

tried the administration of topic niflumic acid on the volar surface of the forearm, without any adverse reactions. Then another placebo-controlled oral trial was performed, with a cumulative dose of 125 mg of niflumic acid, which was negative, allowing the use of the drug.

This case illustrates that not even the most recent NSAIDs are free from adverse reactions and that sometimes other old alternatives must be considered.

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Vesicular and bullous eczema in response to intravenous immunoglobulins (IVIG)

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Key words: IV immunoglobulin therapy; pompholyx.

Standard (0.4 g/kg/day) and high dose (2 g/kg/day) intravenous immunoglobulins (IVIG) are used for therapy of several dermatological and neurological autoimmune diseases (e.g. dermatomyositis, pemphigus vulgaris, multifocal motor neuropathy) (1–3). Cutaneous adverse effects to IVIG have only rarely been reported and encompass case reports on eczema, alopecia, erythema multiforme, and anaphylactic reactions; the latter, however, is usually explanatory by a deficiency in IgA and can be prevented by measuring IgA levels prior to treatment.

We want to draw attention to a peculiar cutaneous side effect which may be more frequent than reported as it resembles common vesicular eczema (pompholyx, dyshidrotic eczema), and which might lead to undue interruption of therapy for fear of a more severe bullous drug reaction.

A 33-year-old patient with multifocal motor neuropathy received 0.4 g/kg/day IVIG for 5 days. One day after completion he developed a vesicular eczema at the lateral aspect of his fingers, which within 3 days extended to volar aspect of fingers and to both palms while vesicles progressed into bullae. He also developed a slightly scaling erythema on the face and capillitium. When after 10 days treatment with topical corticosteroids was initiated bullae started to empty clear fluid and the lesions showed extensive desquamation and healed within 1 week.

For a second course of IVIG the patient received systemic antihistamines and remained under close observation. One day after completion he again

developed vesicular eczema, which however, ran a markedly milder course with fewer lesions and without bullae. Local corticosteroids were not necessary. IVIG were then continued and during the subsequent seven courses the patient developed only very mild vesicular reactions. When he stopped taking antihistamines after the fourth course, there was slight aggravation of the vesicular reaction, but it was transient and did not recur after the following infusions even though antihistamines were not resumed.

For allergologic work-up after the severe bullous reaction we performed (epicutaneous) patch testing as well as prick testing with the corresponding IVIG preparation and preservatives such as chlorocresol and sulfite. All reactions but controls remained negative (patch test up to day 7).

There are only few reports on vesicular eczema or pompholyx after treatment with IVIG: 3 of 23 patients (4) and 1 of 10 patients with IVIG for neurological diseases (5). Extension of vesicular eczema to arms, breast and head area was described for only few of these cases.

The pathogenesis of this adverse effect is not well understood (4, 5). It may be a unique side effect of IVIG therapy, as it has not been reported for other medications (4). It has been suggested to occur only in those patients, which show very high plasma IgG concentrations directly after administration of IVIG (> 3000 mg/dl) (5), but this was not the case in our patient who showed only slightly elevated IgG (11.6–19.7 g/l). However, he presented with remarkably high IgE levels (1806 U/ml) already before IVIG treatment, which were not associated with lymphoma, other myeloid disorders or atopic diathesis. Since imbalances in plasma levels of immunoglobulins are known to be associated with conditions resembling atopic eczema (6) we speculate that IVIG therapy may result in development of dyshidrotic eczema in patients with a certain, transient imbalance in serum immunoglobulins.

If IVIG therapy is to be continued in these cases, companies recommend prophylactic administration of corticosteroids and antihistamines. However, according to our experience and to the few published reports we suggest that vesicular eczemas following IVIG

therapy are benign and may even become milder in subsequent courses. Thus, continuation of IVIG therapy is possible in conjunction with systemic antihistamines and local corticosteroids if necessary, while systemic corticosteroids should be withheld in order not to interfere with the immunomodulatory effects of IVIG. We encourage evaluation of immunoglobulins including IgE in other patients experiencing vesicular eczemas following IVIG therapy.

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Bronchospasm induced by inhalant corticosteroids: the role of ethanol

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Keywords: asthma; bronchospasm; ethanol.

The replacement of chlorofluorocarbons (CFCs) with hydrofluoroalkanes (HFAs) in the preparation of pressurized metered dose inhalers (pMDIs) has resulted in the reformulation of inhalant corticosteroids (ICSs) currently available both as a suspension and solution. Ethanol is used as a co-solvent to enhance the solubility of beclometasone in HFA 134a (Norflurane, Solvay Flour, Hannover, Germany), allowing the formulation of extrafine and non-extrafine (Modulite® technology, Chiesi, Parma, Italy) solutions of beclometasone in aerosols.

To date, no difference in the incidence of bronchospasm between ICS formulations containing ethanol and ICS ethanol-free formulations has been demonstrated (1–4).

We report the case of two asthmatic patients suffering from severe persistent and mild persistent asthma, respectively, both of whom presented bronchospasm following inhalation of two puffs of extrafine beclometasone aerosol (Clenilexx Autohaler 100 µg; Chiesi, Parma, Italy).

To identify the bronchospasm triggering agent, bronchial challenges using different formulation drugs were performed.

Only one of our two patients consented to the study.

He was 31 years old, suffering from allergic mild persistent asthma: prick tests were positive to mite and cat, lung function parameters were within the normal range (FVC = 5.88 L, 113% predicted and FEV₁ = 4.36 L, 107% predicted) and fractional exhaled nitric oxide (FeNO) was 61 ppb.

We demonstrate the role of the excipient in a local side-effect induced by some ICS formulations.

Bronchial challenges with the following drugs were carried out at 3-day intervals.

- Beclometasone HFA extrafine aerosol (Clenilexx Autohaler 100).
- Beclometasone HFA non-extrafine aerosol (Modulite® technology) (Clenil 250; Chiesi).
- Beclometasone dry powder formulation (Clenil 100 polvere; Chiesi).
- Fluticasone spray formulation (Flixotide 125; GKS, Verona, Italy).

The patient was taking budesonide Turbuhaler 200 µg b.i.d., a 12-h-medication-free interval before each bronchial challenge was established.

The excipients of the first two beclometasone formulations are HFA 134a (Norflurane) and ethanol. Beclometasone powder is both HFA 134a and ethanol free. As beclometasone spray ethanol-free formulations are not commercially available in Italy, to verify the role of HFA 134a (Norflurane) we used a fluticasone spray formulation which only contained HFA 134a (Norflurane).

The results of the bronchial challenges are summarized in Fig. 1. With the use of the ethanol-containing beclometasone formulations, irrespective of the size of the particles delivered, FEV₁ fell within 5 min by more than 25%.

The administration of two puffs of salbutamol (Ventolin; GKS) resolved the bronchospasm within 30 min.

Neither powdered beclometasone nor the formulation of ICS containing HFA 134a (Norflurane) alone, produced any significant effect.

Whereas the direct contact of ethanol with the bronchial mucous caused bronchospasm, the consumption of alcohol had never caused the patient's asthma to worsen.

Various effects on the bronchial tone after the ingestion of ethanol have been documented and approximately 30% of asthmatics report an exacerbation in their symptoms (5).

In an animal model, it has been shown that ethanol can trigger bronchoconstriction through TRPV1 (transient receptor potential vanilloid-1) activation of the airway sensory neurons in the bronchi (6).

Our findings suggest that bronchospasm is caused by ethanol-induced TRPV1 activation.