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House dust mite allergens in Turkish homes

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Key words: allergy; Der f 1; Der p 1; house-dust mites.

Exposure to house dust mites (HDMs) is a major risk factor for allergic sensitization and asthma (1). Assessing HDM allergen exposure at home is critical to evaluate risk factors for sensitization and can play a role in controlling environmental factors that contribute to asthma severity (2). Although it is reported that the predominated HDM was *Dermatophagoides pteronyssinus* in Turkish homes (3), data on mite allergen levels has never been reported. Therefore, we aimed to investigate HDM allergen levels of homes in Izmir, the third populated city in Turkey situated next to Aegean Sea and to identify predictors of dust mite allergen concentration.

Allergic subjects had higher Der p 1 levels in their home than healthy controls.

Dust samples were obtained from 25 homes of allergic patients with perennial symptoms, consecutively referred to our out patient clinic for the first time for their allergies. Fourteen healthy subjects served as a control group. House dust samples were collected from an area of 1 m^2 with a 1200-W, filtered vacuum cleaner. Dust mite allergen (Der p 1 and Der f 1) concentration was determined by Dustscreen assay, a method easier to perform and as satisfactory as enzyme-linked immunosorbent assay (4). The HDM allergen levels were expressed as $\mu g/m^2$. The minimum detection level of Der p 1 and Der f 1 was 0.1 $\mu g/m^2$. Independent predictors of allergen concentration were assessed.

Either Der p 1 or Der f 1 was detected in 21 of 39 homes (53.8%). *Dermatophagoides pteronyssinus* predominated in most of the houses (71.4%). Twenty-three percent of houses were coinhabited by *D. farinae* and *D. pteronyssinus*. Der p 1 was detected in twenty houses in the range of 0.4–5.4 $\mu g/m^2$ (median 2). We observed Der p 1 >2 $\mu g/m^2$ of dust in 55% of the houses. Whereas Der f 1 was detected in only six houses (median 1, range 0.1–6.4 $\mu g/m^2$). Der p 1 levels were significantly higher in allergic subjects' houses than healthy controls' (median 2 *vs* 0.4 $\mu g/m^2$, $P = 0.041$). Twenty-one of 25 allergic subjects (84%) were sensitive at least to *D. farinae* or *D. pteronyssinus* assessed by skin prick test. Independent predictors of higher levels were evidence of moisture, such as mildew or water stains in the home and residency at seaside.

In conclusion, more than half of the houses in Izmir had detectable levels of dust mite allergen. *Dermatophagoides pteronyssinus* was the most frequently found species. Allergic patients encountered more HDM allergens than normal subjects in their home, and this situation may emphasize the importance of environmental factors in the development of allergic diseases. Indoor moisture and residency at seaside were predictors of higher mite allergens.

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Lavender in pillows. No effect on Der p 1 accumulation

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Key words: Der p 1, lavender, pillows.

Pillows, especially those filled with synthetic materials, contain significant levels of the house dust mite allergen, Der p 1, and new pillows rapidly accumulate Der p 1 within months, at least in the New Zealand domestic environment (1,2). The reason for this is likely because of the

Lavender in pillows has no effect on house dust mite allergen accumulation over time.

Table 1. Geometric mean Der p 1 levels in pillows with and without lavender

	Synthetic (μg/g)	Lavender (μg/g)	*P*-value	Synthetic total (μg)	Lavender total (μg)	*P*-value
0 months	1.51 (0.62–3.65)	0.51 (0.17–1.56)	0.08	0.004 (0.001–0.012)	0.020 (0.015–0.024)	0.19
3 months	2.26 (1.14–4.46)	1.67 (0.68–4.07)	0.50	0.10 (0.04–0.27)	0.10 (0.04–0.28)	0.94

larger pore size of synthetic pillow coverings, allowing house dust mites and dust containing allergens to enter the pillow (3). Various volatile plant oils are miticidal. Lavender oil is pleasant smelling and, as such, is used in bedding. Lavender oil vapours kill house dust mites in cultures and in clothing when placed in small-enclosed containers (4). The aim of this study was to investigate whether inclusion of lavender sachets within new synthetic pillows affected Der p 1 accumulation over time.

Six new pairs of pillows, each pair consisting of a synthetic pillow with and without a lavender sachet inside, were placed on six beds. Dust was collected from each pillow at the start and after 3 months by vacuuming each side of the pillow for 1 min with a Hitachi CV-2500 vacuum cleaner (1100 W; Hitachi Ltd., Singapore, Singapore). The dust samples were extracted with phosphate-buffered saline (containing 0.05% Tween-20) at room temperature and Der p 1 levels in the supernatant measured by established double-monoclonal antibody enzyme-linked immunoabsorbent assay (5). Because of non-normal distribution, Der p 1 levels were log-transformed and expressed as geometric means with 95% confidence intervals (95% CI). Der p 1 levels from pillows with and without lavender sachets were compared by paired *t*-test.

Table 1 shows pillows Der p 1 accumulation over 3 months, expressed per gram of dust and total Der p 1 recovered. Mean accumulation of Der p 1 was similar for pillows with and without lavender sachets (1.16 μg/g and 0.090 μg/m^2, and 1.11 μg/g and 0.096 μg/m^2 respectively). Mean vacuumed dust weights (95% CI) were not significantly different after 3 months, these being 0.072 g (0.026–0.118) and 0.050 g (0.023–0.077) for pillows with and without lavender sachets, respectively ($P = 0.30$).

