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Mometasone furoate nasal spray improves olfactory performance in seasonal allergic rhinitis

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Key words: allergic rhinitis; olfactory function; nasal steroids; 'Sniffin' Sticks'; mometasone furoate.

Impairment of olfactory function is frequently present in patients with allergic rhinitis (1, 2). This seems to be associated particularly with inflammatory processes (3). The aim of this study was to investigate the effects of mometasone furoate nasal spray on olfactory performance in patients with seasonal allergic rhinitis.

Mometasone furoate nasal spray improves olfactory function in patients with seasonal allergic rhinitis.

Twenty-four patients (age 27.3 ± 4.9 years) took part in this double-blind, placebo-controlled, randomized, prospective study (11 placebo, 13 verum). Allergic rhinitis was diagnosed on the basis of a medical history and skin prick tests.

Allergy symptoms were quantitatively assessed before and after treatment. Nasal airflow was measured with anterior rhinomanometry. Psychophysical measures of olfactory function were obtained using the 'Sniffin' Sticks' test kit (Heinrich Burghart Elektro- und Feinmechanik GmbH, Wedel, Germany; bilateral testing of butanol odor threshold, odor discrimination and identification) (4). Patients received mometasone furoate nasal spray (Nasonex, Essex Pharma GmbH, München, Germany) or placebo for 2 weeks.

The results were normalized to baseline values. SPSS software (v. 10) was used for statistical analyses. After testing for normal distribution, investigations were performed with the help of variance analyses for repeated measures; nasal air-flow was used as a co-variate. *t*-tests were employed for between-group analyses and for *posthoc* comparisons. For correlational analyses, Pearson statistics were used.

Symptom scores were reduced in both groups (placebo: 24.7 ± 12.9 to 20.4 ± 14.8 units, mometasone 18.4 ± 13.1 to 8.8 ± 7.6 units; $t = 0.85$, $P = 0.41$). Nasal flow decreased in the placebo group (731 ± 122 to 688 ± 145 cm^3/s) and increased in the mometasone group (747 ± 177 to 805 ± 93 cm^3/s). However differences between groups were not significant ($t = 1.79$, $P = 0.08$).

When investigating olfactory function, the main effect for the factor 'treatment' narrowly missed statistical significance ($F[1,21] = 3.75$, $P = 0.066$). However, there was a significant interaction between the factors 'test' and 'treatment' ($F[2,42] = 3.93$, $P = 0.027$) indicating that test results differed between groups. *Posthoc* comparisons revealed that mometasone subjects became more sensitive to butanol than subjects treated with placebo ($t = 2.22$, $P = 0.037$) while there was no such difference for odor identification ($t = 1.41$, $P = 0.17$) or odor discrimination ($t = 0.92$, $P = 0.37$). There was a nonsignificant correlation between normalized air-flow and normalized results of olfactory tests: $r_{24} < 0.13$, $P > 0.55$.

Odor threshold significantly improved after 2 weeks of treatment with mometasone furoate nasal spray. This appeared to be independent of the accompanying improvement in allergic symptoms or nasal airflow. This supports the notion that impairment of olfactory function in allergic rhinitis is mostly because of the allergic inflammation and not because of reduced nasal airflow alone.

Following topical treatment with steroids, Meltzer et al. (5) reported significant improvement of odor identification, but not of odor thresholds. As they used the Connecticut Chemosensory Clinical Research Center evaluation, differences may relate to different methods of assessing odor threshold.

In conclusion, anti-inflammatory treatment with topical nasal steroids not only reduces 'classical' symptoms of allergy but improves olfactory function in patients with seasonal allergic rhinitis.

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Exercise-induced bronchoconstriction and respiratory symptoms in elite athletes

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Key words: elite athletes; exercise-induced asthma; exercise-induced bronchoconstriction.

Currently there are no standardized guidelines for exercise-induced bronchoconstriction (EIB) diagnosis in elite athletes, although recently the International Olympic Committee (IOC) (1) asked for EIB diagnosis proof by the eucapnic voluntary hyperpnea (EVH) test or field exercise challenge prior to the Salt Lake City Olympic Winter Games.

Comparison between self-reported exercise induced respiratory symptoms and results of exercise challenge in elite athletes.

As many top athletes continue to have diagnosis made by self-reported exercise-induced symptoms and therapeutic response to β_2 agonists we wanted to evaluate whether these symptoms always occur with EIB in elite athletes or not.

We included Portuguese elite athletes (internationals and more than 5 years in high competition) attending our section of 'Sports, Allergy and Asthma' for EIB complaints. Exercise-induced respiratory symptoms were assessed by Portuguese translation of the United States Olympic Committee Exercise-Induced Bronchoconstriction Questionnaire. The questionnaire was filled and responses reviewed with the athlete. All performed basal spirometries, bronchial challenge with methacholine and skin-prick tests with common aeroallergens. Exercise challenge was performed either in laboratory, using the treadmill with a continuous protocol, 2% fixed inclination, initial speed of 8 km/h, increases of 2 km/h each 2 min, until 95% of calculated maximum heart rate and maintaining this speed for at least 4 min or until exhaustion; or in the field, performing the free athletic sport test (FAST) in which the athletes perform their usual sport activity in their usual environment. First, practising the most 'asthmogenic activity' for 8 min (or to exhaustion), and secondly, if negative, continuing normal training session until appearance of symptoms. Pulmonary function tests were performed before and 1–3 min after exercise and then every 3–5 min up to 30 min. A 10% fall of baseline forced expiratory volume (FEV_1) after exercise was considered a positive test.

We studied 15 elite athletes (three females) of age 23.0 ± 6.7 years (mean ± SD). They had 7.0 ± 1.8 training sessions per week and were in competition for 8.9 ± 2.6 years. There was a gap of 3.5 ± 3.3 years between beginning of competition and appearance of symptoms. None smoked. Nine practiced in outdoor environment (three soccer players and six runners), two indoor (basketball and gymnastics) and four water sports (two water polo and two swimmers). Five practiced 'speed and power' sports, six 'endurance' and four 'water sports'.

Major complaints were: (i) inability to get deep breath with exercise ($n = 13$; 88%); (ii) cough ($n = 11$; 73%); (iii) chest congestion or chest tightness ($n = 8$; 53%); and (iv) noisy breath and wheezing ($n = 6$; 40%). Eleven (73%) reported chest tightness and nine (60%) cough after running 1 mile and 15 min rest. All had normal resting spirometries. Seven (46.6%) had positive methacholine challenge with median PC20M of 2.1 mg/dl. Prevalence of atopy was 60%, with nine athletes sensitized to house dust mites. Seven of 12 FAST and one of three laboratory exercise challenges were positive (EIB+ group). Two additional FAST performed in athletes were negative. The mean percentual variability of FEV_1 after challenge was 1.6 ± 2.7 and −21.3 ± 11.0 for EIB− ($n = 7$) and EIB+ ($n = 8$) groups, respectively. Proportion of true diagnosis was greater for 'wheezing' (60%), 'inability to get deep breath' (53%), 'noisy breathing' (53%), and smaller for 'would you experience cough after 1 mile?' (26%) and 'would your chest feel tighter after 1 mile?' (40%).

There were no differences concerning age (21.9 ± 3.7 years *vs* 24.1 ± 8.9 years), years in competition (8.7 ± 3.4 years *vs* 9.1 ± 1.9 years), training sessions per week (6.8 ± 1.7 *vs* 7.1 ± 2.0), nor in resting spirometries, with mean forced vital capacity (FVC) of (102.5 ± 13.1% *vs* 95.4 ± 11.6%; $P = 0.302$), FEV_1 (108.2 ± 9.5% *vs* 92.5 ± 21.5%; $P = 0.119$) and forced expiratory flow ($FEF_{25–75}$) (116.0 ± 16.3% *vs* 85.5 ± 34.0%; $P = 0.067$), respectively, for EIB+ and EIB− groups. The proportion of positive challenges was similar for different environments: outdoor practicing athletes five (55.5%) positive challenges; indoor one (50.0%) and water two (50.0%); and for different kind of sports: four (66.6%) endurance, two (50.0%) water sports, two (40.0%) speed and power sports. There were no differences between reported symptom scores and exercise challenge result (4.50 ± 2.78 for EIB+ and 5.29 ± 1.60 for EIB−; $P = 0.523$).

Although questionnaires provide reasonable estimates of EIB prevalence among athletes, the use of self-reported symptoms for EIB diagnosis in elite athletes will likely yield high frequency of both false positive and negative results.

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Late onset of type-1 allergic conjunctivitis in an elderly woman

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Key words: allergic conjunctivitis; elderly; late onset; type-1 allergy.

A 75-year-old woman presented at our allergy outpatient clinic with conjunctivitis in both eyes and pruritic, mild edema and erythema of the lower eyelids. The symptoms first appeared 5 months ago in early spring when she had undergone surgery for the cataract on her left eye. Since then, she has been using various eye drops on both of her eyes. All of the eye drops contained the preservative benzalkonium chloride. She had been referred by her ophthalmologist for patch testing due to suspicion of a type-4 contact allergy.

***De novo* sensitization to type-1 allergens in an elderly woman as a rare differential diagnosis.**

Patch testing to benzalkonium chloride and the European standard series remained negative.

The patient's history was negative for atopic diseases. Total IgE was within the normal range, specific IgE for aeroallergens, determined by UniCAP® (Pharmacia, Vienna, Austria), was negative. However, prick-testing to common type-1 allergens was positive to the following: ash tree, rye grass, mugwort and olive pollen. In central Europe, the pollen season starts in early spring with the blossoming of birch, alder, hazel, and the concomitant blossoming of the ash tree, followed by the flowering of grasses during early summer and mugwort and ragweed in the late summer. Olive pollen is not common in central Europe, but it represents a cross-reactive allergen to the ash tree pollen. The sensitization pattern corresponds perfectly to the patient's symptoms from March through mid-September.

