Secretion of Interleukin 4 and Immunoglobulin G From Peripheral Blood Mononuclear Cells in Allergic Rhinitis

Y Hidaka, K Tatsumi

Department of Laboratory Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

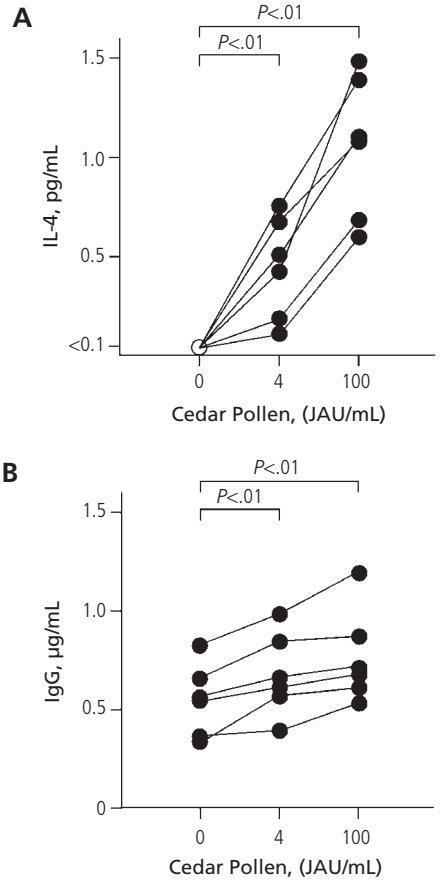
Key words: Interleukin 4. Immunoglobulin G. Allergic rhinitis. Japanese cedar pollen.

Palabras clave: IL-4. IgG. Rinitis alérgica. Polen de cedro japonés.

We previously found an association between the recurrence and onset of Graves' thyrotoxicosis and increased thyrotropin (TSH) receptor antibody titers following attacks of allergic rhinitis [1-3]. The TSH receptor antibody of Graves' disease belongs to the immunoglobulin (Ig) G1 subclass [4]. Therefore, the present study was performed to examine the effect of allergen on the release of interleukin (IL) 4, IgG, and IgG1 from peripheral blood mononuclear cells (PBMCs).

Peripheral blood was obtained from a patient with allergic rhinitis secondary to exposure to Japanese cedar pollen, diagnosed by the presence of IgE specific to that pollen. PBMCs were isolated by density centrifugation with the Ficoll-Paque Plus device (Amersham Biosciences, Uppsala, Sweden). Cells at a concentration of 2×10^6 cells/mL were incubated in X-VIVO 10 medium (Cambrex BioScience Walkersville, Maryland, USA) for 7 days in the presence of different concentrations (0, 4, and 100 Japanese allergy units [JAU]/mL] of Japanese cedar pollen (Torii, Tokyo, Japan). Concentrations of IL-4 and IgG were then measured in supernatant using commercially available enzyme-linked immunosorbent assay (ELISA) kits (IL-4, BioSource, Camarillo, California, USA; IgG, Bethyl Laboratories, Montgomery, Texas, USA). Concentrations of IgG1 were also measured in supernatant using biotin-conjugated antihuman IgG1 monoclonal antibody and avidin–horseradish peroxidase conjugate (BD Biosciences, San Jose, California, USA), instead of the antihuman IgG horseradish peroxidase conjugate found within the ELISA kit for IgG. Experiments were repeated 6 times and each measurement in supernatant was performed in triplicate. The points in the figures correspond to the means of these 3 determinations. The minimum detectable concentration for IL-4 was 0.1 pg/mL. The paired *t* test was used to compare concentrations of IL-4, IgG, and IgG1 at the different concentrations. Linear correlation analysis was used to examine the correlation between concentrations of IL-4 and IgG.

Production of IL-4 was not detected when PBMCs were incubated without Japanese cedar pollen. As shown in Figure 1A, the mean (± SD) production of IL-4 increased when PBMCs from the patient with allergic rhinitis were incubated with increasing concentrations of Japanese cedar pollen (4 JAU/mL, 0.44 ± 0.25 pg/mL, $P < .05$; 100 JAU/mL, 1.05 ± 0.36 pg/mL, $P < .01$). The production of IgG also increased when PBMCs



Secretion of A) interleukin (IL) 4 and B) immunoglobulin (Ig) G into the culture supernatant of peripheral blood mononuclear cells cultured with various concentrations of Japanese cedar pollen (0, 4, and 100 Japanese allergy units [JAU]/mL). An open circle indicates values less than 0.1 pg/mL.

from the patient were incubated with increasing concentrations of Japanese cedar pollen (0 JAU/mL, 0.55 ± 0.18 µg/mL; 4 JAU/mL, 0.68 ± 0.21 µg/mL, $P < .01$; 100 JAU/mL, 0.77 ± 0.24 µg/mL, $P < .01$) (Figure 1B). Likewise, the production of IgG1 increased when PBMCs from the patient were incubated with Japanese cedar pollen (0 JAU/mL, 0.55 ± 0.14; 4 JAU/mL, 0.58 ± 0.14, $P < .05$; 100 JAU/mL, 0.64 ± 0.11, $P < .05$), with absorbance at 450 nm. A positive correlation was observed between the concentrations of IL-4 and IgG ($r = 0.525$, $P < .05$).