This study has shown that addition of lavender inside synthetic pillows had no effect on Der p 1 accumulation over 3 months in the domestic setting. It is unlikely that the potency of the lavender diminished significantly as it could still easily be detected by smell at 3 months. A limitation of our study is that we were unable to estimate house dust mite numbers. These are easily established by the heat escape method in blankets and duvets, but not in thicker bedding items, such as pillows (6).

In conclusion, pillows containing lavender are unlikely to be of benefit as an interventional measure to reduce house dust mite allergens in synthetic pillows.

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A human dermatitis caused by *Thaumetopoea pityocampa* (Denis and Schiffermüller, 1775) (order: Lepidoptera) caterpillars in Istanbul, Turkey

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Key words: allergy; dermatitis; Lepidoptera; *Thaumetopoea pityocampa*; thaumetopoein.

More than 50 species, at least 10 families belonging to Lepidoptera have urticating and cautery hairs including allergic substances (thaumetopoein) (1–4). General symptoms include sudden burns, swellings, rusty spots, lymphangitis, leucocytosis and eosinophilia. Sometimes weakness, lymphadenopathy and pustules could also appear. These symptoms are used for diagnosis. Caterpillars' hairs cause pustules and wounds on the oral and nasal mucosa of human beings and animals. They can cause gastrointestinal disorders like vomiting and diarrhoea. In contact with the respiratory system, it causes acute bronchitis and severe coughing. The hairs that sting eyes cause hyperaemia with ache and urtica on conjunctiva and wounds on cornea (2–4).

The first dermatitis case in Turkey caused by *Thaumetopoea pityocampa* (Denis and Schiffermüller, 1775).

In the summer of 2002, a woman with complaints of urtica on her face, neck

Figure 1. Caterpillars going around home.

and arms consulted the Istanbul Medical Faculty. Physical symptoms on the patient's face, neck and arms corresponded to local oedema and maculopapular lesions. No other pathological symptoms were found out on other parts of her body. The lesions had appeared in contact with the hairs of caterpillars (*Thaumetopoea pityocampa*) (Fig. 1). Two laboratory personnel, who had collected the caterpillars, had the same symptoms on their hands and arms after a few hours.

Thaumetopoein, a protein found in the hairs of caterpillars, was found to be the underlying cause.

Staphylococcus aureus was isolated from patient's lesions.

The skin, which was partially irritated, was infected with secondary bacterial dermatitis because of severe itching.

Loratadine (as an antihistaminic) 10 mg 1 × 1 per day was used; amoxicillin 500 mg + clavulanic acid 125 mg was used for *S. aureus*. After this period the patient's complaints disappeared.

In Middle Europe especially in France, Israel, and in the southern states of USA species of Lepidoptera are present (2, 5).

Corkey (1) reported that the urticating hairs caused blindness in human.

In Israel (5) both hands of a 4-year-old child swelled symmetrically. Vomiting was also observed.

The symptoms and the lesions could be mixed up with bug stings or snakebites that need more specific treatment. More attention is needed in these kinds of situations (5).

This case is reported as the first dermatitis event in Turkey caused by *Thaumetopoea pityocampa*.

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Levothyroxine-induced hyperthyroidism

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Key words: hyperthyroidism; levothyroxine.

Levothyroxine (LT) has been used for the treatment of hypothyroidism and for the suppression of thyroid-stimulating hormone (TSH) levels in patients with thyroid nodules and/or thyroid gland enlargement. Allergic or idiosyncratic reactions are extremely rare with the synthetic LT. However, there was a report of hypersensitivity caused by synthetic thyroid hormone in a hypothyroid patient with autoimmune Hashimoto's thyroiditis (1). Therefore, these adverse effects of the drug are of critical importance in the clinical management of patients. In this report, we present a non-autoimmune goiter patient, who developed hyperthyroidism while receiving LT for thyroid suppression therapy.

The occurrence of levothyroxine-induced hyperthyroidism is rare but possible.

A 43-year-old Vietnamese woman complained of 'neck enlarged' over the last few years. She denied symptoms of weight changes, temperature intolerance and tremor. She had no history of allergy to drugs or food. Her past medical history was unremarkable. On physical examination, she was found to have a diffuse enlargement of thyroid gland. The laboratory data were as follows: leukocytes, $7.1 \times 10^3/mm^3$ (normal, 5–10); triiodothyronine uptake (T_3U), 28% (normal, 22–37); thyroxine by the radioimmunoassay (T_4RIA), 5.4 mcg/dl (normal, 5–15); triiodothyronine by the radioimmunoassay (T_3RIA), 111 ng/dl (normal, 86–187); free thyroxine index (FTI), 1.5 (normal, 1.5–4); TSH, 0.93 mlU/L (normal, 0.2–5); antimicrosomal autoantibodies, < 0.1 U/ml (normal, < 0.3); anti-thyroglobulin autoantibodies, < 0.1 U/ml (normal, < 0.3); serum thyroglobulin level (Tg), 7.9 ng/ml

(normal, 0–60). The ultrasonography of thyroid gland revealed a homogenous thyromegaly (right lobe, $5.7 \times 1.6 \times 2.5$ cm and left lobe, $5.2 \times 1.7 \times 2$ cm) and no focal nodule.

