Follow your nose and keep an ear out : systemic dermatitis caused by prednisone derivatives in nose and ear drops

Follow your nose and keep an ear out: systemic dermatitis caused by prednisone-derivatives in nose- and ear drops.

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Running head: Systemic dermatitis to corticosteroids

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Introduction

Systemic dermatitis caused by corticosteroids (CS) may be underreported and is likely to be the result of previous skin sensitization to the **corticosteroid** molecule involved (1). We present a case in which nose- and ear drops were pinpointed as the specific allergen sources responsible for a recurrent, widespread skin eruption.

Case report

A 40-year-old, non-atopic, female patient was referred to us by her orthopaedic surgeon, treating her for a frozen shoulder, for the evaluation of **suspected** corticosteroid allergy. The patient reported the recent occurrence of an itchy maculopapular rash, originating in the main body folds, with subsequent involvement of the trunk, arms and legs, without any systemic complaints. History revealed that the dermatitis had occurred approximately 2 to 3 days following treatment with a nasal spray (Sofrasolone ®, Melisana Benelux NV, Brussels, Belgium), containing prednisolone acetate. Remarkably, no skin lesions of the face or around the orifices (nostrils, nose) nor nasal congestion or rhinitis were present. The patient had experienced a very similar, generalized eruption several years ago following the use of ear drops, compounded by her local pharmacist, and containing, according to what she could still retrieve from the pharmacist, either prednisolone or its derivative methylprednisolone. Also during that episode a rash had developed initially in the main body folds without any dermatitis of the ears being present. Furthermore, she recalled having had a localised skin reaction during childhood, with worsening of a pre-existent dermatitis, after applying a compounded pharmaceutical cream containing a corticosteroid of which she no longer could remember the name. The surgeon, planning to treat her with methylprednisolone perorally (Medrol®, Pfizer, Brussels, Belgium), wanted to clarify (i) the existence of corticosteroid allergy and (ii) the possible safe treatments he could initiate.

Because of the suspicion of delayed hypersensitivity, patch tests were performed with a baseline series (containing 3 corticosteroid screeners: tixocortol-21-pivalate 0.1% petrolatum [pet.], budesonide 0.01% pet. and hydrocortisone-17-butyrate 0.1% ethanol [eth.]), a cosmetic and pharmaceutical series and, additionally, **a commercial corticosteroid series of molecules diluted 1% in petrolatum (betamethasone-17-valerate, triamcinolone-16α-17-acetonide, alclomethasone-17,21-dipropionate, clobetasol-17-propionate, dexamethasone-21-phosphate). A supplementary, in-house prepared, corticosteroid series of molecules diluted 1% in ethanol 96° (triamcinolone-16α-17-acetonide, betamethasone -17,21-dipropionate, clobetasol-17-propionate, betamethasone-17-valerate, dexamethasone-21-phosphate, hydrocortisone-17-butyrate and 6α-methylprednisolone) was tested as well**. All commercially available tests were from Chemotechnique Diagnostics (Vellinge, Sweden) and patch test chambers from Allergeaze® (Smartpractice®, Phoenix, AZ, USA). The tests were fixed using Fixomull® stretch (BSN medical GmbH, Hamburg, Germany) and occluded for 2 days with readings at D2, D4 and D7. The reading at D7 showed a ++ reaction to nickel and to methylisothiazolinone (MI) 2000 ppm (0.2%) aq., a + reaction to the mixture of MI and methylchloroisothiazolinone (MCI/MI) 200 ppm (0.02%) aq. and a + reaction to methylprednisolone 1 % eth., with the early readings at D2 and D4 being completely negative for the latter. The 3 corticosteroid screeners of our baseline series, as well as the CS diluted in petrolatum, remained completely negative. The patient agreed to be patch tested again a few weeks later with some additional CS (methylprednisolone, this time at 0.1% eth., prednisolone 0.1% eth., hydrocortisone 0.5% in eth./DMSO [being an equal mixture of ethanol 96° and dimethyl sulfoxide], **betamethasone**

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Comment [M2]: This was added.

(un-esterified) 0.1% eth., **triamcinolone-16α-17-acetonide 0.1% eth. and dexamethasone-21-phosphate 0.1% eth.)**, this in order to allow us to better define the culprit sensitizer(s) and to offer her alternative CS for treatment. These patch tests confirmed the reactivity to the prednisone-derivatives prednisolone and methylprednisolone, as well as to the related Group-1 corticosteroid hydrocortisone with, however, already doubtful reactions (+?) at D2 and clear positive reactions at D4 (Fig. 1), which were still present at D7. The tests for **betamethasone** , **triamcinolone-16α-17-acetonide and dexamethasone-21-phosphate** remained negative at all readings. **In order to definitely rule out contact allergy to triamcinolone-16α-17-acetonide, the patient was a second time re-tested with much lower test concentrations of this corticosteroid (i.e. 0.01%, 0.001% and 0.0001%, all in ethanol 96°), as recommended before (2), but no reactions were observed at D2, D4, D7 or later.**

The reactions to nickel and to the isothiazolinones (MI and MCI/MI) were not considered relevant for the drug eruptions she had experienced, **but an MI-containing dish washing liquid was later found by the patient as the most probable cause of a mild hand dermatitis.** She was thus diagnosed with a type IV allergy to CS from Group 1 while **triamcinolone-16α-17- acetonide** (Group 2) and betamethasone (Group 3) were shown to be possible safe alternatives. **Triamcinolone-16α-17- acetonide** (Kenacort A10®, Bristol-Myers Squibb, Braine-l'Alleud, Belgium), dexamethasone (compounded by a pharmacist) or betamethasone (Celestone®, MSD, Brussels, Belgium), among others, are available in Belgium for systemic treatment and the latter drug was successfully administered to the patient without any adverse events.