Secretion of IL-4 into the supernatant of PBMCs cultured with grass pollen allergen from selected patients has previously been demonstrated [5]. IgG production by allergen-stimulated PBMCs has also been found [6]. However, the relationship between IL-4 and IgG secretion has not been examined in previous studies. In the present study, we found that allergen induces the secretion of IL-4,

IgG, and IgG1 from PBMCs, and that IL-4 and IgG concentrations are correlated. Allergic rhinitis is associated with type 2 helper T-cell (T_H2) mediated autoimmune diseases, such as Graves' disease and systemic lupus erythematosus [7,8]. Moreover, serum antithyroid autoantibodies increase after attacks of allergic rhinitis [3]. The thyroid stimulating autoantibody of Graves' disease belongs to the IgG1 subclass [4]. IL-4 plus CD40 induces an immunoglobulin isotype switch from IgM to IgG1, IgG3, and IgG4, but not to IgG2 and enhances production of total IgG, IgG1, IgG3, and IgG4, but not IgG2 [9]. The present results suggest that secretion of IL-4 in allergic rhinitis might induce autoantibody production, thereby exacerbating T_H2-mediated autoimmune disease.

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Yoh Hidaka
Department of Laboratory Medicine
Osaka University Graduate School of Medicine
2-2-D2 Yamadaoka, Suita
Osaka 565-0871, Japan
E-mail: hidaka@hp-lab.med.osaka-u.ac.jp

Flare-up–Like Phenomenon in a Skin Prick Test After Oral Challenge With Ibuprofen

D González de Olano, E González Mancebo, M Gandolfo Cano, A Menéndez Baltanás, MJ Trujillo Trujillo
Allergy Unit, Hospital Fuenlabrada, Madrid, Spain

Key words: Allergy. Flare-up. Ibuprofen. Nonsteroidal anti-inflammatory drugs. NSAIDs. Skin prick test.

Palabras clave: Antiinflamatorios no esteroides. AINEs. Alergia. Exantema. Ibuprofeno. Prueba cutanea.

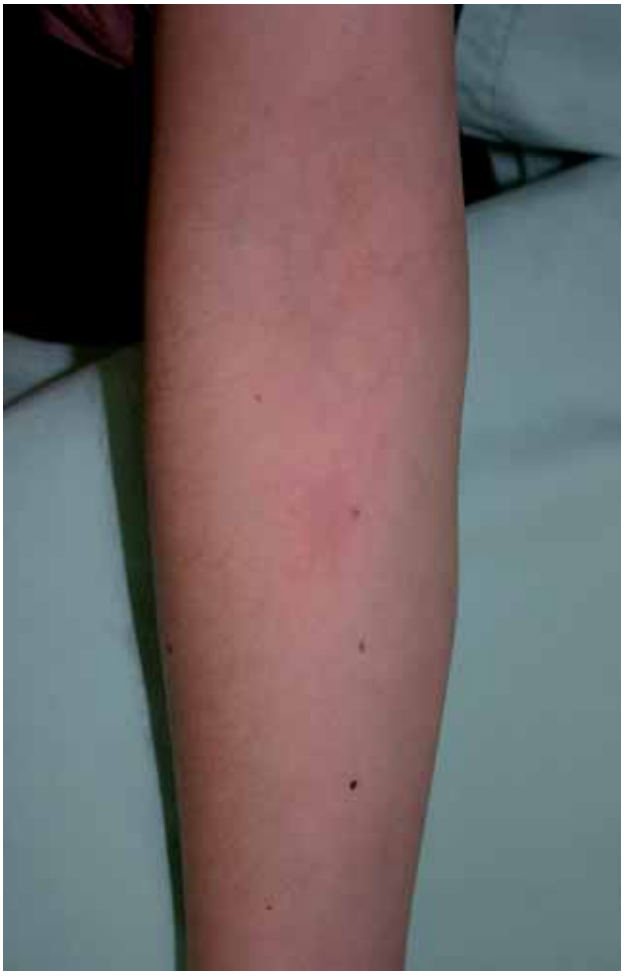
Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed. Ibuprofen belongs to the group of aryl-propionic acid derivatives and is one of the most frequently used NSAIDs. Cases of single-NSAID–induced urticaria are presumed to be immunoglobulin (Ig) E mediated, but specific antibodies are rarely demonstrated.

A 46-year-old-woman was treated with 600 mg of ibuprofen. Twenty minutes after intake, she experienced itching, swelling of her lips, scattered erythematous papules, and chest tightness. She had previously tolerated ibuprofen well. After this episode, she took no other NSAIDs. She had no history of previous allergic diseases or adverse reactions to drugs.

A skin prick test (SPT) with ibuprofen, 60 mg/dL in saline solution, was performed with no immediate reaction. An oral challenge was then carried out. The patient was administered doses of 150 mg, 300 mg, and 600 mg of ibuprofen at 1-hour intervals. The first 2 doses were well tolerated. Ten minutes after the intake of 600 mg, however, the SPT performed 3 hours earlier turned positive (figure) and the patient experienced itching, an erythematous papular eruption, and chest tightness. SPTs performed with ibuprofen in 10 controls were negative. Tolerance was good to further oral challenges with acetylsalicylic acid and pyrazolone. One month later, an SPT was again performed with ibuprofen at 60 and 90 mg/dL, with negative results.

Ibuprofen is a 2-aryl-propionic acid derivative which is believed to work through inhibition of cyclooxygenase (COX), thereby diminishing prostaglandin synthesis. Ibuprofen inhibits both COX-1 and COX-2.

