulfoxide) may provoke irritant reactions (11, 41). A xerogel formulation could be an alternative, but more research is needed (9). Finally, certain authors use intradermal testing, but it is necessary to bear in mind that intradermal preparations are not well standardized and may induce generalized and/or skin reactions. Furthermore, intradermal testing does not resemble the clinical situation of allergic contact dermatitis (18, 34, 39–41). In our patients, a 1% solution in eth proved better for diagnosis of hydrocortisone, prednisolone, triamcinolone acetonide, and flucinolone acetonide sensitization than a 20% mixture in pet. With tixocortol pivalate and Bd, we suggest as a routine procedure to start with 1% pet, and, when the test remains negative, 20% pet and 1% eth could be used (in our case, the strong reaction with Bd 1% pet led us to avoid tests with 20% and 1% eth). For the other CS, both 20% pet and 1% eth could be tested simultaneously.

In summary, we report the case of a patient with previous history of eczematous reaction due to hydrocortisone who suffered a cutaneous-mucosal reaction from the use of Bd in a nasal spray form, and in a bronchial inhaler. Patch tests with a series of 25 CS, some of them at different concentrations and in different vehicles, were positive to seven of them. Some multiple positives may represent sensitization to several CS independently, true cross-reactions, or both. For some CS, a 1% solution in eth gave a positive reaction when a 20% mixture in pet did not.

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