The patient was symptom-free during treatment with the oral antihistamine desloratadine 5 mg (Aerius™, AESCA, Traiskirchen, Austria) once daily and topical treatment with the mast cell stabilizer cromoglicinic acid (Cromoglin™ eye drops; Ratiopharm, Vienna, Austria) q.i.d. The patient herself discontinued the therapy in the beginning of September, when mugwort pollen was still in the air, and the symptoms reappeared. Topical treatment with Levocabastine eyedrops (Livostin™ eye drops; Janssen-Cilag, Vienna, Austria) bid made the symptoms disappear again. At a follow-up visit after the end of the pollen season in November, the patient reported to be symptom-free in the absence of any therapy.

De novo sensitization to type-1 aeroallergens is rare in the mature population. In a Swiss study by Wüthrich et al. (1), only 3% of patients suffering from type-1 allergic diseases acquired their sensitization after their 40th birthday. Nevertheless, type-1 allergies might be an underestimated differential diagnoses in elderly patients (2–4).

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Blepharochalasis misdiagnosed as allergic recurrent angioedema

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Key words: blepharochalasis; IgA deposits; recurrent angioedema.

Recurrent angioedema is a syndrome of multiples causes (1), although allergic conditions are frequently claimed. A 43-year-old woman was referred to an allergy unit for multiple drug allergy. At the age of 13, she started episodes of painful bilateral eyelid oedema of several days' duration, with frequency ranging from 3 to 4 per year to one monthly. They were treated with corticosteroids and attributed to drug, food or food-additive allergy, so the patient was advised to avoid several drugs and went onto a diet. Over the years and after repeated episodes, eyelid laxity, progressive bilateral ptosis and ectropion developed and exophthalm became patent. At the age of 38, autoimmune hypothyroidism was detected and treatment with levothyroxine was started but angioedema episodes persisted.

Uncommon eyelid disease mimicking recurrent allergic angioedema.

Physical examination revealed no abnormalities except bilateral severe eyelid laxity with ptosis of upper eyelids and ectropion of lower eyelids, orbital fat atrophy and secondary keratoconjunctivitis of the right eye.

Orbit magnetic resonance was normal. Skin tests to common inhalant allergens and foods were negative. Blood cell count, C_3, C_4, C_1-inhibitor, IgG, IgA, IgM, IgE, ANA, T_4 and TSH were normal. Anti-peroxidase antibodies were 63 IU/ml ($n < 40$). Provocation tests with the suspicious drugs proved

negative. Eyelid histology disclosed oedema of the dermis with periadnexal lymphocytic infiltrate and absence of elastic fibres. Eyelid immunofluorescence revealed spotty IgA deposits in the dermoepidermic junction and around small vessels. Clinical and histological data established the diagnosis of idiopathic blepharochalasis and surgical reconstruction was performed with good result.

Blepharochalasis is a rare disorder in young people, characterized by recurrent episodes of non-pitting, non-painful, non-erythematous periorbital oedema, leaving wrinkled, redundant and thinned eyelid skin and resulting in atrophy and relaxation of the eyelid structures with ptosis (2). An hypertrophic and an atrophic clinical stages have been recognized, and functional vision impairment is common (2, 3). Swelling attacks become less frequent as the patient ages and eventually most cases enter a relatively quiescent stage (2). The condition must be differentiated from other floppy eyelid syndromes (4). Dermal atrophy, loss of fibrillar collagen, decrease in or absence of elastic fibres and inflammatory perivascular cellular infiltrates are characteristic (2). Immunohistological studies carried out in two previous cases show, as in our patient, IgA deposits around blood vessels (5, 6), which may be involved in the pathogenesis of the disease (6), or be an epiphenomenon of damage of elastic fibres.

As a disease in youngsters, blepharochalasis is easily mistaken for recurrent angioedema and many patients are misdiagnosed of allergy. Multiple skin and patch testing, immunological and parasite determinations, dieting, drug avoidance, phobias, antihistamines, corticosteroids and even allergy shots are used unnecessarily in these patients. Knowledge of the classical features, particularly a history of oedema starting in adolescence and, if necessary, eyelid biopsy can help in unmasking this condition and establish a proper diagnosis and treatment.

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Occupational contact dermatitis to turnip (*Brassica napa*)

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Key words: allergy; *Brassica napa*; delayed hypersensitivity; contact dermatitis; occupational; turnip.

Sensitization to food allergens, presenting as cutaneous symptoms, has been widely published. The *Brassica* genus includes salad vegetables (broccoli, cauliflower, cabagge, Brussels sprouts), fodder vegetables (turnip, radish), oleaginous seed plants (colza) and spices (mustard). Here, a case of occupational contact dermatitis to turnip in a farmer is reported.

A case of occupational contact dermatitis to turnip in a farmer.

The patient was 45-year-old man who had been suffering for the last 3 years with episodes of pruritus, erythema and swelling affecting the fingers and the back of his hands. He related such symptoms to handling turnip leaves and sticks during flowering. He noted the cutaneous symptoms after 24 to 48 h of handling, without conjunctival, nasal or bronchial manifestations. Dermatitis subsided without medical treatment after approximately 2 weeks.

Skin prick tests were carried out on the volar side of his forearms with a series of standard inhalant allergens (including latex) and foods, including legumes and vegetables. Skin prick-by-prick tests were also carried out in the same way with fresh turnip (leaf, stick and root). Skin prick tests were all negative but a weak positive reaction to fresh turnip root was noticed.

Patch tests were applied to the skin of the upper back with fresh turnip leaves, sticks and root. Immediate reaction (at 30-min reading) was not elicited. Positive reactions were observed at 48-h reading with leaves (++), sticks (+) and root (+). The results of patch tests with the previously described materials were negative in five controls.

Allergy to plants of the *Brassica* genus, although uncommon, has been previously published (1–9). Immediate hypersensitivity has been described from turnip (1), mustard (4, 6, 7), rape (4) and stock (8). Delayed hypersensitivity has been described to cauliflower (3), mustard (5), radish (2) and broccoli (9). So, it would be easy to think that contact dermatitis to turnip is feasible. Nevertheless, as far as it is known, contact dermatitis to turnip has not been previously published, perhaps because of its limited use, mainly as fodder vegetable.

Given that this patient suffered contact dermatitis during turnip-flowering season, suspicion was directed towards turnip pollen. He had no contact with turnip leaves in other seasons. Nevertheless, results from epicutaneous tests showed positive results to leaves, sticks and root (turnip-pollen extract was unavailable). Probably, allergens responsible for contact dermatitis are present in the different parts of the turnip (leaves, sticks and root).

This patient did not have symptoms when exposed to other members of the Cruciferae family. In contrast, some authors (1, 8, 9) detect cross-reactivity among vegetables of that family.

Contact dermatitis from pesticides was not considered feasible in this patient because he handled the same substances other times without any symptoms.

Hänninen et al. (10) demonstrated that activating defense mechanisms of plants may considerably increase their allergen content by using turnip as a model plant; a 18.7-kDa protein which showed high homology to prohevein and to many other prohevein-like defense proteins. In that study, a great majority of patients allergic to prohevein tested positive to the 18.7-kDa protein also, suggesting a close structural relationship between those two allergens. In contrast, this patient showed negative result in skin prick test to latex.

These results agree with those of Sanchez-Guerrero et al. (9), who concluded that patch tests with fresh vegetables are reliable in the diagnosis of work-related contact dermatitis induced by vegetables.

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Chronic urticaria in latex allergic patients: two case reports

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Key words: chronic urticaria; diet; foods; crossreactivity; latex allergy.

Fifty to sixty-five per cent of latex allergic patients are sensitized also to plant-derived foods (latex-fruit syndrome). Class I chitinases seem to be the main allergens involved in these crossreactions (1). Usually ingestion of foods crossreacting with latex provokes immediate-type symptoms (itching, urticaria, angioedema, rhinoconjunctivitis, asthma, vomiting, diarrhoea), while there are no reports about chronic urticaria.

We report two cases of chronic urticaria, which dramatically improved following the avoidance of latex-crossreacting foods.

We report two cases of chronic urticaria, dramatically improved following the avoidance of latex-crossreacting foods. They were investigated to find out a correlation between chronic urticaria of unknown origin and latex allergy.

Patient A was a 18-year-old man (hairdresser) who presented cutaneous itching while wearing latex gloves. Patient B was a 38-year-old woman (beautician) with dyspnoea and local erythematous-papular rash after wearing latex gloves. Furthermore they presented chronic urticaria for several months, which was not latex-induced (patients avoided latex items and environments where they were used) and although they were receiving allergy medication (cetirizine: 10 mg/die).

They underwent a complete allergological evaluation. Antihistamines were withheld for 10 days before tests.

Both patients had positive latex skin tests. Patient A had class 3 (12.3 kU/l) specific immunoglobulin E (IgE) to latex proteins, while patient B had class 2 (1.26 kU/l). Serum total IgE were normal. Skin tests with foods allergens were negative.

They were diagnosed as suffering from a type I, IgE-mediated allergy to latex.

As their urticaria was not related to latex exposure they were instructed to avoid foods which, according to literature, crossreact with latex, for 1 month.

They recorded antihistamine medication intake, frequency and severity of symptoms for 2 weeks before starting the diet, for 1 month during the dietary intervention and for 1 month after coming back to a free dietary regimen.

During the diet period, urticaria progressively improved, with an important progressive decrease in the number of antihistamine tablets taken (until complete interruption of therapy). At the end of the follow up period patients were asymptomatic, without taking any drug. No nutritional deficiencies occurred.

Symptoms appeared again in both patients when they came back to a free dietary regimen, confirming the strict relation between urticaria and latex crossreacting foods.

Adverse reactions to foods are a frequent cause of both acute and chronic

urticaria. Expecially in chronic urticaria, elimination diet provides an important diagnostic and therapeutic tool. Patients with chronic urticaria of unknown origin and latex allergy should be studied also for foods crossreacting with latex. Classic hypoallergenic diets are ineffective for these patients, while a diet with a low content of latex crossreacting proteins may improve their condition.

A prolonged strict foods avoidance represents the only effective therapeutic mean to prevent chronic urticaria in these patients. Anyway, such a long-term diet is very difficult to be performed in terms of compliance and may have nutritional consequences. As a strong connection between food allergy and latex allergy has been assessed, an alternative therapeutic tool could be specific desensitization to latex. In fact, according to Literature, some latex-fruit allergic patients undergoing specific desensitization to latex, become tolerant also to some foods, they could not eat before desensitization (2, 3). Further studies are needed on a larger number of patients to confirm these results.