Since ibuprofen is widely used, reports of adverse reactions involving this drug are frequent, ranging from maculopapular eruptions to Stevens–Johnson syndrome [1]. An association between atopy and single-NSAID–induced urticaria [2,3] or NSAID intolerance [4] has been proposed as the immunological mechanism involved. A history of sensitivity to a single NSAID usually suggests an IgE-mediated pathogenesis, but IgE antibodies are not usually identified. Though Palma-Carlos et al [5] observed a high level of agreement between patients reporting reactions to NSAIDs and positive skin tests to those drugs, additional cases of positive SPTs to a selective NSAID have only been reported with pyrazolone [6,7], glaphenine and meclofenamate sodium [8], and ibuprofen [9]. In the case we report, the immediate reaction after the intake of 600 mg of ibuprofen and the SPT which turned positive during the challenge suggest an IgE-mediated mechanism.



Flare-up–like phenomenon after oral challenge. The upper dot shows the location of the skin prick test performed with ibuprofen. The dot in the middle is the prick test with saline solution, and the one at the bottom corresponds to histamine.

The flare-up phenomenon is known to occur by a type IV immunological mechanism, mediated by T cells. An SPT is recommended as the primary method to identify immediate hypersensitivity, based on the presence of specific IgE antibodies. In this report, the SPT performed before challenge turned positive after the intake of the dose which had originally prompted the first reaction. We suggest that the presentation of the antigen through the skin might not be the right pathway, but during the acute systemic reaction, the preformed IgE antibodies against ibuprofen might have recognized the remaining drug in the skin, inducing a wheal-and-flare where the SPT had been carried out. Thus, it should be considered as a type I reaction, in a so-called "flare-up–like" phenomenon.

The accuracy of skin testing is limited in drug allergies. Only a few kinds of drugs, mainly β-lactams and muscle relaxants, have been traditionally considered to cause IgE-mediated reactions. Studies have tried to assess the usefulness of SPTs as a screening method in adverse cutaneous reactions [10], but there are still no standardized criteria concerning such testing in the diagnosis of drug allergy. Even though we could not clearly demonstrate IgE antibodies, physicians should consider the possible usefulness of SPT as a first-line approach in the diagnosis of IgE-mediated allergy.

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David González de Olano
Allergy Unit
Hospital Fuenlabrada
Camino del Molino, 2
28942 Fuenlabrada, Madrid, Spain
E-mail: dgolano@yahoo.es

No Association Between Placental Weight or Ratio at Birth and Risk of Atopy, Hay Fever, or Asthma at the Age of 31 Years

L Keski-Nisula, [1,2] MR Järvelin,[3] J Pekkanen [1,4]
[1] *Environmental Epidemiology Unit, National Public Health Institute, Kuopio, Finland*
[2] *Department of Obstetrics and Gynecology, Kuopio University Hospital, Kuopio, Finland*
[3] *Department of Public Health and General Practice, University of Oulu, Oulu, Finland*
[4] *Department of Public Health and Clinical Nutrition, University of Kuopio, Kuopio, Finland*

Key words: Asthma. Atopy. Hay fever. Placenta.

Palabras clave: Asma. Atopia. Polinosis. Placenta.

The intrauterine environment may influence the development of immunity and therefore be associated with allergies in later life [1]. At present, the mechanisms behind these associations are largely unknown. During pregnancy, the placenta is the key endocrine organ producing steroid hormones and it also controls the passage of maternal hormones and metabolites into the fetus. However, the relationship between intrauterine growth in relation to placental size and the development of allergic diseases later in life is not known.

We used data from the northern Finland birth cohort of 1966 [2] to compare placental weight and placental ratio with allergic disease in the same individuals at age 31 years. Placental ratio was calculated as the placental weight at birth divided by the weight of the newborn. Data on self-reported and physician-diagnosed hay fever or asthma, parental allergies, and vocational training were obtained by postal questionnaire when the subjects reached 31 years. Clinical examinations included measurements of weight and height, and skin prick tests (cat, birch, timothy grass, and *Dermatophagoides pteronysimus*).

Multivariate analyses were carried out with adjustment for sex, parental allergy, maternal parity, maternal smoking during pregnancy, paternal occupation (farmer or other), season of birth, gestational age at birth in quartiles, current vocational training at the age of 31 years, and current body mass index at the age of 31 years in quartiles. The data were analyzed by logistic regression using SPSS software. Subjects who weighed up to 2500 g at birth (low birth weight, n = 115), 2501–3999 g (normal birth weight, n = 3522), and 4000 g or more (high birth weight, n = 738) were analyzed separately as regards allergic diseases. Placental ratios were recategorized as tertiles: <0.19, 0.19–0.23, and >0.23 for low birth weight, and <0.17, 0.17–0.19, and >0.19 for normal and high birth weight.

The prevalence of atopy and physician-diagnosed hay fever and asthma at the age of 31 years was 30.8% (1346/4375), 23.1% (862/3733), and 9.6% (345/3577), respectively. Symptoms of hay fever and asthma during the last 12 months were reported by 29.0% (1252/4316) and 5.0% (216/ 4322) of patients, respectively. The mean (SD) placental weight was 645.8 (134.7) g (range, 250–1400 g) and the mean placental ratio was 0.18 (0.03), with a range of 0.07 to 0.40. No associations were detected between placental weights or placental ratios and allergic diseases in adjusted analyses (table).

In sensitivity analyses, placental ratios were recategorized within 3 birth weight groups as regards allergic outcomes and no significant associations were detected between allergic diseases and placental weights or ratios in stratified analyses (data not shown).

