

before admission, he felt breathless and inhaled two puffs of formoterol. He then inhaled several puffs of salbutamol. Within a few minutes, he developed acute respiratory distress. The emergency team arrived 15 min later. The patient cyanotic and in respiratory arrest, received non-invasive ventilation, and was given 80 mg methylprednisolone i.v., nebulized terbutaline sulfate and ipratropium bromide. One hour later, chest auscultation was normal. Peak expiratory flow rate was 500 l/min. Common laboratory tests fell within normal limits. He was placed on nebulized terbutaline-ipratropium q.i.d. and methylprednisolone 2 mg/kg/day. At day 3, he was prescribed formoterol 12 µg b.i.d., methylprednisolone 1 mg/kg/day and salbutamol on demand (not needed by patient).

Skin prick tests (SPTs) for common aeroallergens were positive for house dust mite and birch. At day 5, forced expiratory volume in 1 s (FEV1) was 3.22 l (85% predicted) and forced vital capacity (FVC) 4.8 l (105% predicted). Three minutes after a puff of salbutamol, the patient became acutely breathless with audible wheezes and a 25% drop in FEV1 (to 2.41 l). Bronchial provocation challenges (one challenge/day) demonstrated: (i) a symptomatic decrease in FEV1 from 3.15 to 1.94 l (38% drop) after inhalation of terbutaline dry powder; (ii) an increase in FEV1 after inhalation of formoterol or ipratropium (10% and 12% respectively). SPT was positive with albuterol/salbutamol sulphate for aerosolization, nebulization or i.v. (5, 8 and 6 mm wheal respectively; saline no wheal, codeine 5 mm), terbutaline sulfate for inhalation, nebulization, dry powder (5, 5 and 7 mm respectively) and pirbuterol acetate for inhalation (7 mm). Allergy to preservative was unlikely, as the various galenic preparations produced a positive SPT. SPTs were negative for formoterol, salmeterol, bambuterol, ipratropium and methylprednisolone. SPTs were negative in five asthmatics (exposed to β2-agonists) and in five nonasthmatic controls.

In vitro, histamine release (HR) was 22%, 10% and 7% for salbutamol, terbutaline and formoterol on whole-blood assay (cutoff value 5% of total histamine content) and 9% for salbutamol on isolated leucocytes. Excess

concentrations of salbutamol, terbutaline but not formoterol caused inhibition of HR. There was no HR in the absence of calcium. This supported an IgE-dependent mechanism at least for salbutamol and terbutaline. HR was negative with prednisolone and ipratropium.

At 3-year follow-up, the asthma is controlled with formoterol 12 µg b.i.d., budesonide 800 µg b.i.d., methylprednisolone 4 mg/day and omalizumab 375 mg every other week.

Several arguments support an IgE-dependent mechanism: (i) the reaction occurred very shortly after inhalation; (ii) the patient was reproducibly rechallenged with salbutamol or terbutaline; (iii) SPTs with salbutamol, terbutaline and pirbuterol were positive in 15 min; and (iv) HR was positive.

Of note, the three short-acting β2-agonists share a tert-butyl group attached to the nitrogen atom (6). Whether the lack of adverse effect to nebulized terbutaline seen on admission day resulted from refractoriness, protection by ipratropium or real lack of bronchoconstriction with terbutaline nebulization remains unknown. We did not challenge the patient with this drug as the response with terbutaline powder was dramatic.

In conclusion, allergic mechanism should be investigated in patients with paradoxical bronchoconstriction following inhalation of short-acting β2-agonists.

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References

1. Finnerty JP, Howarth PH. Paradoxical bronchoconstriction with nebulized albuterol but not with terbutaline. *Am Rev Respir Dis* 1993;**148**:512–513.
2. Mutlu GM, Moonjelly E, Chan L, Olopade CO. Laryngospasm and paradoxical bronchoconstriction after repeated doses of beta 2-agonists containing edetate disodium. *Mayo Clin Proc* 2000;**75**:285–287.
3. Spooner LM, Olin JL. Paradoxical bronchoconstriction with albuterol administered by metered-dose inhaler and nebulizer solution. *Ann Pharmacother* 2005;**39**:1924–1927.
4. Charpin D, Beaupre A, Orehek J. Deep-inspiration induced bronchoconstriction: a mechanism for beclomethasone aerosol intolerance. *Eur J Respir Dis* 1983;**64**:494–497.
5. Cocchetto DM, Sykes RS, Spector S. Paradoxical bronchospasm after use of inhalation aerosols: a review of the literature. *J Asthma* 1991;**28**:49–53.
6. Waldeck B. Beta-adrenoceptor agonists and asthma – 100 years of development. *Eur J Pharmacol* 2002;**445**:1–12.