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Occupational asthma in an agronomist caused by the lentil pest *Bruchus lentis*

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Key words: *Bruchus lentis*; lentil; occupational asthma; pests.

Lentils are the most common legume involved in allergic reactions in paediatric patients in the mediterranean area (1). Allergic reactions to legumes by inhalation have rarely been described (2), and asthma because of inhalation of legume pests have not been reported. A 34-year-old male agronomist suffered rhinoconjunctivitis and asthma episodes when he manipulated lentils infested with *Bruchus lentis* (Fig. 1).

Occupational asthma by lentil pests.

Extracts prepared either from insect bodies or from lentils and infested lentils were used for skin prick testing (SPT), bronchial challenge and *in vitro* studies [immunoglobulin E (IgE)-immunoblotting].

The SPT and challenge tests were positive to infested lentil and *B. lentis* extracts but not to noninfested raw or boiled lentil extracts. By IgE-immunoblotting, specific IgE was detected to infested lentil but not to pure lentil extract, and a IgE-binding protein band of about 18 kDa was revealed in the infested lentil extract (Fig. 2).

Martin et al. (2) described the case of a 20-year-old man who experienced asthma when exposed to the steam from cooking either chick pea or lentil. In our patient, sensitization to lentil antigens was ruled out, but extrinsic antigens from pests living in the lentils (e.g. enzymes produced by the parasite) probably was the cause of the allergic symptoms. The IgE-immunoblotting results suggested that the response may be specific for this pest (*B. lentis*) and not for other legume pests (Fig. 3).

An increasing number of legume proteins or glycoproteins have been characterized as food allergens (3), but limited data tend to indicate that they are probably different from legume inhalant allergens. Our study indicates that exposure of workers to parasite

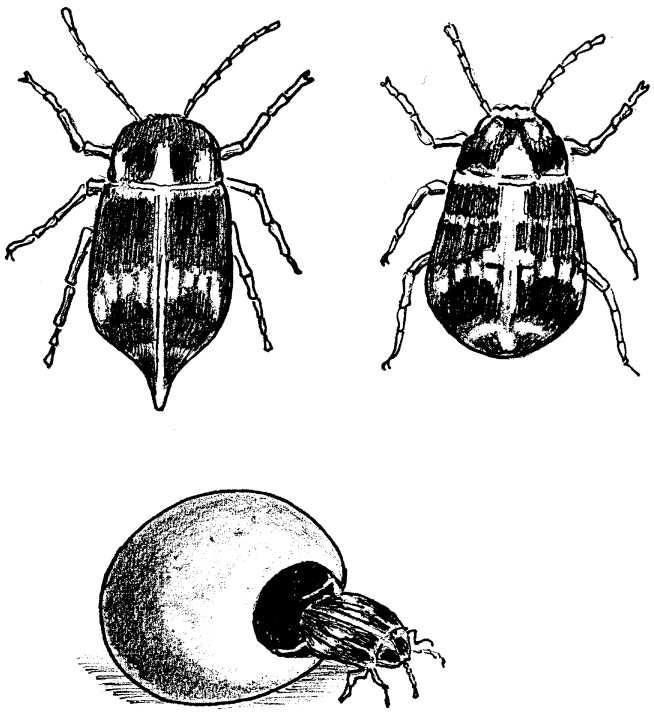

Figure 1. Bruchus lentis male and female.

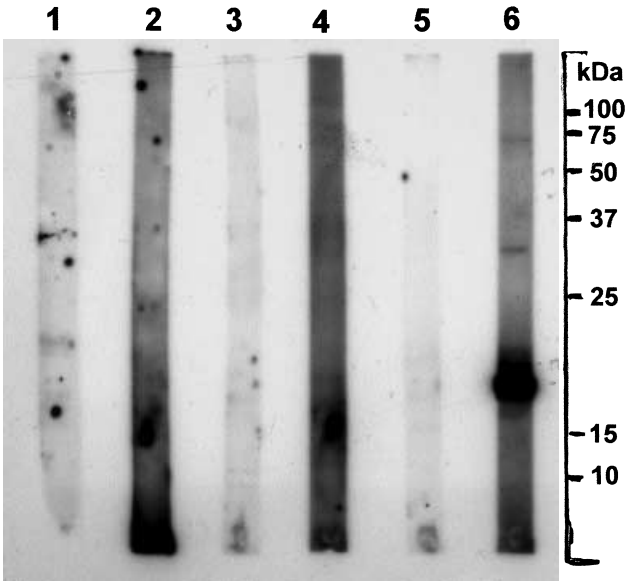

Figure 2. Immunoglobulin E-immunoblotting with patient's serum. (1) pure lentil extract, negative; (2) pure lentil extract; (3) *B. bean* whole bodies extract, negative; (4) *B. bean* whole bodies extract; (5) infested lentils extract, negative; (6) infested lentils extract. The m.w. of prestained markers run in parallel are indicated on the right.

Figure 3. Lentil parasited by *Bruchus lentis*.

emanations when handling infested lentils can be a cause of IgE-mediated rhinoconjunctivitis and occupational asthma. The allergic response may be different if infested lentils are consumed and may explain the negative oral challenge that was observed in other studies after lentil provocation in patients that experienced allergic symptoms after eating lentils or inhaling their emanations when cooking.

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IgE-mediated allergic rhinitis and conjunctivitis caused by *Calocedrus decurrens* (incense cedar)

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Key words: allergy; conjunctivitis; incense cedar; rhinitis.

Incense cedar (*Calocedrus decurrens*) is a West North American tree belonging to the *Cupressaceae* family. It reaches 30–40 m in lenght. We are unaware of previous reports of allergic complaints due to exposure to incense cedar.

A 40-year-old woman was seen because she had been suffering from rhinitis and conjunctivitis since 12 years in January and February. Symptoms were partially controlled by oral antihistamines and topical nasal steroids. During the season, lung function test showed no abnormalities. Out of season, she remained asymptomatic. The patient underwent skin prick tests (SPT) with common commercially available inhalants (Lofarma, Milano, Italy), histamine (1 mg/10 ml), and the diluent. Blood sample was obtained to measure both total IgE antibodies and specific IgE antibodies to common inhalants (CAP RAST, Pharmacia, Uppsala, Sweden). Total serum IgE level was 48 IU/ml. SPT to cypress was positive (++) (1). CAP RAST revealed class 3 (0.86 kUA/l) to cypress.

Incense cedar pollens cause IgE-mediated allergic rhinoconjunctivitis during the winter.

Cypresses are unusual in the area where the patient lived. Further questioning revealed that she had more intense allergic symptoms in the garden near to some incense cedars.

A crude extract was prepared from 5 g of cones of incense cedar that were crushed in the saline solution. The SPT with the incense cedar solution produced a positive reaction (++++) (1).

Specific serum IgE antibodies to incense cedar were measured using a commercial kit (Sferikit IgE spec, Lofarma SpA, Milano, Italy), where solid phases were polystyrene beads to which an extract obtained from cones of incense cedar was added. Incense cedar pollen extract was prepared by mixing 5 g of cones of incense cedar with 100 ml of phophate-buffered serum (PBS). The resulting suspension was extracted overnight at room temperature under stirring. After centrifugation (2500 *g* for 15 min), the supernatant was prefiltered and dialyzed against PBS containing Thimerosal, in a tube with a cut-off at 3500 D at 4°C for 24 h and then filtered through 0.8 μm Millipore filters (Millipore Corp; Bedford, MA, USA). This extract was considered nondiluted. The allergenic extract was prepared at 5% w/v in PBS (0.15 M) pH 7.2. With this extract the solid phases were prepared and we detected in the patient's serum specific IgE to *Calocedrus decurrens*. The serum examined gave a positivity in class 3, the IgE content was 5.2 RAST arbitrary units.

The patient underwent an exposure test (2) with fresh cones of incense cedar that she had brought from her garden. After exposure test, the patient immediately had the onset of sneezing, rhinorrea, obstruction of the nose, redness of the conjunctiva, tearing and itching of the eyes. An exposure test with extracts of cypress pollens was carried out and gave a negative result.

Our report provides evidence that incense cedar was able to provoke a distinct form of allergic IgE-mediated rhinitis and conjunctivitis (3). We think that the prevalence of sensitization to incense cedar may be increasingly important because this tree has recently become popular as an ornamental tree in Northern Italy where the pollen season is the winter (January and February).

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Asthma induced by the inhalation of vapours during the process of boiling rice

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Key words: allergens; asthma; food allergy; rhinoconjunctivitis; rice.

Hypersensitivity reactions to rice are scarce despite its universal consumption. Most reports have described immunologically mediated urticaria after contact with raw rice (1, 2). Reports of immediate hypersensitivity reactions after the inhalation of rice fumes, or consumption are rare (3, 4).

A case of rhinoconjunctivitis and asthma in a housewife who referred respiratory symptoms during exposure to vapours released by boiling rice.

We present a case of rhinoconjunctivitis and asthma in a housewife caused by the inhalation of vapours from boiling rice. She was able to consume cooked rice without symptoms. Physical examination, clinical tests, spirometry, chest and sinus radiographs were all normal. Total IgE was 526 kU/l.

Raw and boiled rice extracts, as well as an extract of concentrated fumes, collected during the rice boiling process using a refrigeration column, were prepared to perform *in vivo* and *in vitro* test, including skin-prick testing, sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and immunobloting. Five non-atopic and 12 atopic subjects served as controls. The patient underwent a pulmonary inhalation provocation test (PIPT) with raw rice extract.

Skin-prick testings with the raw rice and rice vapour extracts were positive (7 and 6 mm, respectively) and negative with the boiled rice extract. The controls had negative skin test results. The PIPT with the raw rice extract gave a positive immediate response at a concentration of 1/10 w/v. Spirometry revealed a decrease

of 36.9% for forced vital capacity (FVC) and of 25.6% for forced expiratory volume (FEV_1). No late reactions were observed. Serum-specific IgE antibodies were positive against rice (8.37 kU/l), oat (2.09 kU/l), and corn (10.4 kU/l) (Pharmacia Diagnostics, Uppsala, Sweden). The antigenic profile of the extracts revealed 22 bands in the raw rice extract, six bands in the fumes and no bands in the boiled extract. Several bands were recognised by the patient's IgE in the raw rice extract and only a 33 kDa allergen in the extract of concentrated fumes.