The placenta affects the growth of the fetus via metabolic and endocrine mechanisms. It is a major site of endocrine activity, including synthesis of a broad range of steroid and peptide hormones, growth factors, cytokines, and other bioactive factors [3]. Placental size is influenced by maternal factors such as smoking and nutritional status [4-5], and placental function reflects possible pregnancy disorders. After term pregnancy, placental size correlates with birth

Influence of Placental Weight and Ratio on Prevalence of Atopy, Physician-Diagnosed Hay Fever, and Asthma at the Age of 31 Years in 4375 Individuals*

	Atopy	Hay Fever	Asthma
Placental weight, g			
<550	1	1	1
551-640	0.90 (0.74-1.09)	0.87 (0.69-1.09)	0.89 (0.64-1.23)
641-720	0.99 (0.83-1.19)	0.97 (0.79-1.20)	0.82 (0.60-1.12)
>720	1.07 (0.89-1.29)	0.95 (0.76-1.19)	0.95 (0.69-1.30)
Placental ratio			
<0.16	1	1	1
0.161-0.18	0.97 (0.80-1.18)	1.01 (0.88-1.39)	1.08 (0.77-1.50)
0.181-0.20	0.97 (0.79-1.17)	1.09 (0.86-1.37)	1.01 (0.73-1.41)
>0.20	1.09 (0.89-1.32)	1.00 (0.80-1.27)	0.92 (0.66-1.30)

*Data are shown as the odds ratio (OR) and 95% confidence interval adjusted for sex, parental allergy, maternal parity, maternal smoking during pregnancy, paternal occupation, season of birth, gestational age at birth, current vocational training, and body mass index.

weight [5-6]. However, a disproportionately large placenta may represent an adaptive response to adverse intrauterine conditions. In pregnancies complicated by intrauterine growth retardation, impaired glucose tolerance, gestational diabetes, or maternal anemia, the placental ratio has been shown to exhibit a compensatory increase [7-10]. Our study is the first in which placental weight and ratio has been analyzed in relation to the subsequent development of allergic diseases.

Our data indicate that the effect of prenatal environment on the development of allergic diseases reported in early adulthood is not mediated by or associated with placental size differences. It is nevertheless possible that these factors may behave differently if studied at an earlier age.

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Leea Keski-Nisula
Department of Obstetrics and Gynecology
Kuopio University Hospital
Kuopio, Finland
E-mail: leea.keski-nisula@kuh.fi

Hypersensitivity to Spiramycin With Good Tolerance of Other Macrolides

L Sánchez-Morillas,[1] JJ Laguna-Martínez,[1] M Reaño-Martos,[2] E Rojo-Andrés,[1] P Gómez-Tembleque,[1] M Santaolalla-Montoya[1]

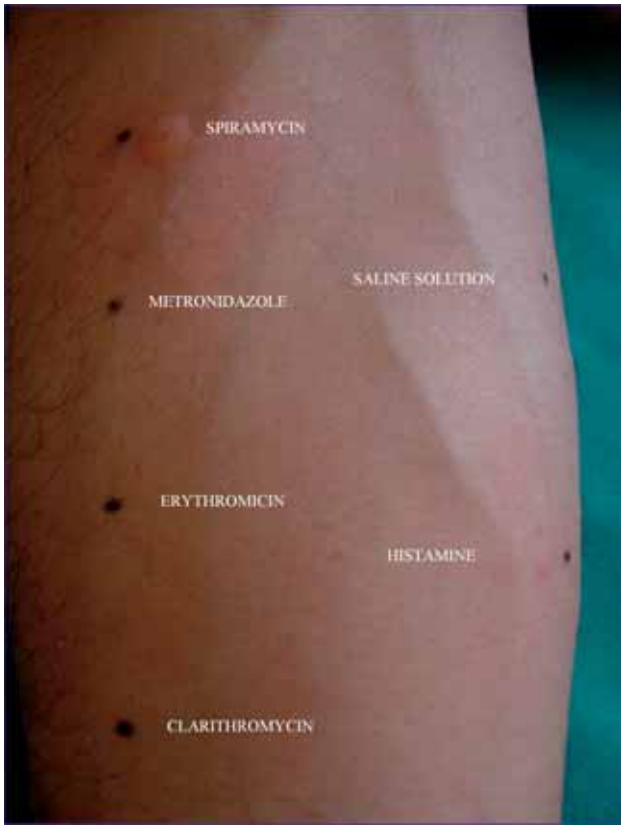
[1] *Allergology Department, Hospital Central de la Cruz Roja, Madrid, Spain*

[2] *Allergology Department, Hospital Puerta de Hierro, Madrid, Spain*

Key words: Hypersensitivity. Macrolides. Skin prick test. Spiramycin. Urticaria.

Palabras clave: Hipersensibilidad. Macrólidos. Prick test. Espiramicina. Urticaria.

Macrolides are classified according to the number of carbon atoms in the ring as 14-membered macrolides (erythromycin, troleandomycin, roxithromycin, dirithromycin, clarithromycin), 15-membered macrolides (azithromycin), and 16-membered macrolides (spiramycin, josamycin, midecamycin) [1]. Allergic and pseudoallergic reactions to macrolide antibiotics appear to be relatively uncommon (0.4% to 3% of treatments) [2]. However, there is little information in the literature concerning relevant diagnostic tests [1].



Skin-prick tests with the different macrolides.

A 43-year-old man, with no history of atopy or allergy, received Rhodogil (spiramycin-metronidazole) 2 years previously for a dental infection. Five minutes after the first dose, the patient developed facial erythema; 10 minutes after the second dose, he developed pruritus on his legs and generalized urticaria. The treatment was immediately stopped. Urticaria subsided in about 24 hours with systemic corticosteroids. He had previously tolerated this antibiotic 2 years earlier.