She was placed on LT 50 mcg/day for thyroid suppression therapy. A blood test 2 months after LT treatment showed T_3U of 31%, T_4RIA of 8.1 mcg/dl, T_3RIA of 109 ng/dl, FTI of 2.5, and TSH of 0.16 mIu/ml. Four months later, however, she complained of insomnia, fatigue, poor appetite, heat intolerance, hand tremors and losing weight (12 lbs.). Laboratory data revealed T_3U of 41%, T_4RIA of 19.9 mcg/dl, FTI of 8.2, T_3RIA of 409 ng/dl, TSH of <0.1 mIu/ml, and Tg of 28 ng/ml. The LT was discontinued and she was treated with propylthiouracil 100 mg, twice a day. One year later, the lymphocyte stimulation test showed the stimulation index of 181% for LT.

It is interesting that our non-autoimmune thyroid patient developed hyperthyroidism while taking LT for the thyroid suppression therapy. The abnormal thyroid function tests were reported in LT-treated patients (2). Salmon et al. (3) suggested that serum T_3 determination is the procedure of choice for the evaluation of LT-treated individuals. LT-treated patients with high T_4 levels but normal T_3 levels were clinically euthyroid.

On rare occasions, thyrotoxicosis factitia (TF) has been described in patients taking large amounts of thyroid hormone or ingesting of food contaminated with animal thyroid tissue (4). However, the increased levels of Tg and persistence of hyperthyroidism after the cessation of LT in our patient would rule out TF (5). There were some reports about the development of hyperthyroidism following treatment with LT in hypothyroid patients with history of Graves' disease. But, these patients had been known to have an autoimmune disease, in contrast to our patient.

The PHA-P-induced ^3H-thymidine incorporation into lymphocytes was significantly increased in the presence of T_3. The transformation of lymphocytes from the peripheral blood into blast-like cells *in vivo* in patients with certain drug eruptions in the presence of the appropriate drug has been used as a test for hypersensitivity. Sarkany (6) has shown the value of the lymphocyte transformation in seven patients with suspected clinical drug hypersensitivity. Furthermore, Shibata et al. (1) reported that a hypothyroid patient developed fever, eosinophilia, and liver dysfunction after the thyroid hormone replacement, either with T_3 or T_4. The symptoms disappeared on the cessation of the replacement therapy. They initially noted the high stimulation index (up to 500%) for both hormones in lymphocyte stimulation tests, but the index decreased to mild and no response (160 and 100%) 7–13 months later. Therefore, the high stimulation index with LT in our patient, even a year later, might suggest that thyroid hormone administered exogenously induced hypersensitivity. It has been known that cytokines, such as interferon γ and interleukins, were secreted by activated lymphocytes, which occur in response to the cellular injury or allergen activation. In the literature, interferon and interleukin therapies have been known to cause thyroid dysfunction.

In conclusion, the complex concurrence of LT-induced hyperthyroidism is rare but possible. These symptoms may be attributed to hypersensitivity.

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'Daily pattern' of an asthmatic reaction due to isocyanates

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Key words: occupational asthma; specific inhalation challenges.

We describe the case of a subject who developed changes in forced expiratory volume (FEV1) that were significant when examined from day to day ('daily pattern' of reaction) but were not significant when values up to 7 or 8 h after ending challenge were considered.

We previously reported on temporal patterns of asthmatic reactions after exposure to occupational agents (1) and, more specifically, to diisocyanates (2) in the 7–8 h following exposure. We herein report on a subject in whom significant changes in airway function and inflammation were first documented on a 'day-to-day' basis.

Significant changes in FEV1 from day to day in a case of occupational asthma.

A 44-year-old car painter developed work-related respiratory symptoms approximately 1 year before being examined. He underwent specific inhalation challenges 3 months after leaving work. Table 1 summarizes the results of specific challenges to hexamethylene diisocyanate (HDI); these were carried out in a small cubicle by using a closed-circuit apparatus and a realistic approach (3). On

Table 1. Summary of results of inhalation challenges to hexamethylene diisoyanate

Date	Exposure	Baseline FEV1 (L)	Day-to-day % change*	Lowest FEV1 (L)	Hourly change†	PC20 (mg/ml)	Sputum eosinophils (%)
14 April 2003	CC (1 min)	4.3	–	4.3	0	>128	0
15 April 2003	CC (4 min)	4.3	0	3.9	−9.3	–	–
16 April 2003	CC (20 min)	4.2	−2.3	3.9	−7.1	>128	–
22 April 2003	CC (2 h)	4.3	0	3.9	−9.3	>128	–
23 April 2003	R (30 min)	3.6	−16.3	3.2	−11.1	–	–
24 April 2003	R (120 min)	3.3	−23.3	2.8	−15.1	19	11
30 April 2003	Control	3.8	−11.6	3.6	−5.3	–	0
01 May 2003	R (90 min)	3.8	−11.6	3.0	−21.1	3.8	24

CC, exposure to hexamethylene diisocyanate (HDI) with a closed-circuit apparatus; R, realistic exposure to HDI; control, control day of non-exposure to HDI.
* Assessed as the difference between baseline FEV1 on day 14 July 2003 and baseline assessment of the actual day; †calculated as the % difference between baseline FEV1 and lowest FEV1 of the actual day.