We present a case of suspected IgE mediated hypersensitivity caused by the inhalation of vapours released during the boiling process of rice. *In vivo* and *in vitro* studies confirmed the presence of at least one allergen in the vapours. The 33 kDa allergen, designated as Glb33 by Usui et al. (5), has been described as a glyoxalase I activity protein and seems to be an important allergen in boiling rice vapours. The results of this study could be of help when evaluating occupational settings, such as kitchens, or food allergic patients who experience symptoms when exposed to fumes of boiling rice, or other foods.

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Food allergy to moulds: two cases observed after dry fermented sausage ingestion

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Key words: dry sausage; food allergy; labial challenge; mould allergy; *Penicillium nalgiovense*.

Food allergy to moulds is rare. However hypersensitivity due to dry sausage (DS) mould in workers who brush off the excess, is a well-recognized occupational disease. Two cases of mould allergy after ingestion of DS are reported.

Dry fermented sausages are coated with various *Penicillium* strains. Two cases of recurrent angioedema (AO) after dry sausage (DS) ingestion are reported. Skin prick tests (SPT) with *Penicillium* and DS skin and labial challenge with DS skin were positive in both patients.

Case 1. A 5-year-old boy referred three episodes of labial angioedema (AO). One episode occurred 15 months after eating two slices of DS. The other episodes occurred after eating camembert cheese. The child presented with perennial rhinitis. The indoor study revealed dampness and especially mould stains on a wall, behind a desk where he sat for many hours playing video games. Air fungal contamination near this desk reached 433, 550 and 811 CFU/m^3, respectively, for *Aspergillus*, *Penicillium* and *Cladosporium* sp. In other rooms, mean values were 20 and 60 CFU/m^3, respectively, for *Penicillium* and *Cladosporium* sp. Skin prick tests (SPT) revealed sensitization to grass pollens, *Alternaria* (2 mm), *Penicillium* (1.5 mm) and *Ulocladium* (2.5 mm) (codeine 3 mm). SPT to foods including pork were negative and positive to DS stuffing (2 mm) and DS skin (4.5 mm). IgEs (CAP System RAST; Pharmacia, Uppsala, Sweden) to *Alternaria alternata* were slightly positive 0.63 kIU/l. Labial challenge with DSS resulted after 15 months in labial urticaria, palpebral AO, conjunctivitis and rhinorrhea (1). Culture of the DSS showed *Penicillium nalgiovense* and some strains of *P. chrysogenum* and *Aspergillus ochraceus*.

Case 2. A 13-year-old girl with allergic rhinitis from May to July, referred two episodes of AO and urticaria occurring a few minutes after eating a slice of DS. She reported pruritus after having eaten camembert cheese. The indoor study revealed 10 plants, a cat and no visible mould traces in the dwelling. SPT are positive to grass and birch pollens (6 and 3 mm), *Ulocladium* (2.5 mm), *Alternaria* (1 mm) and *Penicillium* (1 mm) (codeine: 1.5 mm). IDR to moulds at 1/1000 (mass/volume) were positive for *Penicillium* and *Alternaria* (9 mm). SPT with DS stuffing and DSS were, respectively, 1 and 3.5 mm. SPT to foods, including pork, were negative, except for peanut (4 mm). However, specific IgE to peanut and oral challenge (cumulated dose: 7 g) were negative. IgE to *Penicillium notatum* was 0.69 kIU/l. The patient basophil activation was measured by CD63 expression: after incubation with a 1% *Penicillium* mix (*P. digitum*, *expansum* and *notatum*), the flow cytometry showed 33% CD63+ basophils (14% CD63+ basophils in a positive control allergic to *Penicillium*). Labial challenge with DSS resulted in urticaria and lip AO. Culture of the DSS showed *P. nalgiovense* and some strains of *P. chrysogenum* and *Wallemia* sp.

Food allergy to moulds occurs not only after accidental food poisoning (2) but also after ingestion of traditional meals. DS are coated with various *Penicillium* strains enhancing the flavour. *Penicillium camembertii* (3) and *P. nalgiovense* induce asthma and hypersensitivity pneumonitis among sausage-makers. Other agents, such as mites, have also been incriminated (4).

Rare cases of mould allergy after DS ingestion have been reported including exercise-induced anaphylaxis (5).

Contact urticaria from handling salami and a singular inhalation challenge of DS (6) were described too.

We report two further cases: the first one might document sensitization to moulds, an indoor air biocontaminant, causing both rhinitis and food allergy after ingestion of fungal species cross-reacting with those found in the dwelling.

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Hidden shellfish allergen in a fish cake

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Key words: allergen matrix; fish; hidden food allergens; Norwegian National Register for Severe Food Allergy Reactions; shellfish.

Hidden allergens in processed foods represent a health risk (1). About 2–3% of all adults and 6–8% of children are affected. About five times as many have experienced allergic symptoms after food intake at least once (2). In a case from the Norwegian National Register for Severe Food Allergy Reactions (MAR), a patient experienced an anaphylactic incident after having eaten a particular brand of fish cake. According to the ingredients list, it contained only fish (20% catfish), milk and vegetable proteins, components which had been inoffensive in the patient's medical history.

Severe allergic reaction to hidden shellfish protein in a fish cake.

The patient's serum was tested against 12 allergens with the UniCAP® System (Pharmacia Diagnostics, Uppsala, Sweden), and on a matrix of 150 allergens, developed for the detailed specification of immunoglobulins (IgEs). All signals higher than twice the variance were evaluated, employing an empirical threshold value (0.05). Serum from a patient with a known shellfish allergy and pooled serum from healthy volunteers were used as controls. The fish cake sample, protein extracts from several fishes and shellfishes, and purified cod parvalbumin and shrimp tropomyosin were analysed by dot and Western blots, using the sera.

With UniCAP®, the patient had specific IgE class 2 (0.7– < 3.5 kUA/l) reaction against four allergens not related to this case. On the allergen matrix, the serum reacted against lobster (0.39) and not against fish proteins, but weakly against cod (0.07). The positive control serum elicited signals to shrimp (5.24), lobster (9.66), crab (2.89), crawfish (10.42) and squid (0.346). The negative control reacted weakly to some fishes but not to shellfishes. On Western blots, the patient's serum reacted against shrimp (36 kDa, 20 kDa), lobster (37 kDa, 20 kDa), tropomyosin (36 kDa) and cod (45 kDa), but not against catfish, salmon and parvalbumin. A protein of a molecular weight (35 kDa) similar to the major shellfish allergen tropomyosin was recognized in the fish cake extract, confirmed by the positive control serum and not detected by the negative control.

Food allergy is one major form of adverse reaction to foods (3), and about 200 ingredients are confirmed as causative agents. Alert systems (4) and correct food labelling are therefore actual issues with the Food Authorities. In this case, elevated anti-lobster IgE and low anti-cod IgE were found by our sensitive allergen test matrix, whereas they were below the quantification limit for UniCAP® (< 0.35 kUA/l). The results of the blot experiments can be explained by cross reactions between similar epitopes in the Crustacea tropomyosins (5), a pan-allergen group which causes 80% of all shellfish incidents. The identified 45 kDa cod protein hints at a monospecific cod allergy (6). Our study encouraged the manufacturer of the fish cake to intensify the washing between different product batches, as the hidden allergen could be tracked down to cross-contamination by a shellfish pastry produced on the same manufacturing line.

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Anaphylactic reaction to 'Tudela' lettuce hearts

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Key words: *Artemisia vulgaris*; epitope; *Platanus acerifolia*; poli-sensitization; 'Tudela' lettuce hearts.

We describe an uncommon case of a 42-year-old female who presented a widespread erythema with pruritus after ingesting 'Tudela' lettuce hearts (*Lactuca sativa* var.) with tomato and onion. She experienced an anaphylactic shock episode a few days later after eating the lettuce hearts alone dressed with olive oil.

A case of anaphylaxis to lettuce heart and cross-reactivity to *P. acerifolia* and *A. vulgaris*.

The patient suffered from seasonal rhinitis which coincided with the pollination of *Platanus acerifolia*. Prick tests were positive to 'Tudela' lettuce heart, lettuce, endive, pollen from *P. acerifolia* and *Artemisia vulgaris*, and negative to leek, potato, carrot and latex (extracts prepared by DIATER Lab., Madrid, Spain). The patient tolerated well-fried potatoes, raw and cooked carrots and boiled leeks. Tests from 10 healthy controls were negative to the same extracts.

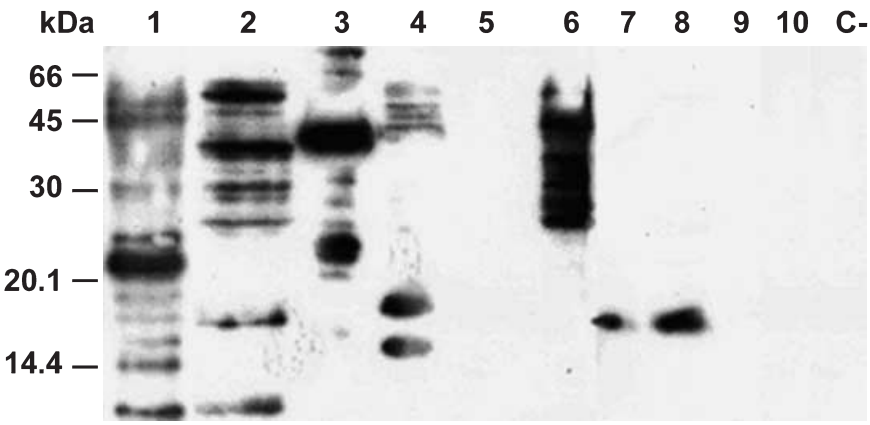

Figure 1. SDS PAGE IgE immunoblot. (1) Baby lettuce. (2) *A. porrum*. (3) *S. tuberosum*. (4) *P. acerifolia*. (5) *C. scolymus*. (6) *D. sativus*. (7) *A. vulgaris*. (8) *H. annus*. (9) *T. officinale*. (10) *H. brasiliensis*. (C-) negative control. The molecular weight (kDa) of markers run in parallel are indicated.

