

Anaphylaxis to Dimenhydrinate Caused by the Theophylline Component

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Palabras clave: Anafilaxia. Dimenhidrinato. Difenhidramina. Alergia medicamentosa. Teofilina.

Dimenhydrinate is an over-the-counter, widely used drug for motion sickness. It consists of 2 drugs: diphenhydramine, an ethanolamine, and 8-chlorotheophylline, a xanthine derivative that reduces the sedating properties of diphenhydramine. Allergic reactions to dimenhydrinate are rare and typically manifest as fixed drug eruptions [1,2]. To our knowledge, no episodes of anaphylaxis have been reported.

Herein, we present the case of a 27-year-old woman who was admitted with sudden pruritic rash on the palms that rapidly progressed to the soles and the flexural surface of the elbows. Within 30 minutes, she developed emesis, diarrhea, and pain in the lower abdomen. The symptoms resolved without treatment within an hour. Ten minutes prior to the onset of the rash, she had taken an antiemetic pill (50 mg dimenhydrinate) due to a planned car trip. She reported multiple intakes of dimenhydrinate in the past without any reaction. History was insignificant for other allergic disease, with no reports of atopic dermatitis, physical urticaria, or food or drug allergy.

Based on the concurrent manifestation of symptoms affecting the skin and the gastrointestinal tract together with the pain in the lower abdomen (attributed to uterine contractions), we considered the possibility of an anaphylactic reaction to dimenhydrinate and proceeded to perform skin prick tests (SPTs) with the suspected agent. The tests were performed with increasing concentrations (0.5 mg/mL, 5 mg/mL, and 50 mg/mL) of dimenhydrinate (Drimen tablet in normal saline, Coup); they were all positive with progressively increasing wheal and flare reactions. The same tests performed in 5 healthy controls were negative, indicating no irritating effect of the drug. SPTs performed with a panel of food allergens (egg white, cow's milk, wheat, and fish) and aeroallergens (grass mix, weed mix, *Olea europea*, *Parietaria judaica*, cat epithelia, and *Dermatophagoides pteronyssinus*) were all negative, confirming the negative atopic profile of the patient. The patient did not exhibit dermatographism. To assess the specificity of the reaction, we performed SPTs with 4 antihistamines of different drug classes. We tested an alkylamine (dimetindene

maleate at 4 mg/mL [Fenistil injectable solution, Novartis]), 2 piperazines (cetirizine hydrochloride at 10 mg/mL [Zirtek tablet in normal saline, UCB] and levocetirizine dihydrochloride at 5mg/mL [Xozal tablet in normal saline, UCB]) and a piperidine (desloratadine at 5mg/mL [Aerius tablet in normal saline, Schering-Plough]). All were negative.

To study the allergenic properties of the 2 compounds we proceeded to perform SPTs with the pure substances (Figure). Interestingly, there was no reaction when we tested diphenhydramine (1 mg/mL, 10 mg/mL, and 100mg/mL; powder provided by Recordati, Italy), as previously reported [3]. In contrast, all the theophylline-containing drugs tested were positive. Specifically, we tested anhydrous theophylline (0.6 mg/mL, 6 mg/mL, and 60mg/mL [Theodur tablet in normal saline, Lavipharm]), choline theophyllinate (0.8 mg/mL, 8mg/mL, and 80 mg/mL [Choledyl syrup, Galenica]), and aminophylline (0.25 mg/mL, 2.5 mg/mL, and 25 mg/mL [injectable solution, Cooper]). The results were increasingly positive. Again, 5 healthy individuals tested negative. Of interest, SPTs for allopurinol (3 mg/mL, 30 mg/mL, and 300 mg/mL [Zylapour tablet in normal saline, Farmanic]), which is a structural isomer of hypoxanthine resembling theophylline, were negative. It can be concluded thus that the reactivity in our patient was specific to the theophylline compound. Unfortunately, the patient refused to undergo a diagnostic oral drug challenge. Of note, previous reports on aminophylline reactivity have not been attributed to theophylline but rather to ethylenediamine, a well-known allergen [4,5].