23 April 2003, the day-to-day % change in FEV1 was significant (−23%) whereas at hourly changes it was not (−15.1%). On the same day, PC20 fell significantly to 19 mg/ml, although remaining within normal values (PC20 > 16 mg/ml). There was also a significant increase in sputum eosinophils. Six days after stopping the challenge, on day 30 April 2003, baseline FEV1 improved and sputum eosinophils were back to 0%. After exposure to HDI on 01/05/03, there was a significant (−21.1%) hourly change accompanied by a fall in PC20 to an abnormal range and an increase in sputum eosinophils to 24%.

This case report illustrates that, while changes in FEV1 documented 7–8 h after challenge did not reach significance, the changes in FEV1 from one day to the next can do so. This illustrates a 'daily pattern' of reaction which has so far been described with serial monitoring of peak expiratory flow rates (4). Interestingly, PC20 fell significantly and sputum eosinophils increased before significant hourly changes could be demonstrated, pointing out that these tools are at times more sensitive than hourly changes in FEV1 for documenting a reaction (5, 6). It is interesting to note that discontinuation of exposure to the causal agent for almost 1 week resulted in the documentation of an 'hourly pattern.' We therefore think that it is relevant to assess FEV1 24 h after stopping exposure in cases where borderline changes in FEV1 are obtained after 7–8 h.

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Contact dermatitis due to Edding 3000

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Key words: abitol; colophony; contact dermatitis; Edding 3000; permanent marker.

A 28-year-old woman presented with skin lesions on her right thigh 24 h after liposuction. It was the fifth liposuction that the patient had undergone. A blue permanent marker (Edding 3000, Edding International GmbH, Ahrensburg, Germany) was used to outline the area at each liposuction. Pruritic, erythematous and infiltrated plaques, with vesicles and papular spread, developed on these lines within a few days.

Edding 3000 contained abitol, a potent allergenic resin.

The manufacturers provided us with the safety data sheets: rosin (colophony), colorants and organic dissolvents were the components of Edding 3000.

Epicutaneous tests were carried out with the suspected agent, the permanent marker (Edding 3000), in three different colours: blue, red and black.

European Standard Series, plastics and Glues Series PG-1000, Acrylate Series MA-1000 and Colorants Series were also tested.Results of the European Standard Series were negative.

The rest of the series tested showed negative results, except the plastics series, that showed a positive result to abitol at 48 (++) and 96 h (+++).

All of the permanent markers (blue, red and black) were positive at 48 (+ +) and 96 h (+ + +).

We usually utilize Edding 3000 to demarcate patch test sites. Thus, for many years about 700–800 patients per annum have acted as control.

The incidence of allergic reactions to colophony has increased to such an extent that in most countries it has become one of the 10 most important sensitizations (1). However, the use of only one type of colophony for patch tests in the standard series does not address all aspects of the problem. The question arises as to whether we are testing with the right material, which raises the suspicion that the real number of cases of colophony allergy is much higher than commonly thought. Three things seem to become quite clear, namely: 1) that rosin has been replaced in recent years by its chemically modified forms; 2) that modified colophony products commonly cause stronger sensitizations than do unmodified ones; 3) that cross-reactions between modified and unmodified products are not the rule.

Our patient did not have a positive patch-test reaction to colophony in the standard series; instead, she had a positive reaction with a modified product of colophony, abitol.

Contact dermatitis due to acrylates present in ultraviolet curing ink has been described (2) but there is only one article published in the literature about contact allergic dermatitis caused by a permanent marker. In this case, a dye (Solvent Yellow 146, Bio-Diagnostics Ltd, Worcestershire, UK) was the causative agent of contact dermatitis (3).

This report represents the first documented case of allergic contact dermatitis due to abitol as a component of a permanent marker, the Edding 3000.

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Allergic bronchopulmonary aspergillosis without clinical asthma caused by *Aspergillus niger*

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Key words: allergic bronchopulmonary aspergillosis; *Aspergillus niger,* clinical asthma.

Allergic bronchopulmonary aspergillosis (ABPA), a disease of the asthmatics, is caused principally by hypersensitivity to *Aspergillus fumigatus*. ABPA is rarely thought of in the absence of asthma, as this is the first criterion for diagnosis. We report a 28-year-old male referred to us as 'multidrug-resistant tuberculosis', who was eventually diagnosed as ABPA without clinical asthma caused by *A. niger*.

ABPA without clinical asthma can pose diagnostic difficulties.

One-and-a-half years prior to presentation, the patient had experienced cough with minimal expectoration along with intermittent low-grade fever and one episode of blood tinged sputum. There was no history of wheezing, dyspnoea, or chest pain, nor any personal or family history of atopy. Despite repeated stains and cultures for tuberculosis being negative, he had received antituberculous therapy for 1 year without relief. A review of three chest roentgenograms revealed transient pulmonary infiltrates. The total leucocyte count was 5800 cells/mm^3 with 16% eosinophils. Spirometry was normal with forced vital capacity (FVC) of 4.07 l (85% of predicted), forced expiratory volume in 1 s (FEV_1) of 3.26 l (81% of predicted), FEV_1/FVC ratio of 80%, and no change after bronchodilators. Postexercise spirometry too was normal. The patient did not consent to bronchoprovocation testing. CT of the thorax showed bilateral central bronchiectasis with a mucoid impaction in the left upper lobe bronchus. Intradermal testing elicited strong immediate reactions to *A. niger*, *A. fumigatus*, *A. flavus*, and *A. tamarii*. Sputum cultures yielded pure growth of *A. niger*, and agar gel double diffusion test demonstrated strong bands of serum precipitins against *A. niger* and *A. fumigatus*. Specific immunoglobulin (IgG) against *A. fumigatus* was positive by ELISA, but was not performed with *A. niger*. The serum total IgE level was 29 724 IU/ml.