Protein extracts of *L. sativa* var. ('Tudela' lettuce heart), *A. porrum* (leek), *Solanum tuberosum* (potato), *P. acerifolia* (plane tree), *Cynara scolymus* (artichoke), *Daucus sativus* (carrot), *Artemisia vulgaris* (mugwort), *Helianthus annus* (sunflower), *Taraxacum officinale* (dandelion) and *Hevea brasiliensis* (latex) were separated by sodium dodecyl suphate-polyacrylamide gel electrophoresis (SDS–PAGE). The binding of IgE antibody to allergens was analyzed by Western blot using serum from the allergic patient and anti-human IgE peroxidase conjugate (Dako, Carpinteria, CA) (Fig. 1).

Contact dermatitis with lettuce is somewhat frequent in workers who handle these vegetables, but can also be found in people sensitized to various pollens (1). Helbling et al. (2) described two cases of sensitization to lettuce with positive radioallergosorbent test (RAST) and prick tests to carrot. A case of an allergic reaction to lettuce intake has been described depicting the absence of cross-reaction with *A. vulgaris* (3). Nevertheless, Vila et al. (4) presented another case of a mucous–cutaneous response to lettuce ingestion, demonstrating some antigenic commonality with *A. vulgaris*. In a recent study, Enrique et al. (5) have shown that 52.45% of patients sensitized to *P. acerifolia* present allergy to food, including lettuce.

Western blot experiments with serum from this patient revealed several bands predominantly in the range of 15–65 kDa. In our study, we found IgE antibody binding to a mugwort allergen (approximately 18 kDa), the same molecular weight as the one found in sunflower extracts, and several proteins of *P. acerifolia*. Moreover, this patient, in spite of tolerating the ingestion of leeks, potatoes and carrots, presented IgE recognition of proteins from these foods.

In conclusion, this patient has revealed an infrequent case of anaphylaxis to 'Tudela' lettuce hearts (*L. sativa* var.), skin reactivity to plane tree (*P. acerifolia*) and mugwort (*A. vulgaris*), and IgE recognition by Western blot to these and also some vegetable extracts (potato, carrot, and leek). These results may be indicative of a case of poly-sensitization, the expression of general epitopes in different proteins or most likely both.

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Peanut and tree nut allergy in children: role of peanut snacks in Israel?

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Key words: anaphylaxis; food allergy; peanuts; tree nuts.

Prevalence rates of peanut and tree nut allergy in Israel are 0.04 and 0.02%, respectively (1). Children are often exposed to peanuts very early owing to the popularity of locally produced peanut snacks, which have a spongy texture and melt on contact with saliva, making them safe for consumption even before 6 months of age. The aim of this study was to determine the age of first allergic reaction to peanuts and tree nuts in Israel and to outline the clinical features of these allergies.

Early exposure to peanut snacks may lead to an early age of first allergic reaction.

File review of all 992 infants and children evaluated for food allergy between January 1999 and July 2002 yielded 21 with peanut allergy (including three also with tree nut allergy) and eight with tree nut allergy. Diagnosis was based on an unequivocal history of immediate reaction to peanuts or tree nuts involving one or more organ systems (skin, gastrointestinal, respiratory) and a positive skin prick test (ALK Abello, Port Washington, NY) or blood test for specific IgE (>0.35 IU/ml) (AlaSTAT, DPC, Los Angeles, CA). Sixteen patients had atopic dermatitis and 18 (15 with peanut allergy) had additional food allergies (13 to eggs, four to sesame, seven to milk, one to apples). The characteristics of the first allergic reaction to peanuts or tree nuts are shown in Table 1. In 18 patients with peanut allergy (86%), the first allergic reaction occurred to peanut snacks.

Table 1. Characteristics of the first allergic reaction to peanuts or tree nuts

	Peanuts ($n = 21$)	Tree nuts ($n = 11$)
Age (months)		
Range	3–108	36–144
Median	8.25	50
Foods causing reactions	18: peanut snacks 3: peanuts	6: cashew/pistachio 1: pistachio ice cream 1: pecan 1: walnut 1: mixed nuts (granola) 1: nut spread
Symptoms and signs (one or more)		
Skin	21 (100%)	11 (100%)
Gastrointestinal	5 (23.8%)	5 (45.5%)
Respiratory	6 (28.5%)	5 (45.5%)
Cardiovascular	0	1 (9%)

Skin: urticaria, angioedema, rash, exacerbation of atopic dermatitis.
Gastrointestinal: vomiting, abdominal pain, diarrhea.
Respiratory: rhinorrhea, cough, hoarseness, shortness of breath, wheezing.
Cardiovascular: hypotension.

The prevalence of atopic dermatitis and other food allergies and the clinical presentation were similar to findings in the literature (2). Of interest is the low prevalence of peanut/tree nut allergy, with our 29 patients accounting for 2.9% of patients evaluated for food allergy, compared with 28 and 50% reported in French studies (3, 4). At the same time, the median age of the first allergic reaction to peanuts of 8.3 months in our patients was considerably lower than in series from the USA and Europe (14 months to 4.4 years) (2–6). The lower prevalence of peanut allergy can be explained by the lower average consumption of peanut products in Israel (1.4 kg per person per year) (7) compared with the USA (2.7 kg) (8) and the different methods of production. The peanuts in most of the locally produced peanut snacks in Israel are boiled in water for 30 min at 80°C (Local factories, personal communication), whereas most peanuts in the USA are dry-roasted at a much higher temperature of 170°C, which increases the allergenicity of the three major peanut proteins (8).

Early exposure to peanut snacks may lead to an early age of first allergic reaction. Clinicians need to educate parents to refrain from offering peanut snacks to children younger than 2 years.

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Maculopapular rash induced by diltiazem: allergological investigations in four patients and cross reactions between calcium channel blockers

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Key words: calcium channel blockers; cross-reaction; drug intradermal test; drug patch test; drug prick test; drug skin testing; lymphocyte activation test.

Drug skin tests were performed in four patients who have developed a maculopapular rash (MPR) 8–12 days after the beginning of a treatment with diltiazem, in order to determine the value of patch tests (PT) and cross reactions among calcium channel blockers (CCB). Six weeks after the MPR, drug PT were performed with the commercialized forms of diltiazem following the guidelines of the European Society of Contact Dermatitis (ESCD). The PT were also done with the commercialized forms of other CCB. When PT were negative, prick tests (prick T) were performed in two cases and one intradermal test (IDT) with nimodipine in one case. Lymphocyte activation tests (LAT) were performed in three cases. The PT were positive in all cases without any cross reactions with other CCB, except in one patient who had positive PT with verapamil. Prick T in two of two cases and IDT with nimodipine in one of one case remained negative. The LAT were positive in three of four cases. This study emphasizes the value of PT with diltiazem in cutaneous adverse drug reactions (CADR) because of this CCB, but PT could have a lesser value with other CCB. Cross reactions on PT seem to be rare. More, although CCB are usually divided in three classes, we suggest to divide them into dihydropyridines and 'nondihydropyridines'.

Suggested guidelines following the division of CCB into dihydropyridines and 'nondihydropyridines'.

Maculopapular exanthema is the most common cutaneous CADR and can be induced by almost all drugs. In literature, many cases have been reported on CADR induced by CCB, more often with diltiazem which has been associated with a variety of cutaneous reactions from exanthema to severe cutaneous reactions such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). We report on four patients who had developed MPR because of diltiazem with a likely imputability, confirmed in all cases by positive PT and also the study about cross reactions between CCB as cross reactions between CCB have not so much been studied.

Four patients (one man and three women; mean age 60 years) developed a MPR, 8–12 days after the beginning of a treatment by diltiazem. All routine laboratory investigations were normal except the sedimentation rate (mean SR 26.3 mm). Six weeks after the CADR, drug PT were performed with the commercialized form of diltiazem, following the guidelines of the ESCD (1). Drug PT with the commercialized forms of diltiazem were performed with pills crushed, reduced in powder then diluted at 30% in water, petrolatum (pet.) and alcohol in three of four cases; pur, diluted at 30% in water and pet. in one of four cases. In all cases, PT were also performed with the commercialized forms of other CCB diluted at 30% in pet.: verapamil, nicardipine, nifedipine, nitrendipine, nimodipine, in order to study cross-reactivity between CCB. Skin tests were read at 20 min, day 2, and day 4. When PT were negative, prick T with these drugs were performed in two of four cases and in one case an IDT with injectable nimodipine was performed. In three of four cases, LAT were performed, according to the method described by Kohler et al. (2). All the patients had a very likely intrinsic imputability according to criteria proposed by Moore et al. (3).

Drug skin test and in vitro test are shown in Table 1.

In all cases, PT were positive with diltiazem diluted at 30% whatever the vehicle used. There were no cross reactions on PT with nimodipine and nifedipine. The three patients tested with nicardipine and nitrendipine had negative PT. There were cross reactions on PT between diltiazem and verapamil diluted at 30% in pet. in only one of four patients. The prick T were negative with nifedipine (one of one case tested), verapamil (one of one case tested), nicardipine (one of one case tested), nimodipine (two of two cases tested) and diltiazem (two of two cases tested). The IDT with nimodipine was negative in one of one case tested. The LAT with diltiazem were positive in three of four cases tested.