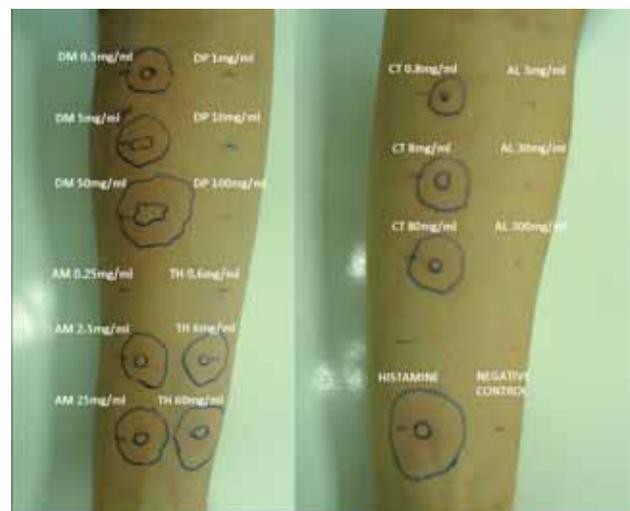


Figure. Skin prick tests, performed using the standard prick method, for the various compounds. DM indicates dimenhydrinate; DP, diphenhydramine; AM, aminophylline; TH, anhydrous theophylline; CT, choline theophyllinate; and AL, allopurinol.

In summary, this is the first report of an anaphylactic reaction to dimenhydrinate attributed to 8-chlorotheophylline. Anaphylactic reactions to either theophylline or dimenhydrinate have not been previously reported. Moreover, SPTs seem to be a reliable method for detecting immunoglobulin E-mediated anaphylaxis to theophylline. Therefore, even though anaphylaxis to dimenhydrinate is very rare, the possibility of such a reaction should be kept in mind, especially for patients with high exposure in the past presenting with compatible symptoms. Finally, patients who develop anaphylactic reactions to dimenhydrinate should be instructed to avoid xanthine derivatives without prior testing.

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Allergy to Crayfish

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Crayfish, also known as crawfish or crawdad, are crustacean members of the Astacoidea and Parastacoidea superfamilies. Distributed throughout the world, there are more than 500

reported species. More than half of these species occur in North America. Europe, however, is home to just 7 species and most of them are currently endangered species. Crayfish is a very popular food worldwide but few cases of adverse reactions after its ingestion have been reported.

An 18-year-old woman presented with chest tightness, wheezing, headache, and hives on the abdomen that had appeared within minutes of eating *Procambarus clarkii*, a crayfish belonging to the Cambaridae family. She said that she had never developed symptoms after eating crustaceans or molluscs on previous occasions. As the only additional atopic background, she reported a history of pollen-induced seasonal rhinoconjunctivitis.

Protein extracts from raw and boiled *P clarkii* shell (PCSr and PCSb, respectively) and flesh (PCFr and PCFb) were prepared by homogenization in phosphate buffered saline, dialyzation, and lyophilization. Skin prick tests (SPTs) to common commercial aeroallergens, crustaceans, molluscs, and *Anisakis simplex* were performed, with positive results (wheal diameter ≥ 3 mm) only to grass and olea pollen. Prick-by-prick tests with PCFr and PCFb yielded a wheal of 3 mm in both cases. Serum-specific immunoglobulin E (sIgE) against commercial crab extract (Pharmacia CAP system) was <0.35 kU/L, and sIgE determinations against PCSr, PCSb, PCFr, and PCFb (enzyme allergosorbent technique) yielded 0.4 kU/L for PCSr (total IgE of 90 IU/mL) and were negative for the rest of the extracts. All the extracts were analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis

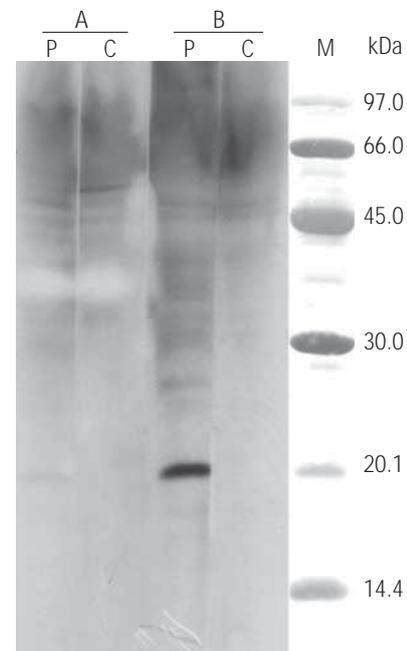


Figure. Immunoglobulin (Ig) E-binding proteins in crayfish extracts. A, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) IgE-immunoblotting of raw *Procambarus clarkii* flesh. B, SDS-PAGE IgE-immunoblotting of raw *P clarkii* shell. Lane P, patient serum; lane C, control serum (pool of sera from nonatopic individuals); lane M, molecular mass marker.

(SDS-PAGE) as described by Laemmli [1], showing protein bands ranging between 14 and 99 kDa for the PCFr and PCSr extracts. SDS-PAGE IgE-immunoblotting assays revealed IgE-reactivity with a 21-kDa protein in both extracts, but with stronger labeling in PCSr (Figure). In order to identify this IgE-binding protein, the 21-kDa band from the PCSr extract was manually excised from the gel, digested with trypsin, and analyzed by MALDI-TOF (matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry) and LC-ESI-IT [liquid chromatography electrospray ionization tandem mass spectrometry/LC-MS/MS]), as described by Pastor et al [2]. Protein identification was performed by searching a nonredundant protein sequence database (NCBI) using the Mascot program (<http://www.matrixscience.com>). To identify the 21-kDa protein, we performed MS/MS and obtained the sequence of an internal peptide with the sequence AGTSGLGFLFDKELK. Research conducted with protein databases identified the sequence as ferritin.

Ferritin is a globular protein complex consisting of 24 protein subunits that is present in all cell types [3]. It is the primary intracellular iron-storage protein in prokaryotes and eukaryotes and maintains iron in a soluble, nontoxic form. In vertebrates, these subunits can be light-type (L) or heavy-type (H) subunits, with a molecular weight of 19 kDa and 21 kDa, respectively [3]. An additional subunit resembling *Lymnaea* soma ferritin is associated with shell formation in the pearl oyster and its primary sequence is similar to that of the vertebrate H-type [4]. Because of the importance of iron in mineralization, ferritin is employed in the shells of organisms such as molluscs and crustaceans to control the concentration and distribution of iron, and to sculpt shell morphology and coloration. The function and structure of ferritin vary by cell type and are controlled by an RNA-binding protein (iron-regulatory protein). Ferritin sequences have been obtained in molluscs [5], and a ferritin subunit in the hepatopancreas of the freshwater crayfish *Pacifastacus leniusculus* has also been described [6]. To the best of our knowledge, however, no cases of allergy to ferritin or crayfish have been reported.

In this report, we present a case of IgE-mediated allergy to *P. clarkii*, a crayfish belonging to the Cambaridae family, and suggest that the allergen involved was a 21-kDa protein.

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Successful Rapid Rituximab Desensitization for Hypersensitivity Reactions to Monoclonal Antibodies in a Patient With Rheumatoid Arthritis: A Remarkable Option

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Key words: Desensitization. Rheumatoid arthritis. Rituximab.

Palabras clave: Desensibilización. Artritis reumatoide. Rituximab.