Skin prick test (SPT) with spiramycin (10 mg suspended in 1 mL saline) was positive, whereas a negative result was obtained with metronidazole (5 mg suspended in 1 mL saline). Histamine (10 mg/mL solution) and buffered saline were used as positive and negative controls, respectively. A wheal at least 3 mm larger than that seen with the negative control was considered positive. SPT with clarithromycin and erythromycin (10 mg suspended in 1 mL saline) proved negative (figure). Intradermal test with spiramycin, clarithromycin and erythromycin (0.1, 1 and 10 mg/mL dilution) were all positive. Intradermal tests performed with the same macrolides in 10 controls were also positive. We considered these results as an irritant response and not a true positive result. SPT with spiramycin (10 mg suspended in 1 mL saline) in 10 control subjects (5 atopic and 5 non-atopic) were negative.

After obtaining informed consent from the patient, we performed a single-blind oral challenge with metronidazole with a negative result. To investigate possible cross-reactivity among macrolides, we carried out single-blind oral challenges with clarithromycin and erythromycin, with no reaction. Therefore, we recommended the use of clarithromycin or erythromycin for future treatments that require a macrolide antibiotic.

Allergy to spiramycin is extremely rare and usually involves occupational asthma [3-6]. Malet et al [3] described a woman with rhinoconjunctivitis and asthma after exposure to acetylspiramycin in a pharmaceutical factory. Prick and intradermal tests with acetylspiramycin were performed with positive results. The diagnosis was confirmed by a nasal challenge test. Moscato et al [4] described 2 cases of asthma due to spiramycin in workers at a pharmaceutical factory. They reproduced the symptoms by inhalation challenge test with aerosolized spiramycin. There are also previous reports of rashes, pruritus, urticaria [7], and Schonlein-Henoch purpura [8] with the use of spiramycin. Igea et al [7] described 5 patients with generalized skin reactions due to spiramycin. All prick and patch tests were negative. Since our patient presented an immediate reaction, we did not do a patch test.

In summary, we report a case of immediate urticaria due to spiramycin. We suggest an immunoglobulin E-mediated mechanism, as demonstrated by positive SPT results with spiramycin. The patient tolerated single-blind oral challenges with clarithromycin and erythromycin, indicating that in our case there was no cross-reactivity with the macrolides tested.

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Leticia Sánchez Morillas
Servicio de Alergia
Hospital Central de la Cruz Roja
Reina Victoria 22
28003 Madrid, Spain
E-mail: lsanchezmorillas@hotmail.com

Food-Induced Anaphylaxis Caused by Inhalation of Soy Protein

E Burches, R Cervera, A Peláez
Allergy Unit, Hospital Clínico de Valencia, Valencia, Spain

Key words: Soy. Anaphylaxis. Inhalant food allergy.

Palabras clave: Soja. Anafilaxia. Alergia alimentaría por inhalación.

While at home, a 53-year-old woman developed a sudden episode of pruritus, swelling of the lips and tongue, dysphonia, and throat closure with moderate shortness of breath. The reaction was ongoing and progressive, and symptoms were aggravated rapidly with appearance of cough, dyspnea, and wheezing due to bronchoconstriction. Simultaneously, a rash with urticaria appeared that gradually became generalized. The patient required emergency medical care and hospitalization.

At the time of the initial assessment, physical examination showed skin involvement with generalized urticaria and swelling of the hands, feet, face, and eyelids. Auscultation revealed bronchoconstriction and wheezing. The symptoms responded to treatment with injected epinephrine, antihistamines, and corticosteroids.

The patient was later referred to our allergy unit for evaluation. She denied drug or food ingestion prior to the onset of the episode described. She reported that the outbreak

occurred while she was at home and that symptoms were initiated while she was cooking a processed food–sausages made of pork meat. A few minutes prior to the episode she had noted nasal symptoms: obstruction, sneezing, hypersecretion, and itching. She reported that some years ago she had noted nasal itching and sneezing occasionally associated with inhalation of fumes caused by cooking beans or other legumes. In addition, she reported that 2 years earlier she had suffered a generalized skin reaction while she was eating a meal consisting of rice, beans, and meat.

These findings in her clinical history led to the hypothesis that a common food-related factor participated in these episodes, and that they may have been the result of legume hypersensitivity. The possibility was considered that this last episode was the result of soy protein–a derivative of soybeans found in numerous processed foods [1]–and that the anaphylactic reaction was caused by inhalation of fumes during cooking. When the patient was asked to bring the processed-food (sausages) that had caused the reaction, the label revealed the presence of soy protein.

Skin prick tests performed with a battery of commercial inhalant allergens were negative. The patient had immediate responses to commercial food extracts of lentil, pea, bean, and soybean. A prick-by-prick test with the implicated processed food was positive. Specific immunoglobulin E levels were determined by commercial CAP immunoassay (Pharmacia, Uppsala, Sweden). Levels greater than 0.35 IU/mL were considered positive. Results were positive for soy (1.76 IU/mL), bean (1.64 IU/mL), and pea (0.41 IU/mL), whereas pork meat was negative. Finally, oral provocation was not done due to the severity of the reactions reported by the patient. The patient was instructed to avoid ingestion and cooking of all legumes and processed foods containing soy protein. With careful avoidance of these foods the patient has experienced no recurrence of these episodes in 1 year.

Diagnosis of food allergy or food-induced anaphylaxis seems to be more difficult if the reaction does not occur with ingestion [2]. It is well known that food hypersensitivity can produce respiratory manifestations [3] and inhalation of food allergens carried in the air can provoke rhinitis and asthma [4-6]. However, it is not as well known that food antigens carried in cooking fumes can produce anaphylaxis.

