

and IL-4 in our study and IL-4 from mast cells.⁷ However, we believe the primary effect of the (S,S)-isomer is to modulate the structure and function of the β_2 receptor in response to its engagement by the (R,R)-isomer. This would explain the observed lack of effect of (S,S)-formoterol alone, but induction of proinflammatory effects in the concomitant presence of (R,R)-formoterol, which are blocked by propranolol.

In summary, these data indicate that (S,S)-formoterol is not biologically inert, such that in racemic mixtures, it inhibited the beneficial effects of (R,R)-formoterol on proliferation, anti-inflammatory cellular surface marker expression, and cytokine secretion. The overuse of racemic formoterol and other racemic β_2 -adrenergic agents may worsen asthma exacerbations by increasing airway inflammation.

John W. Steinke, PhD
Dawn Baramki, BSN
Larry Borish, MD

From the Asthma and Allergic Diseases Center, Beirne Carter Center for Immunology Research, University of Virginia Health System, Charlottesville, Va.

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Symmetric, drug-related, intertriginous, and flexural exanthema in a patient with polyvalent intolerance to corticosteroids

To the Editor:

Adverse drug reactions to corticosteroids mostly arise after topical application¹ but rarely after systemic or

intralesional application. However, immediate-type reactions, mainly to succinated esters, and non-immediate-type reactions, most frequently to betamethasone and dexamethasone, have been reported.^{2,3}

Here we report the case of a 50-year-old woman with chronic nasal congestion who had been treated for years with different topical corticosteroids (she only remembered mometasone furoate, Nasonex, Essex, Germany), leading repeatedly to discomfort and swelling, and also with different oral corticosteroids detailed below. She reported having had exanthematous skin lesions at 3 previous occasions, always about 1 day after oral intake of prednisolone in 1985 (no data about preparations available) and methylprednisolone (Urbason, Sanofi-Aventis, Bad Soden, Germany; M-Prednihexal, Hexal AG, Holzkirchen, Germany) in 1990 and 2005.

When presenting in our department in October 2005, standard allergy testing resulted in an IgE level of 173 kU/L, and skin prick test (SPT) responses were positive for birch and grass mix, which is compatible with a history of pollinosis. Patch tests (PTs) were performed with the standard corticoid series (Hermal, Reinbek, Germany), including amcinonide, hydrocortisone, triamcinolone-acetonide, clobetasol-17-propionate, hydrocortisone-17-butyrate, betamethasone-17-valerate, budesonide, prednisolone, and dexamethasone-21-phosphate disodium salt. Additional skin tests (PTs, SPTs, and intradermal tests [IDTs] with immediate and late readings) were performed with commercially available corticosteroids. For SPTs and PTs, we used either pure tablets that were crushed and diluted in 0.9% NaCl or intravenous preparations, and for IDTs, a 1:10 dilution of intravenous preparations in 0.9% NaCl was applied.

Skin test responses were positive for betamethasone (Celestamine N, Essex Pharma, München, Germany), deflazacort (Calcort, Galenpharma, Kiel, Germany), dexamethasone (Fortecortin, Merck Pharma, Darmstadt, Germany), prednisolone (Decortin, Merck Pharma), and methylprednisolone (Urbason, Sanofi-Aventis) (see Table I for details). After oral provocation tests (OPTs) in November 2005 with increasing doses of betamethasone, the patient had a symmetric, erythematous maculopapular rash in her gluteal, perianal, intertriginous, and flexural areas without systemic symptoms about 12 hours after the last dose (total cumulative dose, 5.87 mg). OPTs with dexamethasone (13.5 mg) in January 2006, followed by hydrocortisone (78.75 mg; Hydrocortison Jenapharm, Mibe, Jena, Germany) in February 2006 and clocyprednol (9.375 mg; Syntestan, Teopharma, Pavia, Italy) in April 2006, led to the identical clinical picture at the same localizations and after the same latency period (Fig 1). Further testing was denied by the patient.

We diagnosed polyvalent, non-immediate-type hypersensitivity to corticosteroids with a clinical picture corresponding to *baboon syndrome*, a term introduced in 1984 by Andersen et al⁴ to classify patients with a skin eruption resembling the red gluteal area of a baboon. The main clinical findings include a sharply defined

TABLE I. Results of skin tests and OPTs performed with commercially available corticosteroids

Glucocorticosteroid	Trade name of drug tested	SPT, 20 min/D1/D2	IDT, 20 min/D1/D2	PT	OPT	Cross-reactive group
Betamethasone	Celestamin N	-/-/-	-/-/+	ND	+	C, D1
Cloprednol	Syntestan	-/-/-	ND*	-	+	A
Deflazacort	Calcort	-/+ +/+ +/+	ND*	-	ND	?
Dexamethasone	Fortecortin	-/-/-	-/-/+	ND	+	C
Hydrocortisone	Hydrocortison Jenapharm	-/-/-	ND	-	+	D2
Methylprednisolone	Urbason	-/-/-	-/+ +/+	ND	++‡	A
Prednisolone	Decortin	-/-/-	ND	++†	++‡	A

For definition of cross-reactive groups, see text.

ND, Not done.

*No intravenous preparation available.

†Performed with Hermal test preparation in paraffinum.

‡History positive.