Rheumatoid arthritis (RA) is an inflammatory disease characterized by disturbances in T-cell and B-cell functions [1]. Rituximab is a chimeric monoclonal antibody (mAb) against CD20 that induces a profound depletion of B cells in the peripheral blood of patients with RA [2]. The infusion of this mAb may cause transient hypotension or hypertension, cough, pruritus, and rash [3]. In 5% to 10% of cases, the reactions are clinically consistent with immediate hypersensitivity (IHS) reactions [4]. Desensitization to rituximab has been described in case reports and small series of patients with hematologic malignancies and certain connective tissue diseases [5,6].

We report the case of a 32-year-old woman followed by our rheumatology department for RA for 7 years. In 2007, she had been given adalimumab (Humira, 40 mg/0.8 mL), an anti-tumor necrosis factor (TNF) mAb, in another medical center. After the second dose (15 days after the first dose), she developed labial angioedema and tongue swelling within 2 hours of injection. The following month, the medication was replaced by twice-weekly etanercept (Enbrel Pen, 50 mg), an anti-TNF fusion protein. After the fourth injection, she developed tingling in her lips, syncope, dizziness, and headache. Three months later, the drug was withdrawn following epistaxis and bleeding in the mouth. Skin prick and intradermal tests with adalimumab

Table. Intravenous Desensitization Protocol for Rituximab

	Volume, mL	Concentration, mg/mL	Total Amount of Drug in Each Solution, mg
Solution 1	250	0.04	10
Solution 2	225	0.4	90
Solution 3	225	4	900

Step	Solution Used	Rate, mL/h	Time, min	Volume infused per step, mL	Administered dose, mg	Cumulative dose, mg
1.	1	2	15	0.50	0.02	0.02
2.	1	5	15	1.25	0.05	0.07
3.	1	10	15	2.50	0.10	0.17
4.	1	20	15	5.00	0.20	0.37
5.	2	5	15	1.25	0.5	0.87
6.	2	10	15	2.50	1	1.87

were negative and the patient was therefore restarted on adalimumab treatment. Nevertheless, after 6 months, she presented erythema at the injection sites lasting more than 24 hours. The drug was discontinued and the patient was hospitalized. Rituximab (Mabthera 500 mg/50 mL) therapy was planned and skin tests were performed with a drop (10 mg/mL) for the prick test, and 0.03 mL of 1:100 and 1:10 dilutions for the intradermal test. All were negative. Rituximab was administered and 90 minutes into the infusion (175 mg of the planned 1000-mg dose), the patient developed pruritic papular urticarial eruptions (which subsequently extended to the whole body), dizziness, tachycardia, and blackout. The infusion was stopped; the patient was treated with antihistamines and intravenous steroids, and observed for several hours. After 1 month, given the success of rituximab and the lack of response to other drugs, the patient agreed to be re-treated with rituximab using a desensitization protocol. Written informed consent was obtained and she was admitted to the immunology and allergic diseases ward. She received premedication with an intravenous injection of 20 mg methylprednisone (Prednol-L) and an intramuscular injection of 45.5 mg/2 mL pheniramine (Avil) 30 minutes before the desensitization procedure. Three solutions in normal saline were prepared and delivered in 12 consecutive steps as shown in the Table and described in previous reports [6,7]. Hypertension occurred during the infusion and the patient was treated with 10 mg amlodipine (Vasocard). Two weeks later, a second rituximab infusion was administered within the desensitization protocol. Treatment schedules and concomitant medication for the underlying disease were not altered during desensitization. The patient also received antihistamine and corticosteroid premedication 30 minutes before the second desensitization. The procedure was successful and the patient subsequently tolerated rituximab. Hypertension has not occurred.

The use of biological agents is increasing. RA remains the only nonmalignant condition for which rituximab has received approval from the US Food and Drug Administration [8]. mAbs can cause infusion-related reactions but the exact etiology of these remains unclear. They can arise via immunoglobulin

(Ig) E- or non-IgE-dependent mechanisms. Premedication with antihistamines, acetaminophen, and/or corticosteroids is a common practice to prevent infusion reactions with all mAbs [9].