In summary, we present a case of anaphylaxis associated with inhalation of airborne soy protein particles in cooking fumes. The presence of soy proteins in sausage products as a cause of anaphylaxis (via the digestive tract) has been reported previously [7], but to our knowledge, this is the first report of an anaphylactic reaction induced by inhalation of soy protein present in a processed food.

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Enrique Burches
Allergy Unit
Hospital Clinico de Valencia
Av Blasco Ibañez, 17
Valencia 46010
Spain
E-mail: burches_enr@gva.es

Control of Asthma and Utilization of Medical Resources: Results From a Community Pharmacies Study in the Navarre Region of Spain

JM Olaguibel,[1] B Garcia Figueroa,[1] MJ Alvarez Puebla,[1] F Ezquieta,[2] C Mina,[3] C del Amo[3]
[1] *Sección de Alergología. Hospital Virgen del Camino, Pamplona, Spain*
[2] *FARPLUS, Pamplona, Spain*
[3] *ANAYAS, Pamplona, Spain*

Key words: Asthma control assessment. Primary care. Asthma patient questionnaire.

Palabras clave: Evaluación del control del asma. Atención primaria. Prueba de control del asma.

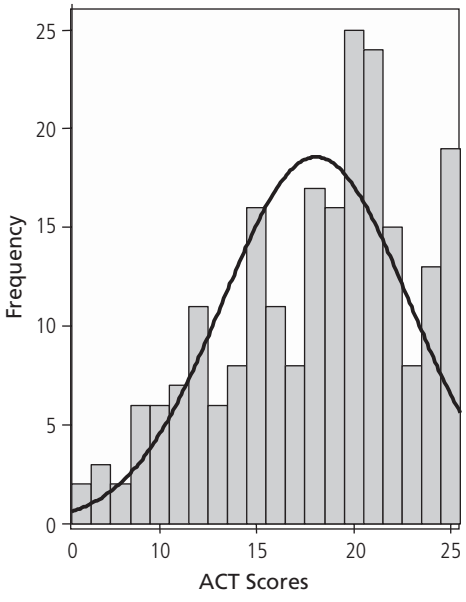
Several real-world studies have shown that the level of asthma control is suboptimal for many patients, with percentages of well-controlled patients ranging from 5% to 35% [1-3]. Most of these studies gathered information by direct or telephone interview, in which standard end points such as symptoms, use of rescue medication or hospitalizations were asked about. Short-term asthma control can be measured more properly with validated questionnaires, such as the Asthma Control Test (ACT), which has recently been translated into Spanish and validated and which has a well-defined cutoff point of 19 [4,5]. Community pharmacies are well placed in the health care system to conduct epidemiological studies. Almost all patients with active disease visit a pharmacy to refill their prescriptions and this represents a window of opportunity to improve such aspects of management as adherence or to conduct asthma educational programs [6].

We present the results of a pharmacy-based survey that aimed to provide data on the level of asthma control and the utilization of medical resources by asthmatic patients. It

was carried out at 76 community pharmacies, mainly in the area near Pamplona, the most populated city in the Spanish autonomous community of Navarre, between October and December 2005. The survey included questions on patients' demographic characteristics and their utilization of medical resources, together with the Spanish version of the ACT. Briefly, the ACT is a patient-completed questionnaire with 5 items assessing asthma symptoms, use of rescue medication, and the effect of asthma on daily functioning. Responses for each of the 5 items are added together to yield a score ranging from 5 (poor control) to 25 (complete control). The pharmacist recruited participants among patients or their parents or guardians who were regular users of the pharmacy. To be eligible, patients were required to have with them a prescription for an anti-asthma medication (category R03 of the Spanish list of pharmaceuticals [CGCOF/Catálogo de Especialidades Farmacéuticas]) and to be able to understand the study questionnaire. In order to mitigate the effect of possible misdiagnosis (chronic obstructive pulmonary disease, bronchiolitis), the age of included patients ranged from 4 to 45 in men and from 4 to 65 in women.

Two hundred sixty patients with a mean age of 34 years were surveyed. The ACT questionnaire was available for 98% of them. Most patients had suffered from asthma for a long time (mean duration 11 years) and 68% regularly used medication to control their disease. Regular follow-up was made by the primary care physician in 65% of the cases. Eighty percent were nonsmokers but there were fewer smokers in the group supervised by specialists (13% vs 27%, $P = .03$). Most patients reported that they had undergone skin testing (83%) and spirometry (84%) at some moment since diagnosis. Fifty-five percent of the patients were checked by a physician at least twice a year and 80% at least once a year. Significantly more patients followed by a specialist used preventive medication regularly than did those who were followed by a primary care physician (75% vs 58%, $P < .05$).

The figure shows the frequencies of ACT scores. Forty-eight percent of the patients had scores of 17 or lower (suboptimal level of asthma control) and 82% had scores lower than 15. In general, our results suggest that control is better than has been previously suggested based on surveys performed by telephone or direct interview without specific instruments to assess the level of asthma control, but they are consistent with those obtained by Laforest et al [7] after another survey with a similar design. Overall, 33% were patients with unstable asthma who needed unscheduled or emergency visits. The ACT scores of this group were significantly lower than the ACT scores of stable patients (19.51 vs 15.45, mean difference 4.06; 95% confidence interval, 2-5; $P < .001$), a finding that supports the measurement properties of this instrument and the cutoff points used. Patients followed by specialists had significantly higher ACT scores compared with those supervised by primary care physicians (19.23 vs 17.21, mean difference, 2.01; $P < .01$), although it must be remembered that patients under a specialist's care usually have more severe disease [8]. There were no differences in ACT scores between patients using regular medication to control the disease or not, illustrating that asthma control and severity are 2 independent concepts and most asthmatic patients respond well to therapy and so can be properly controlled if an adequate therapeutic program is provided [9].