Apart from bronchial asthma, our patient fulfilled seven of the eight major and two of the three minor diagnostic criteria for ABPA (Table 1). The patient

Table 1. Diagnostic criteria for ABPA fulfilled by our patient

Major criteria	
Asthma	–
Presence of transient pulmonary infiltrates (fleeting shadows)	+
Immediate cutaneous reactivity to *A. niger*, *A. fumigatus*, *A. flavus*, *A. tamarii*	+
Elevated total serum IgE	+
Precipitating antibodies against *A.niger* and *A. fumigatus*	+
Peripheral blood eosinophilia	+
Elevated serum IgG to *A. fumigatus*	+
Central bronchiectasis with normal tapering of distal bronchi	+
Minor criteria	
Expectoration of golden brownish sputum plugs	–
Positive sputum culture for *A. niger*	+
Late (Arthus type) skin reactivity to *A. fumigatus*	+

showed remarkable improvement with oral prednisolone, which was stopped after 6 months. The total serum IgE after 6 weeks dropped to 15 097 IU/ml. Spirometry at 1 year remained normal.

Pulmonary infiltrates associated with eosinophilia in an asthmatic subject have always raised the initial suspicion of ABPA. A literature search disclosed 18 patients of ABPA without asthma (1–4). Of the 42 patients of ABPA from Australia, 11 were without asthma (1). However, in our recent review of 95 patients with ABPA, all had clinical evidence of asthma (5). Fungi other than *Aspergillus* can also cause ABPA without asthma. Of the 11 patients with ABPA without asthma, three were reportedly caused by other fungi (1). A Japanese report described an elderly lady with ABPA without asthma in whom *A. niger* was implicated (3).

Although we did not add itraconazole in our patient, it is now being regarded as a potential adjunctive treatment for ABPA. A recent report suggests that itraconazole reduces eosinophilic airway inflammation, systemic immune activation and exacerbations in patients with stable ABPA (6).

A remarkable aspect hitherto not highlighted was that in 13 patients of ABPA without asthma, an initial diagnosis of bronchogenic carcinoma was considered (1, 2, 4, 7). Furthermore, the remarkable radiologic similarity to pulmonary tuberculosis has important clinical implications in high tuberculous prevalent areas (8). Our patient too was suspected of multidrug-resistant tuberculosis. This case reflects the difficulty in recognizing ABPA in the absence of clinical asthma.

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Fondaparinux as a novel therapeutic alternative in a patient with heparin allergy

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Key words: heparin allergy; ultra low molecular weight heparin.

Delayed-type hypersensitivity skin reactions at injection sites are a well known side-effect of high and low molecular weight heparins. The aim of skin provocation tests in patients with heparin-induced eczema is the identification of a safe alternative anticoagulation. In general, heparinoids, hirudins, cumarines and the xylanopolyhydrogensulfate pentosanpolysulfate are available alternatives for anticoagulation in heparin-mediated delayed-type hypersensitivity.

Lack of binding of fondaparinux to dermal proteins may lead to tolerance of fondaparinux in patients with heparin allergy.

A 61-year-old-woman developed a localized pruritic eczema after injection of a high and low molecular weight heparin, a heparinoid and pentosanpolysulfate within hours. On different occasions, the patient had received heparin-Na, nadroparin, certoparin, danaparoid and pentosanpolysulfate for the prophylaxis of deep vein thrombosis and treatment of thrombophlebitis. Patch testing with readings up to day 7 including paraffin as a negative control was performed with two high molecular weight heparins (heparin-Na, heparin-Ca), three low molecular weight heparins (certoparin, nodroparin, enoxaparin), an ultra low molecular weight heparin (fondaparinux), the heparinoid danaparoid and two recombinant hirudins (desirudin, lepirudin). Skin test with pentosanpolysulfate was refused by the patient. Patch testing showed positive reactions with eczema formation after 72 h only to nordoparin and enoxaparin. Preservatives such as chlorocresol and sulfite were negative. Subsequently, patch tests to preservatives were also tested by prick and intracutaneous testing. Prick testing was completely negative for all substances up to 72 h. In contrast, reactions to intracutaneous testing with concentration of 0.01% were found positive for the high molecular weight heparins (heparin-Na and heparin-Ca), the heparinoid (danaparoid) and the low molecular weight heparin certoparin at 72 h. In summary, the recombinant hirudins desirudin and lepirudin as well as the ultra low molecular weight heparin fondaparinux were the only nonreacting substances in all tests applied (Table 1).