We present the first report of successful intravenous desensitization to rituximab performed in rapid succession (double desensitization) in a patient with RA. Although an IgE-mediated mechanism was not confirmed by skin tests, the patient was empirically desensitized because the nature of the reactions indicated IHS. Rapid desensitization can be used for both IgE-mediated and non-IgE-mediated IHS reactions [6].

Rapid desensitization is a promising method for the delivery of rituximab after IHS reactions to mAbs and should be considered in RA when there are no acceptable therapeutic alternatives.

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Anaphylactic Shock Caused by Antihistamines

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Key words: Anaphylaxis. Basophil activation test. Diphenhydramine. Histamine antagonists. Dot-blot.

Palabras clave: Anafilaxia. Test de activación de basófilos. Difenhidramina. Antihistaminicos. Inmunoblot.

Antihistamines are widely used drugs which rarely produce immediate hypersensitivity reactions, although contact or photoallergic dermatitis and fixed drug eruptions have been reported frequently. Dimenhydrinate is an equimolecular preparation of 2 drugs, the antihistamine diphenhydramine and 8-chlorotheophylline, a xanthine derivative which reduces the sedating properties of diphenhydramine. The preparation is used to treat dizziness, nausea, anxiety, and cold symptoms.

We report the case of a patient with anaphylactic shock caused by diphenhydramine and tolerance of other antihistamines.

A 48-year-old housewife with nasal polyps and perennial rhinitis and asthma exacerbated by olive pollen in the spring reported an episode of generalized itchy erythematous lesions

and hand angioedema 10 minutes after the ingestion of a tablet of Cinfamar Cafeína (dimenhydrinate 50 mg and caffeine 50 mg) to prevent car sickness. She recovered spontaneously in 2 hours and said that she had tolerated this drug on 5 previous occasions. Four months earlier, she had experienced a bronchospasm 2 hours after taking an ibuprofen tablet for a headache.

Skin prick tests (SPTs) were performed, with negative results, with Cinfamar Cafeína 10 mg/mL (5×4 mm), Cinfamar 10 mg/mL (4×4 mm), and theophylline 20 mg/mL. Intradermal tests performed with diphenhydramine at dilutions of 5, 0.5, and 0.05 mg/mL were negative. The same tests were also negative in 5 atopic and 5 nonatopic controls. The excipients in Cinfamar Cafeína were also found in other drugs taken by the patient.

We performed a single-blind controlled oral challenge test with diphenhydramine. A few minutes after the intake of 12.5 mg of the drug, the patient presented palm and plantar pruritus, dyspnea, pharyngeal occupation, dizziness, hypotension (65/40 mm Hg), nausea, vomiting, intercostal and abdominal breathing, urinary relaxation, and syncope. She was treated with epinephrine, Actocortina (hydrocortisone sodium phosphate), fluid therapy, and oxygen in the intensive care unit and recovered completely within a few hours.

SPTs with loratadine (5 mg/mL), cetirizine (10 mg/mL), hydroxyzine (5 mg/mL), fexofenadine (12 mg/mL), mizolastine (1 mg/mL), ebastine (10 mg/mL), azelastine (5 mg/mL), and dexchlorpheniramine (5 mg/mL) were negative. Single-blind controlled oral challenges with theophylline, loratadine, and ibuprofen were tolerated. Serum total tryptase levels were normal.

We found no *in vitro* specific immunoglobulin (Ig) E to diphenhydramine using the dot-blot method. The Basotest (a kit for the quantitative determination of basophil activation in human heparinized blood) applied to diphenhydramine was negative.