Frequencies of scores on a Spanish version of the Asthma Control Test (ACT). The mean (SD) score was 18.07 (4.79).

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Jose M Olaguibel Rivera
Alergología
CS Conde Oliveto
Plza Paz sn
31003 Pamplona, Spain
E-mail: jmolaguibel@telefonica.net

Anaphylactic Reaction After Intake of Phenylephrine and Tolerance of Other Sympathomimetic Drugs

B Rojas-Hijazo, MM Garcés, N Segura, L Ferrer, M Sobrevía
Department of Allergology, Hospital Clinico Universitario, Zaragoza, Spain

Key words: Phenylephrine. Rhinoconjunctivitis. Sympathomimetic drugs. Urticaria. Anaphylactic reaction.

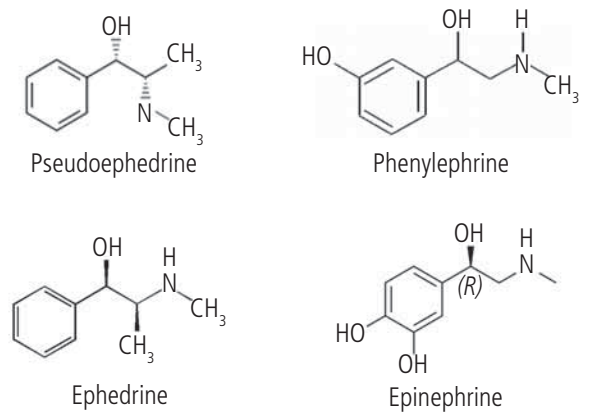
Palabras clave: Fenilefrina. Rinoconjuntivitis. Fármacos simpaticomiméticos. Urticaria. Reacción anafiláctica.

Phenylephrine is mainly used for its vasoconstrictor properties, for nasal congestion, or as a mydriatic agent. It is sold in preparations for oral intake combined with other ingredients intended for the relief of cough and cold symptoms. Although sympathomimetic drugs are used widely, type I allergic reactions to them are rare. The only reported adverse reactions caused by phenylephrine are allergic contact dermatitis caused by eye drops [1,2], eardrops [3], or topical preparations [4].

A 51-year-old man with no history of allergy took a Bisolgrip tablet (paracetamol 500 mg, chlorpheniramine 2 mg, and phenylephrine 10 mg) for a cold. Ten minutes after taking the second dose, he noticed a generalized urticarial eruption and rhinoconjunctival and eyelid edema. The urticaria and the rhinoconjunctivitis cleared in an hour. The angioedema disappeared in 4 days with no desquamation.

Because we did not have pure phenylephrine for skin prick tests, we performed the test with phenylephrine eye drops at concentrations of 25 and 100 mg/mL, with paracetamol, chlorpheniramine, pseudoephedrine and ephedrine (concentrations of 25 mg/mL), and with epinephrine (1 mg/mL). Intradermal skin tests were carried out with phenylephrine eye drops at 0.25 mg/mL and 1 mg/mL, pseudoephedrine and ephedrine at 0.25 mg/mL, and epinephrine at 0.1 mg/mL. All tests were negative.

The patient was challenged orally on different days with paracetamol, chlorpheniramine, and Bisolgrip. The oral challenge tests with paracetamol and chlorpheniramine were negative, but generalized urticarial lesions and rhinoconjunctivitis developed 30 minutes after he took an accumulated dose equivalent to a whole Bisolgrip tablet. Symptoms had disappeared an hour after he took an antihistamine. We performed an oral challenge test with pseudoephedrine and ephedrine; both challenges were negative.



Chemical structures of phenylephrine, pseudoephedrine, ephedrine, and epinephrine.

At a later date we obtained pure phenylephrine and performed prick tests at concentrations of 25 and 100 mg/mL and intradermal skin tests at 0.25 and 1 mg/mL. All tests were negative. Our patient refused a second oral challenge test with phenylephrine.

Phenylephrine is a sympathomimetic amine belonging to the phenylethanolamine family. The very close chemical structures of sympathomimetic drugs could explain potential cross reactions among them (figure), although reported data on this are contradictory [2,5]. Cross-reactivity has only been verified between pseudoephedrine and ephedrine [6]. Gonzalo-Garijo and colleagues [2] reported delayed reactions to phenylephrine and pseudoephedrine in a patient, probably not due to cross-reactivity but rather coincidence. We were unable to demonstrate cross-reactivity between sympathomimetic drugs in our case. Cross-reactions among these drugs seem to be infrequent.

In the present case, an apparent grade II anaphylaxis after taking phenylephrine has been described but could not be completely confirmed because neither positive skin tests nor a positive challenge with pure phenylephrine was obtained. There are published cases of urticaria and angioedema to pseudoephedrine [6] but not to phenylephrine. The clinical features and positive oral challenge test with phenylephrine (Bisolgrip) in this case suggest an immunoglobulin E mediated mechanism. Our patient was instructed to avoid phenylephrine-containing products in oral or topical preparations but not other sympathomimetic drugs.

The authors wish to thank the medical department of Boehringer Ingelheim SA for providing us with pure phenylephrine in order to complete the study.