Heparin is a water-soluble, anionic glycosaminoglycan, consisting of a

Table 1. Results of patch, prick and intracutaneous testing to heparin, high molecular weight heparin, low molecular weight heparin, ultra low molecular weight heparin, heparinoids and hirudins

	Patch test			Prick test	Intracutaneous test			
	D2	D3	D4	D3	20 min	D2	D3	D7
HMW heparin								
Heparin-Ca	–	–	–	–	–	–	++	+++
Heparin-Na	–	–	–	–	–	(+)	++	+++
LMW heparin								
Nodroparin	–	++	+++	NT	NT	NT	NT	NT
Certoparin	–	–	–	–	–	(+)	+++	+++
Enoxaparin	–	++	+++	NT	NT	NT	NT	NT
ULMW heparin								
Fondaparinux	–	–	–	–	–	–	–	–
Heparinoid								
Danaparoid	–	–	–	–	–	–	–	+
Hirudins								
Lepirudin	–	–	–	–	–	–	–	–
Desirudin	–	–	–	–	–	–	–	–

NT, not tested; HMW, high molecular weight heparin; LMW, low molecular weight heparin; ULMW, ultra low molecular weight heparin.

heterogenous mixture of mucopolysaccharides with alternating sulfated D-glucuronic acid and D-glucosamines. Molecular weight discriminates high molecular weight (10–20 kD), low molecular weight heparin (4–6 kD) and ultra low molecular weight heparin (1.7 kD) (1).

Immediate-type allergic reactions to heparins have rarely been reported. In contrast, delayed-type hypersensitivity reactions have been described frequently in the literature (2). In this case we demonstrate a delayed-type hypersensitivity reaction to high and low molecular weight heparins. Our patient also showed a delayed-type hypersensitivity reaction in skin tests to the heparinoid danaparoid. As danaparoid is a mucopolysaccharide derived from porcine intestinal mucosa, it may share identical allergens with heparin leading to cross-reactivity between heparin and danaparoid (3).

As an alternative for patients with heparin allergy, hirudins have been successfully used in patients with immediate-type and in delayed-type skin reactions (4). Hirudin clearly differs in the molecular structure from heparin preventing cross-reactivity between heparins and hirudins. This is confirmed in our case. Thus, hirudins can be recommended for thrombosis prophylaxis in our patient.

Interestingly, the recently introduced substance fondaparinux, a member of the group of ultra low molecular weight heparins with a molecular weight of 1.7 kD, was tested negative in our patient and, thus, offers a new alternative for prophylactic therapy of deep vein thrombosis for up to 9 days. The molecular structure and the resulting antigenicity is similiar in high molecular weight heparins and low molecular weight heparins. This is reflected by the finding that our patient showed hypersensitivity to both heparin classes. By contrast, testing of the low molecular weight heparin fondaparinux was negative. This supports the view that fondaparinux may lack a part of the epitope recognized by heparin-sensitized clonal T cells, or the binding avidity to dermal proteins required for hapten formation may be hampered. In fact, it is currently assumed that the delayed-type hypersensitivity may require binding of heparins to dermal or subcutaneous proteins (5). The role of local proteins is further underlined by the observation that intravenous treatment with heparin does not lead to an allergic reaction in patients with delayed-type hypersensitivity (6).

In summary, ultra low molecular weight heparins might be a new helpful, cost saving addition to the small armentarium of clinicians, who wish to offer thrombosis prophylaxis for patients with heparin-mediated delayed-type hypersensitivity.

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A case of IgE-mediated hypersensitivity to cefepime

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Key words: cefepime; IgE-mediated anaphylaxis.

Cefepime is considered the first 'fourth generation' cephalosporin because it is active against a broader spectrum of bacteria than the third generation cephalosporins, and is widely prescribed in severe infections. The most commonly reported adverse effects in cefepime trials have been diarrhea, nausea, vomiting, phlebitis, rash, headache, and occasionally encephalopathy, myoclonus, and seizures (1). To our knowledge, however, no case of cefepime-induced IgE-mediated anaphylaxis have been reported to date.

Cefepime may cause IgE-mediated hypersensitivity even in the absence of prior exposure.

A 10-year-old boy with the diagnosis of medulloblastoma and febrile neutropenia developed anaphylaxis (2) (urticaria, angioedema of the lips and tongue, rhinitis, dyspnea, wheezing, tachycardia, and hypotension with a systolic pressure of 60 mmHg) within 10 min of receiving his first intravenous injection of cefepime. After emergency treatment with intramuscular adrenaline, 6-methyl-prednisolone, and chlorphenamine intravenously, his symptoms resolved completely in 6 h.

Four months earlier, he had received and tolerated a 10-day intramuscular ceftriaxone treatment for pneumonia, and before that he had tolerated penicillin and ampicillin. His personal and family histories were negative for atopic diseases. and he had not experienced adverse reactions to other drugs.

Two months after the clinical reaction, an allergic work-up was undertaken.

Prick and intradermal tests were performed, as previously described (3, 4), on the volar forearm skin with penicilloyl polylysine (Allergopharma, Reinbeck, Germany), minor determinant mixture (Allergopharma) (both used according to manufacturer's instructions), benzylpenicillin diluted in 0.9% sodium chloride and administered at increasing concentrations of 0.1–10 000 IU/ml, ampicillin and amoxicillin diluted in 0.9% sodium chloride and used at concentrations of 1 and 25 mg/ml, and cefepime, as well as cefazolin and cefuroxime (as representatives of cephalosporins of first and second generation, respectively), ceftriaxone and cefotaxime (as they have the same side chain structure with cefepime), and ceftazidime (as it has a very similar side chain structure with cefepime) diluted in 0.9% sodium chloride and used at concentrations of 2 mg/ml.

