

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.

*Professor of Dermatology and Allergic Diseases

Department of Dermatology
University of Ulm
Maienweg 12
89081 Ulm
Germany
Tel: +49 731 21850
Fax: +49 731 21867
E-mail: cord.sunderkoetter@medizin.uni-ulm.de

Accepted for publication 27 May 2005

Allergy 2006; 61:145–146

Copyright © Blackwell Munksgaard 2005

DOI: 10.1111/j.1398-9995.2005.00937.x

References

1. Rutter A, Luger TA. Intravenous immunoglobulin: an emerging treatment for immune-mediated skin diseases. *Curr Opin Investig Drugs* 2002;3:713–719.
2. Simon HU, Spath PJ. IVIG – mechanisms of action. *Allergy* 2003;58:543–552.
3. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 2004;19:2367–2375.
4. Iannaccone S, Sferruzza B, Quattrini A, Smirne S, Ferini-Strambil L. Pompholyx (vesicular eczema) after i.v. immunoglobulin therapy for neurologic disease. *Neurology* 1999;53:1154–1155.
5. Ikeda K, Iwasakii Y, Yasumitsu I, Kinoshita M. Pompholyx after IV immunoglobulin therapy for neurologic disease. *Neurology* 2000;54:1879.
6. Bos JD. Atopiform dermatitis. *Br J Dermatol* 2002;147:426–429.

Bronchospasm induced by inhalant corticosteroids: the role of ethanol

L. Antonicelli*, C. Micucci, F. Bonifazi

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.

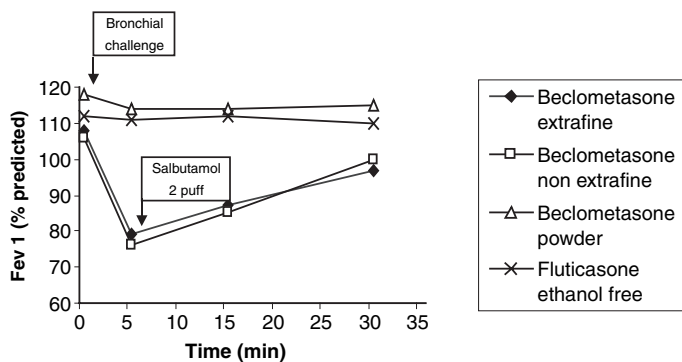


Figure 1. Effects of bronchial challenges with different formulations of inhalant corticosteroids on response of FEV₁. Both Beclometasone extrafine and Beclometasone non-extrafine contain ethanol, while Beclometasone powder and Fluticasone are ethanol free.

Many inflammatory mediators can sensitize or upregulate TRPV1 reactivity (6); it is unknown whether genetic factors or local inflammation are the cause of TRPV1 hyper-reactivity in our patient.

In conclusion, in a subset of asthmatic patients the use of ICSs containing ethanol can trigger bronchoconstriction: the administration of ethanol-free formulations prevents this side effect. Further studies are necessary to evaluate both the prevalence of this side effect and the clinical importance of TRPV1 activation in asthmatics.

*UO Allergologia

Dipartimento di Medicina Interna
Malattie Immuno-Allergiche e Respiratorie
Ospedale Regionale
Ancona
Italy
E-mail: lantoncelli@ao-umbertoprime.it

Accepted for publication 12 June 2005

Allergy 2006; 61:146–147

Copyright © Blackwell Munksgaard 2005

DOI: 10.1111/j.1398-9995.2005.00943.x

References

1. Nayak A, Lanier R, Weinstein S, Stampone P, Welch M. Efficacy and safety of beclomethasone dipropionate extrafine aerosol in childhood asthma. *Chest* 2002;**122**:1956–1965.
2. Pedersen S, Warner J, Wahn U, Staab D, Le Bourgeois M, Van Essen-Zandvliet E, et al. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclomethasone dipropionate formulations: an open-label, randomised comparison of extrafine and conventional aerosols in children. *Pediatrics* 2002;**109**:1–10.
3. Fairfax A, Hall I, Spelman R. A randomised, double-blind comparison of beclomethasone dipropionate extrafine aerosol and fluticasone propionate. *Ann Allergy Asthma Immunol* 2001;**86**:575–582.
4. Bousquet J, Cantini L. Clinical studies in asthmatics with a new non-extrafine HFA formulation of beclomethasone dipropionate (BDP Modulite). *Respir Med* 2002;**96**(Suppl. D):S17–S27.
5. Vally H, Thompson PJ. Allergic and asthmatic reactions to alcoholic drinks. *Addict Biol* 2003;**8**:3–11.
6. Trevisani M, Gazzieri D, Benvenuti F, Campi B, Dinh QT, Groneberg DA, et al. Ethanol causes inflammation in the airways by a neurogenic and TRPV1-dependent mechanism. *J Pharmacol Exp Ther* 2004;**309**:1167–1173.