

Dissertations

Clinical and Experimental Studies in Corticosteroid Contact Allergy

Marléne Isaksson

Department of Occupational and Environmental Dermatology, Malmö University Hospital, S - 205 02 Malmö, Sweden. Tel: +46-40 337859. Fax: +46-40 336213. marlene.isaksson@derm.mas.lu.se.

Corticosteroids are anti-inflammatory and anti-proliferative substances that also can induce sensitization, mainly through skin contact. In a sensitized individual, it can be hard to disclose the contact allergy at patch testing because the anti-inflammatory effect may mask the allergic contact reaction. This is primarily seen when patch testing to potent corticosteroids is performed and the reading is done early, when the anti-inflammatory effect still prevails.

A hypothetical model is presented, which can explain the different situations that emerge, when the anti-inflammatory effect influences the elicitation depending on the individual degree of hypersensitivity in a sensitized subject.

Some patients allergic to the corticosteroid budesonide only reacted to very low concentrations of the sensitizer at early readings. When patch testing the corticosteroid triamcinolone acetonide, concentrations 1,000 to 10,000 times lower than internationally recommended resulted in allergic reactions while the recom-



Marléne Isaksson (*middle*) defended her thesis on April 14th, 2000 at the University Hospital, Malmö, Sweden. Faculty Opponent was Antti I Lauerma (*right*), Skin and Allergy Hospital, Helsinki, Finland and supervisor was Magnus Bruze (*left*), University Hospital, Malmö, Sweden.

mended concentration gave negative reactions. If testing with a corticosteroid at a high concentration results in a negative patch-test reaction, lowering the concentration may result in a positive patch-test reaction.

Introducing another parameter into the model, the time factor, made it possible also to explain why negative patch test reactions are sometimes seen at early readings, while the tests may turn positive on late reading occasions. Therefore, not to miss contact allergy to corticosteroids, a reading after one week in addition to an early reading is advocated. The multicentre study showed that 25% of the allergic reactions to corticosteroids would have been missed if a late reading had not been done.

The edge reaction, consisting of a blank centre representing the whole area of the test unit and surrounded by an eczematous infiltrate, is seen in some corticosteroid allergic patients when potent corticosteroids are patch-tested. This phenomenon can also be explained by the same model. If an edge reaction appears, a late reading or testing with a lower concentration should be done.

The cross-reactivity pattern for the two diastereomers of budesonide, the R and S diastereomers, was also investigated. Results concurred with the theory that the R diastereomer cross-reacts with other substances from the group to which it belongs, group B, while the S diastereomer cross-reacts not only with other group B substances but also with some esters of group D.

No inhibition of the patch test reactions was observed when patch testing the corticosteroid tixocortol pivalate and potentially cross-reacting substances at high concentrations.

Aldehydes of corticosteroids are thought to be intermediates in the sensitization process. The aldehyde of hydrocortisone was therefore tested in subjects allergic to hydrocortisone. Patients reacting to hydrocortisone also reacted to the aldehyde, speaking in favour of the aldehyde being an intermediate in the sensitization.

When trying to elucidate whether a corticosteroid mix, consisting of the three corticosteroids budesonide, tixocortol pivalate and hydrocortisone-17-butyrate (Hc-17-B) in petrolatum, could disclose corticosteroid allergy, it was found that 60% of the patients allergic to tixocortol pivalate were missed. Thus, in a corticosteroid mix containing budesonide and Hc-17-B, tixocortol pivalate should not be a part. Of the separate markers that were patch-tested simultaneously in petrolatum, budesonide 0.10% detected most allergic subjects, followed by budesonide 0.002% and tixocortol pivalate, both concentrations (1.0% and 0.10%) detecting the same number of patients. Hc-17-B at 1.0% detected more than 0.10%.

Investigations on the stability of budesonide, tixocortol pivalate and Hc-17-B patch-test preparations in petrolatum disclosed that these were

stable for at least one year in room temperature, refrigerated and frozen. Budesonide and tixocortol pivalate in ethanol showed the same stability. Hc-17-B 1.0% in ethanol was only stable frozen for one year and at room temperature for three months.

In the study on local clinical relevance, the flare-up reactions in the budesonide-allergic individuals consisted not only of a severe deterioration of the Preferid® treated eczema but also toxicoderma-like eruptions with a conspicuous distribution. A correlation was found between contact allergy to budesonide and deterioration of the eczema treated with Preferid® cream containing budesonide.

To study flare-up reactions at earlier budesonide test sites a systemic provocation with Pulmicort® Turbuhaler® (budesonide) via inhalation was performed in subjects allergic to budesonide but without asthma or other lung dysfunction. The study clearly showed that flare-up reactions were found after normal doses of budesonide. Therefore, a person hypersensitive to budesonide should not be given the drug as an inhalant. In the same study a new method in humans to test for cross-sensitivity was used. When budesonide was inhaled, a flare-up was noted where triamcinolone acetonide had been tested previously, indicating cross-reactivity between budesonide and triamcinolone acetonide.

Key words: corticosteroids, allergic contact dermatitis, budesonide, tixocortol pivalate, hydrocortisone-17-butyrate, dose-response relationship, mixes, stability, clinical relevance, ROAT, inhalation.

List of original publications

- I. Isaksson M, Bruze M, Goossens A, Lepoittevin J-P. Patch testing with budesonide in serial dilutions: the significance of dose, occlusion time and reading time. *Contact Dermatitis* 1999; 40: 24-31.
- II. Isaksson M, Bruze M, Goossens A, Lepoittevin J-P. Patch-testing with serial dilutions of tixocortol pivalate and potential cross-reactive substances. *Acta Derm Venereol* 2000; 80: 33-38.
- III. Isaksson M, Andersen KE, Brandão FM, Bruynzeel DP, Bruze M, Camarasa JG, Diepgen T, Ducombs G, Frosch PJ, Goossens A, Lahti A, Menné T, Rycroft RJG, Seidenari S, Shaw S, Tosti A, Wahlberg JE, White IR, Wilkinson JD. Patch testing with corticosteroid mixes in Europe. A Multicentre Study of the EECDRG. *Contact Dermatitis* 2000; 42: 27-35.
- IV. Isaksson M, Gruvberger B, Persson L, Bruze M. Stability of corticosteroid patch test preparations. *Contact Dermatitis* 2000; 42: 144-148.
- V. Isaksson M, Bruze M, Goossens A, Lepoittevin J-P. Patch testing with serial dilutions of budesonide, its R and S diastereomers, and potentially cross-reacting substances. Submitted.
- VI. Isaksson M, Bruze M. ROAT with budesonide on experimental allergic contact dermatitis from nickel in individuals hypersensitive to budesonide. Submitted.
- VII. Isaksson M, Bruze M. Allergic contact dermatitis to budesonide reactivated by inhalation of the allergen. Submitted.