A positive prick test response was defined as a wheal ≥3 mm than the negative control wheal. When skin prick test responses were negative, 0.01 ml of the reagent was injected intradermally, and reactions were considered positive when wheals larger than 5 mm in diameter. Prick and intradermal test readings were made after 15 min. Histamine at concentrations of 10 and 1 mg/ml were used as positive controls for prick and intradermal tests, respectively. Negative controls were carried out with normal saline.

Intradermal tests with cephalosporins were also administered to 11 healthy control subjects, five of whom had previously tolerated cefepime.

In vitro assays were performed only for specific IgE to penicilloyl G (CAP FEIA; Pharmacia-Upjohn, Uppsala, Sweden), according to manufacturer's instructions. A specific IgE level > 0.35 kU_A/l (class 1) was considered positive. We were not able to perform assays for specific IgE to ampicilloyl, amoxicilloyl, and aforementioned cephalosporins as they were not available in our country.

Total serum IgE was also determined.

Single-blind, placebo-controlled oral challenges with penicillin V (therapeutic dose = 1 000 000 IU), ampicillin (1 g), amoxicillin (500 mg), cefaclor (500 mg), and cefuroxime (500 mg) were performed, each on a different day. Increasing doses (starting with 0.01 of the daily therapeutic dose) were administered at 1-h intervals until the cumulative daily therapeutic dose was reached.

Informed consent was obtained from parents before skin, and oral challenge tests.

The allergic work-up of the patient is shown in Table 1.

The patient responded to intradermal testing with cefepime, ceftriaxone, cefotaxime, and ceftazidime (maximum wheal diameters; 13, 13, 9, and 7 mm, respectively). Prick and intradermal histamine tests produced wheals with maximum diameters of 5 and 9 mm, respectively. No reactions with other reagents were observed.

None of the control subjects had positive skin tests to any of the reagents. Mean wheal diameters with prick and intradermal histamine in control subjects were 6.6 mm (range 4–10 mm) and 11.3 mm (range 7–15 mm), respectively.

Table 1. Allergic work-up of the patient

Reagent	Prick test	ID test*	Oral challenge
Penicilloyl polylysine	–	–	ND
Minor determinant mixture	–	–	ND
Benzylpenicillin	–	–	ND
Penicillin V	–	–	Negative
Ampicillin	–	–	Negative
Amoxicillin	–	–	Negative
Cefazolin	–	–	Negative
Cefuroxime	–	–	Negative
Cefotaxime	–	9 mm	ND
Ceftriaxone	–	13 mm	ND
Ceftazidime	–	7 mm	ND
Cefepime	–	13 mm	ND

* Wheal diameter. ID, intradermal; ND, not done.

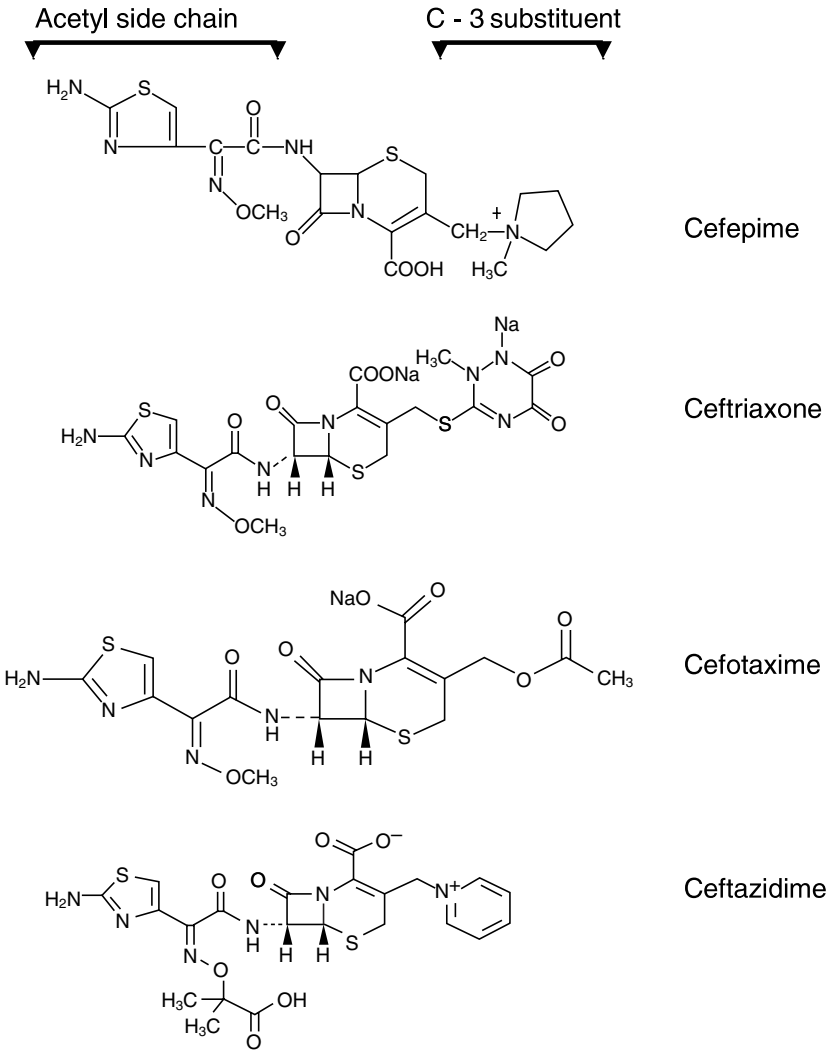

Figure 1. Chemical structures of cefepime, ceftriaxone, cefotaxime, and ceftazidime.