Anaphylaxis caused by allergen sublingual immunotherapy?

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Key words: allergens; anaphylaxis; local reaction; pharmacovigilance; sublingual immunotherapy.

We read with interest the publication by Eifan et al. (1) reporting about a 11-year-old girl treated with Staloral 300 IR mites SLIT, taken in the morning, and grass/cereal pollen, taken in the evening, who developed a severe oral and gastrointestinal reaction associated with high fever, causing her to attend the emergency department.

Following online publication, a medical team from Stallergènes met the

Previous report reveals severe local reaction to SLIT rather than serious anaphylaxis.

authors in Istanbul. The meeting revealed the following information:

In the emergency department, body temperature was 39°C and a blood count was performed but the results were not available. The patient received dextrose infusion, intravenous (i.v.) H₁-antihistamine and i.v. corticosteroids. Review of the clinical notes did not reveal any record of blood pressure/pulse, or clinical symptoms of asthma, urticaria or angioedema. Adrenaline was not administered. Approximately 4 h after admission to the emergency unit, and following significant improvement, the patient was allowed to leave the hospital with a prescription for H₁-antihistamine. On the following day, treatment with Staloral pollen was resumed with recurrence of sublingual oedema and burning sensation. Pollen treatment was permanently discontinued.

Clearly, the reaction described as anaphylaxis was actually a severe local reaction with positive rechallenge. This reaction does not constitute a description of a serious anaphylactic reaction with the characteristics of anaphylactic shock as defined in the EAACI Immunotherapy Position Paper. This may reflect a difference in the way in which the word 'anaphylaxis' is used, as, by definition, a positive skin prick test could be construed as anaphylaxis, although this would lack the same significance as severe laryngeal oedema or life-threatening hypotension. This late statement is in line with a recent editorial by Warner (2).

This report followed two other recent publications of anaphylaxis in patients treated with SLIT (3, 4). Only one case satisfied the criteria for anaphylactic reaction: the patient received latex by a rush administration protocol (3), fortunately administered in a hospital. Rush protocol is associated with a higher risk than conventional protocols. Latex proteins are particularly potent allergens and in this particular context, can be

compared with sublingual use of a full dose of bee venom. The second patient from the USA (4) reported a severe reaction with no clear evidence of anaphylaxis following SLIT with a mixture of six different allergens that was possibly not standardized and probably not used in compliance with the FDA-approved indication. These publications (1, 3, 4) raise two concerns. First, they raise the question of the rationale for administration of SLIT during the pollen season (1), but all clinical trials performed till date have been conducted with pre-seasonal administration without any dose reduction during the pollen season.

The second question concerns the use of mixtures of allergens for the treatment of polysensitized patients (1, 4). The majority of allergic patients are polysensitized even when they do not present multiple allergies. However, a recent large-scale clinical trial of SLIT (5) in 640 patients treated with a mixture of five grass pollens did not reveal any differences in terms of efficacy and safety between patients monosensitized to grass pollens and those also sensitized to other allergens, suggesting that polysensitization is not a contraindication. The first article reporting SLIT was published 20 years ago (6) and numerous studies have been published. Several hundred million daily doses have now been administered. No life-threatening side-effect has ever been described in the peer-reviewed literature (7). These publications emphasize the need for all physicians to comply with pharmacovigilance rules by reporting all serious adverse and unexpected reactions to allow the Marketing Authorisation Holder to complete their obligations.

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References

1. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy* 2007;**62**:567–568.
2. Warner JO. Anaphylaxis: the latest epidemic. *Pediatr Allergy Immunol* 2007;**18**:1–2.
3. Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. *Allergy* 2006;**61**:1236–1237.
4. Dunskey EH, Goldstein MF, Dvorin DJ, Belecanech GA. Anaphylaxis to sublingual immunotherapy. *Allergy* 2000;**61**:1235.
5. Didier A, Melac M, Combebas A, André C. Efficacy and safety of sublingual immunotherapy (SLIT) tablets in grass pollen rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;**117**:721.
6. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clin Allergy* 1986;**16**:483–491.
7. Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006;**117**:1021–1035.