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Beatriz Rojas Hijazo
Servicio Alergología
Hospital Clínico Universitario
Avda. San Juan Bosco 15
50009 Zaragoza (Spain)
E-mail: rojashijazo@yahoo.es

Contact Urticaria to Phthalic Anhydride

D Gutiérrez-Fernández,[1] MS Fuentes-Vallejo,[2] MD Rueda-Ygueravides,[1] B Bartolomé-Zavala,[3] A Foncubierta Fernández,[4] A León Jiménez [1]

[1]*Department of Pulmonology and Allergy, Hospital Puerta del Mar, Cádiz, Spain*
[2] *Alergomedic Allergy and Asthma Clinic, Cádiz, Spain*
[3] *Department of Research and Development, Bial-Aristegui, Bilbao, Spain*
[4] *Joaquin Pece Health Center, San Fernando, Cádiz, Spain*

Key words: Contact urticaria. Maleic anhydride. Occupational allergy. Phthalic anhydride. Polyester resin.

Palabras clave: Urticaria de contacto. Anhídrido maleico. Alergia ocupacional. Anhídrido ftálico. Resina de poliéster.

Occupational illnesses constitute a group of pathological processes in which the main characteristic is the causal relationship between work and the onset of the disease.

A 43-year-old man who had worked in a refinery in contact with petrochemical products for the last 4 years was referred to our allergology clinic by the physician of his health insurance company to rule out hypersensitivity to petrochemicals, maleic anhydride, and phthalic anhydride. The patient described a 7 to 8 month history of generalized urticaria and pruritus with an onset a few minutes after beginning his working day at the refinery. He also described other associated symptoms such as ocular pruritus, rhinorrhea, dry cough, wheezing, and tightness of the chest.

During the physical examination we observed a pale nasal mucosa and hyperemic ocular mucosa, together with isolated rhonchus during lung auscultation. Skin prick test (SPT) was performed with a battery of common inhalant allergens (Stallergenes-IPI, Antony, France). A result was considered positive when the size of the wheal obtained after 20 minutes was similar to that observed with the positive control (histamine, 10 mg/mL). Weak positive results were obtained with olive pollen and *Dermatophagoides pteronyssinus*. Baseline spirometry showed a mild obstructive pattern with positive bronchodilator test. Total immunoglobulin (Ig) E concentration was 350 IU/mL and analysis of specific IgE (ImmunoCap, Phadia, Barcelona, Spain) showed greater than 100 IU/mL for phthalic anhydride and 20.2 IU/mL for maleic anhydride (analyses performed in duplicate). SPT with 1% phthalic anhydride and 5% acetone (Bial-Aristegui, Bilbao, Spain) [1] showed positive results, with papules measuring 11 × 11 mm and 12 × 12 mm, respectively. SPT with those materials was negative in the control group. SPT with phthalic anhydride conjugated with human serum albumin at a concentration of 10 mg/mL (Bial-Aristegui, Bilbao, Spain) [2] yielded a positive result with a papule of 4 × 4 mm. SPT with that material was negative in the control group. The possibility of conducting a bronchial provocation with phthalic anhydride dust was discussed with the patient, but it was rejected due to the high risk of immediate reaction.

Phthalic anhydride is an industrially produced low-molecular–weight compound used for manufacturing plasticizing agents, alkyd resins, and unsaturated polyester resins [3]. Similar to other anhydrides, it can covalently bind to proteins, acting as a hapten and inducing an immune response [4]. Exposure to acid anhydrides causes irritation and can lead to immune-mediated respiratory diseases such as rhinitis, conjunctivitis, and asthma upon repeat exposure [5,6]. Workers exposed to

Results of the Immunological Study*

Test	Results
Total IgE	350 IU/mL
Specific IgE	
Phthalic anhydride	>100 IU/mL
Maleic anhydride	20.2 IU/mL
Skin prick test	
Phthalic anhydride	+++ (11 × 11 mm)
in 1% acetone	Negative in control group
Phthalic anhydride	+++ (12 × 12 mm)
in 5% acetone	Negative in control group
Phthalic anhydride	++ (4 × 4 mm)
conjugated with human serum albumin (10 mg/mL)	Negative in control group

*IgE indicates immunoglobulin E.

phthalic anhydride who suffered from asthma and rhinitis were first described by Kern [7] in 1939. Since then, a few cases of occupational contact urticaria caused by unsaturated polyester resin have been reported [8,9] and the capacity of phthalic anhydride to induce production of specific IgE antibodies has also been described [6]. Immunological tests are crucial to assess immediate hypersensitivity to acid anhydrides [10].

We present a case of occupational contact urticaria caused by phthalic anhydride in a 43-year-old man who worked in a refinery cleaning tubes and other containers with maleic anhydride and phthalic anhydride. This continuous workplace exposure for the last 4 years was associated with the onset of urticaria and rhinoconjunctival and respiratory symptoms. We confirmed immediate hypersensitivity (type I hypersensitivity) to phthalic anhydride by specific-IgE measurement and SPT. Since phthalic anhydride is not soluble in aqueous solvents (usual SPT solution), to obtain the SPT preparation we can either bind this molecule to a carrier protein such as human serum albumin or use an organic solvent in which the molecule can dissolve, such as acetone [2]. In this patient, we used both methods with the same result in both cases.

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Diego Gutiérrez Fernández
Hospital Puerta del Mar
Servicio de Neurología-Alergia
Avenida Ana de Viya, 21
11009-Cádiz, Spain
E-mail: drgutierrez@comcadiz.com