The patient's serum total IgE was 62 kU/l, and serum-specific IgE to penicilloyl G was negative.

The patient did not react to any of the oral challenges.

The type and time of onset of the reaction, and the positive intradermal test response with cefepime indicate that our patient, although he had never received it before, had an IgE-mediated anaphylactic reaction to cefepime.

We may discuss at least three types of recognition when patients react to cephalosporins with immediate type hypersensitivity: one possibility is preexisting IgE directed against the betalactam portion of the molecule (5); another possibility is preexisting IgE directed against the specific cephalosporin that produced the reaction (e.g. recognition of the entire molecule) (6–8); a third possibility is allergic cross-reactivity among different cephalosporins either by recognition of the core ring structure or by recognition of the side chain structures (4, 9, 10).

We suggest this reaction was probably caused by selective sensitization to side chain determinants rather than to entire molecule, or to betalactam ring, which seems likely to have occurred during previous ceftriaxone treatment. We confirmed our suggestion by positive intradermal test responses to cefepime, ceftriaxone and cefotaxime, all have the same acetyl side chains (2-amino-4-thiazolyl), and to ceftazidime, which has a very similar side chain structure with the aforementioned cephalosporins (Fig. 1), and by negative skin tests and challenge results with other betalactams.

Our investigations were of particular importance for the present case as he had a malign disease that led frequent attacks of febrile neutropenia and other serious bacterial infections. Third generation cephalosporins are the most suitable drugs for treating such conditions. Therefore, desensitization should be considered for our patient on the occasion of requiring antimicrobial therapy with third generation cephalosporins.

In conclusion, patients may exhibit the symptoms of IgE-mediated anaphylaxis, even if they have no history of penicillin or cephalosporin allergy and no obvious prior exposure to the culprit drug. Therefore, diagnostic tests should be performed not only with penicillin determinants but also with cephalosporins that involve identical or similar side chain structures with the responsible medication, especially when the patient was previously treated with these drugs.

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Anaphylaxis to dexrazoxane (ICRF-187) following three previous uncomplicated infusions

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Key words: anaphylaxis; breast cancer; dexrazoxane.

Dexrazoxane (DEX) is clinically used as an anthracycline-cardioprotective agent and may act by preventing iron-based oxygen free-radical damage. The phase I trials indicated that DEX could be safely administered, with leukopenia and thrombocytopenia being the dose-limiting toxicities, on a number of different schedules of administration, except in children, in whom the major dose-limiting toxicity was hepatotoxicity (1). Nonmyelosuppressive toxic effects included nausea and vomiting, transient and mild elevations in liver function tests, reversible serum amylase elevations, alopecia, malaise and increased urinary clearances of iron and zinc (2–4). No episode of anaphylaxis related to DEX was ever reported in literature. We report a case of systemic anaphylaxis after intravenous administration of DEX. A 38-year-old patient with breast cancer was admitted, after radical left mastectomy, for adjuvant chemotherapy according to CEF regimen (5-fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 21 days) with concurrent administration of DEX (800 mg/m^2). During the first three cycles the tolerance to chemotherapy was good and only mild chemotherapy-related toxicity was reported. Five minutes after the beginning of the intravenous administration of DEX, during the fourth cycle of chemotherapy, the patient developed a hypersensitivity reaction with a rapidly progressing nettle rash extended over the body, diffuse erythematous urticarioid lesions, angioedema and intense itching. Moreover, laryngeal edema, bronchospasm, severe cough, shortness of breath, dizziness, anxiety and severe hypotension (50/30 mmHg) rapidly developed and increased. Physical examination revealed stridor on auscultation secondary to cervical edema. Intravenous administration of 1000 mg hydrocortisone followed by a rapid intravenous crystalloid solution (1 l) and high flow oxygen was performed. This therapy reversed the immediate symptoms of anaphylaxis with normalization of the emodinamic and respiratory state and reduction of cutaneous rash. Appropriate length of observation was followed till 24 h after anaphylaxis episode. Symptoms resolved completely within 24 h. Skin prick testing performed 2 months after the event identified DEX as the causative agent (1/10 diluted solution). The patient's anamnesis was negative for allergic events and the reported anaphylaxis followed a standard steroid premedication for antineoplastic chemotherapy with 8 mg i.v. of dexamethasone. Furthermore, no allergy to any drug was reported, except steroid, which was given before the reaction occurred.

We describe the case of a breast cancer patient who developed dexrazoxane-induced anaphylaxis.

With the extensive use of anthracycline-based chemotherapy regimens, either alone or in combination with radiation therapy in the management of several malignancies, this uncommon complication should be kept in mind for early detection and successful management.

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