Maculopapular rash is a frequent CADR reported with many drugs, including antibiotics, antineoplastic drugs, antiepileptics which occured usually 24 h to 10 days after the beginning of the treatment. Among CCB, diltiazem has been considered as a causative factor of a wide spectrum of cutaneous adverse

Table 1. Results of drug patch testing

	Patient no. 1	Patient no. 2	Patient no. 3	Patient no. 4
Patch-tests				
Monotildiem® et Tildiem® cp (diltiazem)				
Pure	np	np	np	+
30% water	+	+	+	+
30% vaseline	+	+	+	+
30% alcohol	+	+	+	np
Isoptine® (verapamil)	+	–	–	–
Loxen® (nicardipine)	–	–	–	np
Nidrel® (nitrendipine)	–	–	–	np
Nimotop® (nimodipine)	–	–	–	–
Adalate® (nifedipine)	–	–	–	–
30% vaseline				
Prick-tests				
Adalate® (nifedipine)	–	np	np	np
Isoptine® (verapamil)	–	np	np	np
Loxen® (nicardipine)	–	np	np	np
Nimotop® (nimodipine)	–	np	–	np
Tildiem® (diltiazem)	–	np	–	np
IDR with Nimotop® (nimodipine)	–	np	np	np
LAT with diltiazem	+	+	np	+

np, not performed; LAT, lymphocyte activation test.

reactions such as MPR (4–10), psoriasiform eruption (9), exfoliative dermatitis (5, 11), acute generalized exanthematous pustulosis (12–15), hypersensitivity syndrome (16, 17), severe erythema multiforme, SJS and TEN (4). Other CCB, such as nifedipine or verapamil have also been associated with MPR (7). Skin tests have been reported to be helpful in determining the cause of CADR, their results depend on the drug tested but also on the clinical features of the CADR. In a prospective study involving 72 patients who had developed CADR, 43% had pertinent positive PT (18). Among these 72 patients, one of them had developed MPR after have taken diltiazem with positive PT at 4 days. The results obtained in the herein reported study including four patients, emphasizes the value of PT with diliazem with positivity of all PT with diltiazem (four of four cases) in investigations CADR because of this drug. In literature, skin testing with diltiazem have already been reported to be useful to diagnose eruptions caused by this drug (5, 6, 8–10, 13–15), on contrary, PT with other CCB, such as verapamil, nifedipine, nisoldipine or nicardipine does not seem to be useful because of their low reported positivity (9). This is due either because CADR with diltiazem have been reported in literature more often than other CCB or because diltiazem widely prescribed induces a higher number of CADR.

Skin tests with diltiazem performed following the guidelines of the ESCD (1), seem sensitive (four of four patients had positive PT). These tests have also a good specificity, as on 11 negative control subjects, selected following methods previously published (18), PT with diltiazem diluted at 30% in water and pet. were negative. Positivity of these tests and LAT (three of four positive) is in favor of a mechanism of delayed cellular hypersensitivity.

The CCB are frequently used in cardiology to manage ischemic heart disease or high blood pressure. They belong to a heterogeneous chemical group and the CCB function is not limited to a particular chemical structure. Therefore, bufl-omedil, perhexilline, bepridil, flunarizine and cinnarizine are all CCB. The CCB are usually divided in three classes: dihydropyridines (amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nitrendipine and nisoldipine), phenylalkylamines with verapamil and benzothiazepines with diltiazem. Dihydropyridines molecules have a common membrane receptor that binds tritiated nitrendipine or nimodipine (19). Verapamil and diltiazem have a strereospecific receptor that binds tritiated cinnarizine (19). Thus, we propose to divide CCB into dihydropyridines and 'nondihydropyridines'.

In literature, there are some discrepancies concerning cross reactions between CCB. For example, Kuo et al. (20), reported on the case of a woman who experienced nonthrombocytopenic purpura with nifedipine with a similar eruption 48 h after a new treatment by diltiazem. Baker and Cacchione (21), reported the case of a 52-year-old man who developed a MPR approximately 24–36 h after starting diltiazem therapy. Three days after diltiazem was discontinued, the patient received amlodipine with the same cutaneous reaction within 1–2 h after amlodipine administration. These two cases lead to think that there is a cross-reaction between dihydropyridines and 'nondihydropyridines'. However, we can observe that in the case reported by Kuo et al. (20), a skin biopsy sample taken from a lesion displayed a leucocytoclastic vasculitis which has often a chronic evolution, with sometimes recurrences, perhaps ruling out the responsability of diltiazem in relapse of the purpuric lesions. Concerning the patient presented by Baker and Cacchione (21), the second CCB (amlodipine) was readministered only 3 days after diltiazem was discontinued, which appears to be a very short delay, making difficult to specify if it is a second CADR to amlodipine, with a cross reaction between diltiazem and amlodipine, or if it is the manifestation of a long lasting CADR because of diltiazem. In the case described by Hammentgen et al. (10), a 60-year-old man had a MPR because of diltiazem without any cutaneous reactions after having been rechallenged with nifedipine. In our study, one patient who had a MPR because of diltiazem had a fortuitous well-tolerated challenge with lacidipine, belonging to the dihydropyridines. Concerning cross reactions between the dihydropyridines, Bewley et al. (22), have reported on the case of a

62-year-old patient, with a history of high blood pressure treated by amlodipine for 2 years without any cutaneous eruption. This patient was admitted in hospital to treat a chronic plaque psoriasis and during admission, antihypertensive medication was changed to amlodipine. Three days after this change, he developed an erythema multiforme, after which the amlodipine was stopped and nifedipine readministered without no further complications. Kitamura et al. (9), described a 56-year-old patient who experienced a psoriasiform eruption because of nifedipine, with the same eruption after having taken nisoldipine.

In literature, diltiazem is the CCB the most frequently reported as responsible in inducing CADR. In most of the cases, CADR are MPR which occured usually 10 days after the beginning of the CCB. According to previous reports and these results, PT seem to be useful in diagnosing CADR due to diltiazem, but PT could have a lesser value with other CCB.

Finally, although CCB are divided into three classes, we suggest, from our results, those previously published and the chemical analysis of the chemical structures of CCB to divide them into two chemical classes: dihydropyridines and 'nondihydropyridines'. According to this classification, it could be possible, in case of CADR to CCB, to follow these guidelines:

1. Skin tests should be performed, 6 weeks to 6 months after the CADR, with commercialized forms diluted at 30% in pet. and/or with the pure drug diluted at 10% in pet. and water. In case of severe cutaneous reactions such as SJS, Lyell's syndrome or hypersensitivity syndrome, these tests could also be performed but with caution and in beginning with very low concentrations of the drugs i.e. 0.1% in petrolatum then if negative with progressively enhanced concentrations. We have no experience concerning patch testing in severe CADR because of CCB.
2. In cases of CADR with CCB belonging to the dihydropirydines, it could be possible, to readminister, under hospital surveillance, if PT with these CCB are negative, a 'nondihydropyridine'.

Further larger studies are necessary to validate these guidelines.

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Drug allergy in university students from Porto, Portugal

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Key words: antibiotics; anti-inflammatory agents; aspirin; drug hypersensitivity; lactam; nonsteroidal; penicillins.

Drug allergy is considered responsible for substantial morbidity and mortality, and increased health costs. However, its true frequency is not known because of scanty epidemiological data, and available information requires a cautious interpretation (1).

Drug allergy was recalled by 7.7% of university students in Portugal.

Aiming to quantify the prevalence of self-reported drug allergy, we performed a cross-sectional survey of 2150 Portuguese university students (67.6% females) during 2001. Participants were approached in the classroom, at different days and times, resulting in the study of 37% of all registered students.

The lifetime occurrence of drug allergy, the drugs that are involved and the characteristics of the most serious episode were assessed using a self-administered questionnaire. Symptoms were classified as dermatological (pruritus, erythematous wheals and oedema), ocular and respiratory (redness or eye itching, tears, nose itching or discharge, blocked nose or sneezing, dyspnoea, wheezing or cough), gastrointestinal (vomiting, nausea, diarrhoea and abdominal pain) or systemic (sweating or perspiration, fainting and tachycardia).

The life prevalence of one or more drug allergy episodes was 7.7%, with 3.1% allergic to β-lactams, 2.1% to nonsteroidal anti-inflammatory drugs (NSAIDs) and 3.0% to other drugs. Three participants (0.1%) declared allergy to β-lactams and NSAIDs, three (0.1%) to β-lactam antibiotics and other drugs, four (0.2%) to NSAIDs and other drugs, and two (0.1%) reported allergy to β-lactams, NSAIDs and other drugs. No significant differences were observed according to sex.

When a drug was specifically recalled (44% of participants), penicillin (57.1%), amoxicillin (19.1%) and amoxicillin associated with clavulanic acid (23.8%) were the more frequently incriminated β-lactams, and aspirin (41.4%), lysine acetylsalicylate (27.6%) and nimesulide (20.7%) were the more often reported NSAIDs. Regarding other types of drugs, non-β lactam anti-infectious drugs were the most commonly reported.

Dermatological manifestations were the most frequently described, both in cases of allergy to β-lactams (79.7%) and NSAIDs (58.4%), followed by gastrointestinal (22.0 and 33.4%, respectively), systemic (28.8 and 22.2%, respectively), and ocular and respiratory (17.0 and 27.8%, respectively).

In our survey, the prevalence of drug allergy was lower than previously reported (2, 3). Possible explanations are the young age of our participants, with lower drug consumption, and the fact that older adults evaluated in other surveys may have been exposed to penicillin and ampicillin preparations used before the 1970s, often contaminated with trace quantities of macromolecules or drug polymers, more allergenic than those available nowadays (4).

Highly educated individuals may improve the quality and accuracy of self-reported information, and the recall of a drug allergy is expected to be more accurate in young individuals as less time elapsed since an allergic reaction, increasing the internal validity of our investigation. This is an advantage of our study, but recall bias remains, as perceived by the amount of missing information concerning the characteristics of allergy episodes or brand names of the drugs involved, probably reflecting that many reactions occurred at young ages.

Drug allergy was recalled by 7.7% of university students in Portugal. Although many of these recalls might not reflect true allergy, these individuals will probably be given second-line treatments, usually more expensive and less effective.

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Anaphylactic reactions to formaldehyde in root canal sealant after endodontic treatment: four cases of anaphylactic shock and three of generalized urticaria

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Key words: allergy to formaldehyde; anaphylactic shock; angioedema; anti-formaldehyde IgE; endodontic treatment; formaldehyde; root canal sealant; urticaria.

The authors report seven cases of allergic reactions, four cases of anaphylactic shock and three of generalized urticaria, to formaldehyde contained in root canal sealant after endodontic treatment.

The clinical presentation, skin tests, high levels of anti-formaldehyde immunoglobulin E (IgE), as well as the study of the previous cases reported in the literature, suggest allergic IgE mediated mechanisms. These very infrequent but potentially severe reactions in endodontic therapy focus attention on the different manifestations related to formaldehyde,

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the involved mechanisms, the diagnostic procedure and the prevention possibilities in dentistry.