We hypothesize that during childhood the patient was sensitized topically to one of the prednisone-derivatives (prednisolone, **methylprednisolone**), or to the potentially cross-reacting hydrocortisone, which all three may be used in pharmacy-prepared therapeutical creams, especially for the treatment of (atopic) eczema of the face in children. A less likely sensitization route would have been the previous use of the compounded ear drops, containing either prednisolone or methylprednisolone, with the absence of an ear dermatitis pointing towards primary systemic sensitization which is, however, considered uncommon (1). Other routes of sensitization were considered rare based upon the history of our patient, and based upon the literature (3) .

Discussion

Delayed hypersensitivity to CS is a well-known entity and the prevalence varies between 0.2 % – 5 % among patients attending patch test clinics, with hydrocortisone, methylprednisolone and budesonide as the most reported culprit sensitizers (3). Several cases of allergic contact dermatitis following the use of corticosteroid-containing nasal sprays have been reported, with involvement of budesonide and tixocortol pivalate in particular (3-6).

Systemic dermatitis, on the other hand, may occur following systemic administration of CS, usually in a previously skin-sensitized patient, with the routes of exposure being mainly oral, intravenous, intramuscular, intra-articular and through the use of suppositories. In this subgroup of patients, methylprednisolone appears to be the most reported causal allergen (1).

Patch testing is considered the diagnostic method of choice for a delayed hypersensitivity to CS and delayed readings are required due to their anti-inflammatory properties.
Since a lack of knowledge exists on the penetration of corticosteroids when mixed in petrolatum, they should always be tested in ethanol, with the exception of budesonide

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Comment [M4]: Yes, un-esterified; we added this.

Comment [wu5]: As above.

Comment [M6]: We added the correct nomenclature.

Comment [wu7]: This corresponds largely to the concluding paragraph and can thus be removed – the paper is already quite long …

Comment [M8]: We agree; this part was removed.

and tixocortol pivalate. Furthermore, the test concentrations are usually 1% (7), although 0.1% has been used as well (3), with the exception of hydrocortisone which is better tested at 0.5% ethanol/DMSO. When using the higher concentrations of 1%, the immunosuppressing effect of the CS prevails, with only late readings at D7 being positive, while the lower concentrations of 0.1% might already give reactions at D2 and/or D4.

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Comment [M10]: This was done, reference was added.

Interestingly, our 3 screeners for corticosteroid allergy, which are able to detect 92.5% of all corticosteroid contact allergies (3) were not sufficient for the diagnosis with in particular tixocortol-21-pivalate failing to show reactivity for Group 1 CS. Therefore, it is of utmost importance that the CS used by the patient are tested as well (3, 8, 9).

Which CS exhibit cross-reactivity in patch testing and in clinical practice can be predicted with the recently revised classification of Baeck and Goossens, which consists of three groups of CS and divides the corticosteroid-allergic patients in 2 profiles (10) : profile 1 being patients reacting to molecules from one group only, namely Group 1, while profile 2 patients are capable of reacting to any of the CS. Most patients with systemic dermatitis seem to be profile 2 patients for which an individual approach is mandatory (1), implying patch tests with members of all 3 corticosteroid groups, in order to detect the cause of the skin eruption and to propose safe alternatives that can be used for a provocation test. Accordingly, a negative patch test was observed with both triamcinolone acetonide (Group 2) and betamethasone (Group 3), while the prednisone-derivatives from Group 1 were confirmed as the cause of her recurrent eruptions. In the present case, it would appear that the patient was sensitized only to Group 1, although we did not test an extensive corticoid series as published elsewhere (3). Moreover, we exemplify here that the revised classification might also apply for systemically used CS.

In conclusion, this case illustrates that re-exposure to a corticosteroid in nasal sprays or ear drops, in individuals previously skin-sensitized to this corticosteroid or to a cross-reacting one, may result in a systemic dermatitis, without the presence of concomitant skin lesions i.e. perinasal or ear dermatitis. Furthermore, we confirm that late readings of corticosteroid patch tests, especially with the 1% ethanolic dilutions, are of utmost importance and that screening agents may sometimes be insufficient.

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Figure legends

Fig. 1: Patch test reactions at D4 for n° 2 methylprednisolone 0.1% ethanol (++), n° 3 prednisolone 0.1% ethanol (+) and n° 4 hydrocortisone 0.5% ethanol/DMSO (++).

Tables

Table 1 : Summary of relevant patch test results.

Allergen	D2	D4	D7
Screeners*: Tixocortol-21-pivalate 0.1% pet, Budesonide 0.01% pet., Hydrocortisone-17-buyrate 0.1% eth.	-	-	-
Methylprednisolone 1% eth.	-	-	+
Methylprednisolone 0.1% eth.	?	+	++
Prednisolone 0.1% eth.	?	+	+
Hydrocortisone 0.5% eth./DMSO	?	+	++
Alternatives**: Triamcinoloneacetonide 0.1% eth., Betamethasone 0.1% eth., Dexamethasone 0.1% eth.	-	-	-
Ethanol (control)	-	-	-

* Corticosteroidscreeners in the Belgian baseline series.
**Alternative corticosteroids from corticosteroid Groups 2 and 3

Eth: 96% ethanol.
Eth/DMSO: 50% ethanol 96°/50% dimethyl sulfoxide.
Pet: petrolatum.