FIG 1. A symmetric, intertriginous, and flexural maculopapular exanthema appeared about 12 to 24 hours after an OPT with cloprednol. Identical clinical pictures were observed after OPTs with betamethasone, hydrocortisone, and deflazacort at 4- to 6-week intervals.

symmetric erythema of the gluteal area and in the flexural or intertriginous folds without any systemic symptoms and signs. Latency periods are usually between a few hours and a few days after exposure. Reactions occur after systemic exposure to contact allergens, often mercury, and have also been reported after systemic drug exposure. Because the term *baboon syndrome* is ethically problematic, it was recently suggested to be replaced by the term *symmetric, drug-related, intertriginous, and flexural*

exanthema (SDRIFE), which specifically refers to the distinctive clinical pattern of this drug eruption. The following diagnostic criteria, all met by our patient, were proposed: (1) exposure to a systemically administered drug either at the first dose or on repeated dosing (excluding contact allergens); (2) sharply demarcated erythema of the gluteal/perianal area, V-shaped erythema of the inguinal/perigenital area, or both; (3) involvement of at least one other intertriginous/flexural localization; (4) symmetry of affected areas; and (5) absence of systemic symptoms and signs.⁵

The pathogenesis of SDRIFE is not clear, and an involvement of immunologic type IV mechanisms was discussed. In favor of this are the positive skin test results on PTs, on delayed readings of SPTs and IDTs, or both, just as in the case reported here.⁶ Special predisposing factors for the flexural distribution might be considered, such as anatomic structures (eg, the density of apocrine or eccrine glands with possible excretion of metabolized drugs, temperature or humidity.⁵ Also, a kind of recall phenomenon of previous dermatitis (ie, intertrigo and diaper rash) has been suggested.⁶

Drugs reported to elicit SDRIFE were mainly β -lactam antibiotics, but also several others have been involved (Table II).⁵⁻⁷

Corticosteroids have previously been associated with SDRIFE/baboon syndrome in only 2 cases. One was related to oral intake of deflazacort, resulting in baboon-like exanthema with fever, vomiting, malaise, and hypotension. PT results were positive for this drug.⁸ Another patient had a history of typical exanthema 48 hours after combined topical and oral treatment with betamethasone. PT results were positive for several corticosteroids of the PT series, including betamethasone; no OPT was performed. The authors suggested a sensitization of the patient through the percutaneous route because of long-term topical treatment with corticosteroids.⁹

In our patient corticosteroid sensitization might have been the result of either mucocutaneous contact (nasal decongestions) or of previous systemic application. This is the first report of a patient with SDRIFE

TABLE II. Drugs having been associated with SDRIFE/baboon syndrome

5-Aminosalicylic acid	Cinchocaine (topical)	Mitomycin C
Allopurinol	Ciprofloxacin	Naproxene
Aminophylline	Clindamycin	Neomycin
Amoxicillin (+ clavulanic acid)	Cloprednol	Nystatin
Ampicillin	Deflazacort	Oxycodone
Barium sulfate	Dexamethasone	Penicillin V
Betamethasone	Erythromycin	Pseudoephedrine
Bufexamac (topical)	Heparin	Pivampicillin
Cephalexin	Hydrocortisone	Prednisolone
Ceftriaxone	Hydroxyurea	Roxithromycin
Cefuroxime	Intravenous immunoglobulins	Salsalate
Cimetidine	Methylprednisolone	Terbinafine

Terms in boldface indicate drugs identified in our patient.

that was reproducibly elicited by corticosteroids belonging to all different cross-reacting groups known for contact dermatitis. The corticosteroids for systemic application have been recently assigned to these groups as follows: *group A* (hydrocortisone type)—cloprednol, (methyl-) prednisolone, prednisone fludrocortisone (oral); *group B* (triamcinolone acetone type)—budesonide, triamcinolone (oral); *group C* (betamethasone type)—betamethasone, dexamethasone, flucortolone (oral); *group D1* (betamethasone dipropionate type)—betamethasone (oral/intramuscular); and *group D2* (methylprednisolone aceponate type)—hydrocortisone (oral/intravenous).¹

Even though the allergenicity of corticosteroids is not fully understood, it seems that the epitopes are located on or around the D ring of the corticosteroid structure.¹ The strong sensitization to deflazacort (not yet assigned to a group) in SPTs and the positive OPT results with hydrocortisone in our patient do not support the recent observation that these 2 drugs might be a safe alternative in patients with nonimmediate reactions to corticosteroids.³ We strongly recommended that our patient continue the testing with other available corticosteroid preparations, such as prednylidene (not yet assigned to a group),

flucortolone, and triamcinolone to identify a drug that can be applied safely in case of emergency. Unfortunately, this testing was denied by the patient, and therefore in her allergy pass we had to record a polyvalent corticosteroid intolerance, without giving recommendations for alternative drugs.

In summary, we report on a unique case of SDRIFE developing in a patient after systemic administration of different corticosteroids from all known cross-reactivity groups, thus indicating an absolutely rare polysensitization to corticosteroids.

Regina Treudler, MD
Jan Christoph Simon, MD

From the Klinik für Dermatologie, Venerologie und Allergologie, Universitätsklinikum Leipzig A.ö.R., Leipzig, Germany, and the Global Allergy and Asthma European Network (GA² LEN), Brussels, Belgium. E-mail: regina.treudler@medizin.uni-leipzig.de

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