Formaldehyde (formalin, paraformaldehyde, trioxymethylene) is widely used in industry, cosmetics, disinfectants, medications and root canal sealants (1, 2).

The pathological reactions related to formaldehyde such as nasal, laryngeal and bronchopulmonary lesions appearing upon inhalation, gastrointestinal lesions appearing upon ingestion, and cutaneous necrosis or contact dermatitis, may be caused by simple irritant mechanisms (1–3). In addition, hypersensitivity or allergic reactions such as rhinitis, asthma, generalized urticaria, angioedema and anaphylactic shock, have been described (4–27).

Despite the high frequency of root canal treatments with sealant containing formaldehyde, very few cases of well documented allergy to root canal sealant have been reported in the literature. These sealants are a complex mixture of potentially irritating and/or sensitizing substances, such as metals, eugenol, formaldehyde, menthol, phenol, etc (5, 6).

Formaldehyde release from root canal sealant has been demonstrated *in vitro* and *in vivo*, and as a hapten may induce anaphylactic reactions after reacting with other proteins to become a complete allergen. (12, 18, 28–32).

The authors report seven cases of allergic reactions, four cases of anaphylactic shock and three of generalized urticaria, to formaldehyde contained in root canal sealant after endodontic treatment.

The clinical presentation, skin tests, high levels of anti-formaldehyde immunoglobulin E (IgE), as well as the study of the previous cases reported in the literature, suggest allergic IgE mediated mechanisms. These very infrequent but potentially severe reactions in endodontic therapy focus attention on the different manifestations related to formaldehyde, the involved mechanisms, the diagnostic procedure and the prevention possibilities in dentistry.

Case 1: A 41-year-old nonatopic man presented with a periapical granuloma of tooth 24 requiring endodontic treatment. Several minutes after complete dental treatment the patient complained of a sensation of warmth, generalized pruritus and respiratory difficulty. Thirty minutes later he developed anaphylactic shock with a drop in systolic blood pressure to 50 mmHg and lost consciousness. The outcome was favorable with an emergency resuscitation.

The root canal sealant used was Spad® (Quetigny, France), a mixture of powder and liquids with the following composition: phenylmercury borate, calcium hydroxide, hydrocortisone acetate, trioxymethylene, titanium oxide, barium sulfate, zinc oxide (powder), glycerin, resorcinol, hydrochloric acid (liquid 1) and glycerin and formaldehyde 87% (liquid 2).

Skin prick tests to common aeroallergens and latex performed after the accident were negative. The skin prick test to liquid 1 was negative and to liquid 2 was mildly positive, with a 3 mm diameter wheal *vs* 4 mm to codeine as a positive control. The same tests were negative in five control subjects. Patch tests, performed using finn chambers, to the standard battery of International Contact Dermatitis Research Group (ICDRG) allergens containing formaldehyde and to resorcinol (Trolab Allergenes, Reinbeck, Germany) were negative. Patch tests to the powder and two liquids (1% solution in Vaseline) induced a strongly positive delayed reaction with a confluent eczema beyond the test area. Anti-formaldehyde IgE were class 4 (25 kU/l: RAST CAP RIA, Pharmacia, Uppsala, Sweden).

Case 2: A 45-year-old woman underwent several root canal treatments with Spad® between 1987 and 1997 without any complications (tooth 16, 17 and 26). In 1997, a second endodontic treatment of tooth 26 with Spad® was followed by discomfort, anxiety, pruritus of the hands and pallor, which regressed after antihistamine treatment. The patient underwent treatment of tooth 16 for the second time in 1998 with Method Z® (Zizine France). Fifteen minutes later, she experienced tachycardia with extreme apprehension, pruritus and erythema of the hands and was unresponsive to antihistamines. This was followed by angioedema, dyspnoea and severe systolic hypotension (60 mmHg). The outcome was favorable with administration of adrenaline and systemic steroids.

The root canal sealant Method Z® contains: enoxolone, barium sulfate, excipient (powder), resorcinol, hydrochloric acid, excipient (liquid 1), and formaldehyde 35% and excipient (liquid 2).

Skin prick tests to common aeroallergens, latex and to liquid 1 and 2 at the concentration of 1% were negative. Patch tests with liquid 2 (1% solution) induced a local eczema after 48 h. RAST to formaldehyde was class 1 (0.41 KU/l; AlaSTAT DPC).

Case 3: A 43-year-old woman underwent an endodontic treatment of tooth 42 with Zial Z® (Zizine, France). Several similar procedures had been performed in the past. She experienced thoracic oppression and erythema developing within 24 h on two occasions. Two hours after the last treatment the patient developed generalized erythema, angioedema, vomiting, diarrhea, and hypotension and lost consciousness twice. After the first emergency resuscitation with adrenaline, she developed cardiac arrest whilst in hospital. The final outcome was favorable.

The root canal sealant Zial® contains: hydrocortisone, trioxymethylene, diiodothynol, E110, barium sulfate, zinc oxide, magnesium stearate (powder) and eugenol (liquid).

Skin prick tests and patch tests to liquid and powder at different concentrations were negative. Anti-formaldehyde IgE were class 3 (5.09 KU/l RAST CAP RIA Pharmacia Sweden).

Case 4: A 50-year-old man underwent several root canal treatments with Spad®. The treatment of tooth 45 in July 1996 was followed 2 h later by urticaria of the head and facial edema. In December 1996, 30 min after treatment of tooth 5, the patient developed pruritus, generalized urticaria, abdominal pain and discomfort. An allergy to the local anesthetic agent (lidocaine) was suspected but the skin tests and the challenge test were negative. In September 2002 the patient needed extraction of tooth 45 and endodontic treatment of tooth 44. This procedure was hemorrhagic and tooth 45 treated in 1996 was broken during the extraction. Fifteen minutes later, the patient presented with facial erythema, pruritus, generalized urticaria, abdominal pain, dyspnoea, discomfort with tachycardia and severe hypotension. The

outcome was favorable with administration of adrenaline and steroids given several times in the emergency hospital. One month later, obturation of the pulp chamber of tooth 38 without apical treatment (pulpotomy) was well tolerated.

Skin prick tests to the powder and liquids of Spad® performed with 1% dilution and pure form as used in dentistry were negative. Anti-formaldehyde IgE were class 6 (> 100 KU/l; Unicap Pharmacia Sweden).

Case 5: A 40-year-old woman, with a history of allergy to grass pollen and house dust mite, was treated for the second time for a granuloma of tooth 21 with Resoplast® (Pierre Roland, France) and Temp Bond®. Three hours after dental treatment the patient developed abdominal pain and pruritus of the scalp followed by urticaria of the face, neck, upper extremity and chest without hypotension. Outcome was favorable with symptomatic treatment in the emergency hospital.

Resoplast® has the following composition: deltahydrocortisone, bismuth nitrate (powder); benzalkonium chloride and formaldehyde (liquid 1) and sulfosalicylic acid and resorcinol (liquid 2). Temp Bond® (Kerr, Romulus, MI) contains zinc oxide and eugenol.

Skin prick tests to undiluted liquid 1 were positive giving a 7 mm diameter wheal and edema of the forearm. They were negative in four control subjects. Similar tests with liquid 2 and eugenol were negative. Anti-formaldehyde IgE were class 5 (98.5 KU/l; RAST AlaSTAT DPC).

Case 6: A 64-year-old woman who underwent endodontic treatment with Spad® on two previous occasions, had experienced moderate to severe local edema. On the third occasion, 4 h after the procedure, in addition to local edema, she developed nausea, vertigo and generalized urticaria, which persisted for 3 days despite antihistamine treatment.

Skin tests were not performed. Anti-formaldehyde IgE were class 5 (65 KU/l; RAST Alastat DPC).

Case 7: A 56-year-old man underwent root canal treatment of tooth 28 with Spad® in February 2000 after several previous uncomplicated endodontic procedures. Thirty minutes later he developed first a significant localized edema and than an edema of the whole face. Several hours later he presented with generalized urticaria that lasted 3 days.

Prick skin tests were weakly positive to formaldehyde. Anti-formaldehyde IgE were class 6 (> 100 KU/l Unicap Pharmacia Sweden).

The adverse reactions to formaldehyde, such as respiratory (asthma and rhinitis) and cutaneous (contact dermatitis) reactions and anaphylactic shock in hemodialysis, are well documented. However, despite its widespread use, IgE dependant allergic reactions are rarely described (1–3, 14, 18, 27, 33, 34).

In odonto-stomatology the root canal sealants containing formaldehyde are still widely used. Different side effects related to endodontic treatment have been reported, such as infection, inflammation, necrosis, arthritis, paresthesia of the dental branch of the mandibular nerve, fungal caseous sinusitis etc. (5, 35–44). In dentistry, formaldehyde is used for its antibacterial activity, for devitalization of the tooth pulp and for its role in polycondensation of resorcine. (5, 11–14, 18). Release of formaldehyde from endodontic material has been known for a long time. Different *in vitro* and *in vivo* studies have shown a systemic diffusion of C_{14} labeled formaldehyde from endodontic material. The formaldehyde release may be enhanced by repetitive endodontic treatments, apicetomies, extraction of the treated tooth and dental overfilling with extrusion of sealant in the periapex or in the apical granuloma (5, 28–32, 35). Compared with the pulp chamber, which is relatively inert from an immunological point of view, the periapex constitute a network of vascular and nervous systems joining the tooth to the rest of the immune system (5, 6, 36, 38, 40, 43, 44).

Formaldehyde is a low molecular weight chemical which, acting as a hapten, may react with other molecules such as cutaneous proteins, serum proteins, proteins of the pulp chamber or of the periapex, or even with another component of the root canal sealant to become a complete allergen (3, 5, 12, 14, 15, 17, 18).

Despite the frequency of formaldehyde use and the number of endodontic treatments (453 000 in 1990 in Denmark for 5 million inhabitants) the allergic reactions to it in dentistry remain infrequent (5, 6, 18). They are probably underestimated in endodontic practice. Thirty-five cases of allergic reactions to formaldehyde (7–27) including seven personal observations have been described (Table 1). These allergic reactions can be of different severity ranging from local or focal reactions to life-threatening anaphylactic reactions: 15 cases of anaphylactic shock, 18 cases with urticaria and/or angioedema, nausea, dyspnoea, exanthema, pruritus and two cases with non-clearly defined symptoms. An additional case of formaldehyde related anaphylactic shock in a patient undergoing renal dialysis has been reported (33, 34). The symptoms could be of early onset, appearing within several minutes to 1 h after dental treatment (nine cases), or delayed, appearing from 2 to 24 h after the treatment (21 cases) (Table 1).

The skin tests to formaldehyde are not standardized and may provoke even delayed severe systemic reactions (15, 34). Prick tests to 0.1 and 1% formaldehyde solution are often negative and are inconsistently positive to the pure solution as used in dentistry. Patch tests to the standard battery of ICDRG containing formaldehyde are very often negative. Those skin tests to the native solution used in dentistry, or to 1% formaldehyde solution, sometimes give a delayed positive reaction, but their clinical significance is difficult to establish in some cases (14, 18). Skin tests were positive in 19 cases and negative in 11 cases (Table 1).

The measurement of specific IgE to formaldehyde is an important diagnostic element and may suggest underlying allergic mechanisms. Positive RAST, often with higher class, was detected in all cases when it was analyzed (20 cases). However, in some cases specific IgE have been detected without associated clinical symptoms (2, 3, 44–46). This may raise the question of its real significance in view of ubiquitous exposure to formaldehyde, particularly by respiration. Formaldehyde in powder form or in aqueous solution may be more reactive than in gaseous form and thus may lead to sensitization in odonto-stomatology. This sensitization could result from domestic or occupational contact with formaldehyde (cosmetics,

Table 1. Case reports of immunoglobulin E dependant reactions to formaldehyde after endodontic treatment

Authors (references)	Patients (gender/age)	Symptoms	Time of onset (h)	RAST	Skin tests
Wedental (20)	M/54	AS	2	NMD	NMD
Molina (15)	M/35	AS	3	NMD	+
Ito (25)	M/60	AS	0.7	NMD	+
Ebner (9)	M/57	AS	1	+	–
Ebner (9)	F/33	AS	5–6	+	–
Fehr (11)	M/39	AS	0.5–2	+	+
Gensau (12)	F/43	AS	3	+	+
Wantke (19)	F/67	AS	10–12	+	–
Sayama (26)	F/39	AS	2	NMD	+
Modre (22)	M/31	AS	5	+	+
Kunisada (27)	F/50	AS	8	+	+
Case 1	M/41	AS	0.5	+	+
Case 2	F/45	AS	0.25	+	+
Case 3	F/43	AS	2	+	–
Case 4	M/50	AS	0.25	+	–
Bercher (21)	M/NMD	U	3.5	NMD	NMD
Rousseau-Ducelle (16)	M/30	AOE	Few hours	NMD	NMD
Rousseau-Ducelle (16)	F/37	AOE + U	3.5	NMD	NMD
Al Nashi (23)	F/23	AOE	1	NMD	+
Burri (6)	F/20	AOE + U	NMD	NMD	+
Drouet (8)	F/NMD	U	4–6	NMD	+/–
Forman (24)	M/57	AOE	4	NMD	–
Ebner (9)	M/57	AOE + U	10–12	+	–
Fehr (11)	F/40	AOE + U	NMD	NMD	+
Fehr (11)	F/59	AOE	NMD	NMD	+
Gensau (12)	F/47	AOE	7	+	–
Gensau (12)	F/30	U	12	+	–
El Sayed (10)	F/37	U	Few hours	NMD	+
Sporcic (17)	F/52	AOE + U	9.5	NMD	+
Tas (18)	M/53	U	0.25	+	+
Case 5	F/40	U	3	+	+
Case 6	F/64	U	4	+	NMD
Case 7	M/56	AOE + U	0.5	+	+
Ebner (9)	M/NMD	Not defined	NMD	+	–
Ebner (9)	F/NMD	Not defined	NMD	+	–
Total	14 M 21 F	15 AS 18 U/AOE 2 NMD	9 < 1 H 21 > 2 H 5 NMD	20 + 0 – 15 NMD	19 + 11 – 5 NMD

AS, anaphylactic shock; AOE, angioedema; U, urticaria; NMD, not mentioned or not done.

certain medicines, in dentists, anatomists, pathologists, etc) and especially after previous endodontic treatments (all seven in our case reports). Dental overfilling with extrusion of root canal sealant and also instrumental intervention (apicectomie, dental extraction of treated tooth, repeated treatments of the same tooth, etc) may promote diffusion of the soluble formaldehyde in the apical or periapical region which is inflammatory and hypervascularized in conditions such as apical granuloma (5, 28–30, 32, 35, 40–42). The more or less rapid diffusion of formaldehyde after the endodontic treatment and the necessity of binding with a protein to form an antigenic conjugate may explain the more or less rapid induction of anaphylactic shock in certain cases and the inconsistently positive skin tests (12, 18).

Despite the widespread domestic and occupational use of formaldehyde and the frequency of endodontic treatments with sealant containing formaldehyde, IgE dependant allergic reactions in dentistry appear to be rare but they could be potentially severe and life threatening. Their incidence is unknown and is perhaps underestimated in the literature.

Our cases, as well as those reported in the literature, suggest that in dentistry, in the case of an allergic reaction, it is important to consider formaldehyde contained in root canal sealant as an etiological agent, along with local anesthetic and latex.

There is a need to use biocompatible material which does not contain formaldehyde and which does not release any component in endodontic treatment.

Use of sodium hypochlorite 3% for disinfecting and obturation with gutta percha and/or cements or sealants without formaldehyde AH Plus (Detrey-Dentsply, Konstantz, Germany), Sealapex® (Kerr Romulus, MI, USA), Pulpispad (Spad, Quetigny, France) and avoiding apical extrusion of sealant can be proposed (5, 6, 18, 38, 39, 43, 44, 47, 48).

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Acute hepatitis and rash to fluconazole

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Key words: drug allergy; fluconazole; hepatitis.

Fluconazole is a triazole antifungal agent commonly prescribed for oral, vaginal, and esophageal candidiasis. There have been occasional reports of hypersensitivity reactions including maculopapular rashes, fixed drug eruptions, angioedema, and Stevens-Johnson syndrome (1, 2). We report a case of fluconazole hypersensitivity in a healthy male presenting as a rash and hepatitis with a striking elevation in transaminases.

A 39-year-old healthy male ingests nontoxic doses of fluconazole and develops hepatitis and rash consistent with a hypersensitivity reaction.

A 39-year-old male, previously healthy, ingested 150 mg fluconazole upon suggestion by his wife who had recurrent candidiasis. He took a second dose of 150 mg fluconazole 1 week after the initial dose. After 4 days, he developed generalized weakness and malaise for which he took 500 mg acetaminophen for two consecutive days (1 g total). He then developed jaundice, scleral icterus, and a mildly pruritic erythematous rash on his chest, abdomen, extremities, and back. He did not take any other medications and had no risk factors for liver disease including alcohol use. Aside from the jaundice and rash, the patient was noted to have a temperature of 100.0 F. Laboratory studies were significant for a mild eosinophilia of 810 cells/μl, alanine aminotransferase 4192 U/l (ALT, normal 0–42 U/l), aspartate aminotransferase 2267 U/L (AST, normal 0–48 U/l), alkaline phosphatase 141 U/l (normal 20–125 U/l) and albumin 4.1 g/dl (normal 3.2–5.0 g/dl). The total bilirubin level was 31.5 mg/dl (normal <1.3 mg/dl) with a conjugated bilirubin of 9.9 mg/dl. Prothrombin time (PT) and partial thromboplastin time (PTT) were normal. An abdominal sonogram was normal. He had negative serological studies for viral hepatitis (A, B, and C), toxoplasmosis, cytomegalic inclusion virus (CMV), herpes simplex virus (HSV), parvovirus, Epstein Barr virus (EBV), and autoimmune hepatitis (antinuclear antigen (ANA) and anti-smooth muscle antibodies). A dermatologic biopsy revealed numerous necrotic keratinocytes. Liver biopsy showed both portal and lobular inflammation with cholestasis and apoptosis.

A diagnosis of fluconazole hypersensitivity was made based on the findings. The patient was treated with intravenous methylprednisolone 60 mg twice a day and two doses of intravenous immunoglobulin (IVIG 1 g/kg). The following day, liver parameters declined and the patient subjectively improved. A slow taper of prednisone ensued with eventual normalization of liver parameters approximately 3 months after the initial ingestion of fluconazole.

Due to its extensive metabolism by the liver, ketoconazole is the azole agent most commonly reported to cause hepatotoxicity. Fluconazole-induced liver injury is less common and has been reported primarily in patients with HIV or underlying liver disease (3). In this case, the absence of preexisting liver disease and the presence of eosinophilia, rash, and fever supports an immunoallergic reaction to fluconazole.

The exact mechanism of fluconazole-mediated hypersensitivity has not been well elucidated. The proposed mechanism for drug-induced hepatitis is that a metabolite of the drug serves as a hapten and binds to a hepatic enzyme to form an antigen. Although antibodies to fluconazole have not been clearly identified, autoantibodies have been detected in hepatitis due to halothane, anticonvulsants, and nitrofurantoin (4). Positive patch testing to fluconazole has also been described in a case of fixed drug eruption (5).

Although not necessary, liver biopsy may be helpful in excluding other etiologies of liver disease. A mixed cholestatic and hepatocellular picture is commonly seen in allergic hepatitis.

In general, liver enzymes should return to normal by 4 weeks after withdrawal of the offending medication, although it make take longer in cholestatic injury. Corticosteroids may be helpful especially if there is evidence of concomitant skin manifestations or eosinophilia (4). The use of IVIG in this patient was based on evidence in uncontrolled studies supporting its benefit in the treatment of toxic epidermal necrolysis (6).

To our knowledge, this is the first reported case of fluconazole hypersensitivity in a healthy person that presented as hepatitis with a bilirubin value more than 30 mg/dl and transaminase levels in the several thousands.

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