We believe that the mechanism involved in the anaphylactic shock experienced by our patient might have been an IgE-mediated hypersensitivity reaction caused by diphenhydramine. The clinical symptoms and results of the SPTs and oral challenge support this hypothesis. The dot-blot and Basotest methods failed to demonstrate this mechanism but this is a common problem in drug allergy because drugs can act as haptens or through reactive metabolites likely to haptenate. Barranco et al [1] reported an anaphylactic reaction to diphenhydramine in a nonatopic patient with a positive intradermal test and challenge but a negative SPT and specific IgE *in vitro* tests. Weidinger et al [2], in turn, reported an anaphylactic reaction to mizolastine in a patient with a positive SPT and oral challenge.

Our patient tolerated loratadine, an antihistamine from the piperidine group, and had a negative SPT to an antihistamine from a different group to diphenhydramine (ethanolamine), suggesting selective sensitization to diphenhydramine. This is discordant with the hypothesis of a malfunction of the histamine H1 receptor or nonimmunologic antihistamine intolerance, as has been suggested by other authors in very different clinical cases [3].

We highlight the rapid onset of symptoms and the small

dose of antihistamine necessary to trigger the reaction after reexposure, suggesting previous sensitization [4]. Diphenhydramine is clearly the offending drug, even though in vitro tests showed no evidence of the mechanism [5]. An oral challenge starting with a lower dose could have diminished the severity of the reaction [6].

The potentially life-threatening adverse event experienced by this patient should make us aware of the possibility, albeit small, of allergic reactions to such widely used drugs as antihistamines.

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Measurements of Fractional Exhaled Nitric Oxide With 2 Portable Electrochemical Sensors: A Comparative Study

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Key words: Agreement. Asthma. Fractional exhaled nitric oxide. Electrochemical sensor.

Palabras clave: Acuerdo. Asma. Fracción exhalada de óxido nítrico. Sensor electroquímico.

Fractional exhaled nitric oxide (FE_{NO}) is a marker that enables us to measure eosinophilic airway inflammation. It has potential applications in respiratory allergic diseases for diagnosis, selection of therapy, dose adjustment, and assessment of adherence to inhaled corticosteroids [1]. The emergence of new portable devices for clinical practice has simplified and lowered the costs of the measurements. Although numerous publications analyze clinical uses of FE_{NO}, few studies provide data on whether measurements performed with different devices authorized for clinical use are comparable [2]. The aim of this study was to compare the degree of agreement between FE_{NO} measurements made with 2 devices frequently used in Europe—the Niox Mino (Aerocrine, Lund, Sweden), which is the reference technique, and the NO Vario Analyzer (Filt, Berlin, Germany)—both of which are based on electrochemical sensors. Niox Mino performs well in comparison with the more accurate measurements provided by electrochemiluminescence. Both devices follow the recommendations of the American Thoracic Society/European Respiratory Society [3]. The measurement range is 5-300 ppb for the Niox Mino and 2-5000 ppb for the NO Vario, with an accuracy of 3 ppb or <10% for both instruments. According to the manufacturers, the accuracy of Niox Mino is ±5 ppb for values <50 ppb, ±10 ppb for values 50-100 ppb, and ±25 ppb for values >100 ppb, expressed as the difference ±1 SD between a Niox Mino measurement value and the corresponding value measured with the NIOX instrument from Aerocrine. According to independent investigators, accuracy is within the limits set by the manufacturer, although the readings are consistently higher [4,5].

Our study sample comprised 32 adults (15 healthy controls and 17 patients with respiratory allergy) with a mean age of 38 years (range, 17-63). The measurements were made according to the manufacturers' recommendations and in a random order, with an interval of 2 minutes between readings. In addition to the descriptive statistical analysis and correlation between measurements, we analyzed agreement between the 2 devices using a Bland-Altman test [6].

The mean (SD) FE_{NO} measurement was 21.8 (12.4) ppb for Niox Mino and 22.11 (11.3) ppb for NO Vario; the correlation between the 2 devices was excellent (r=0.971, P<.000). The

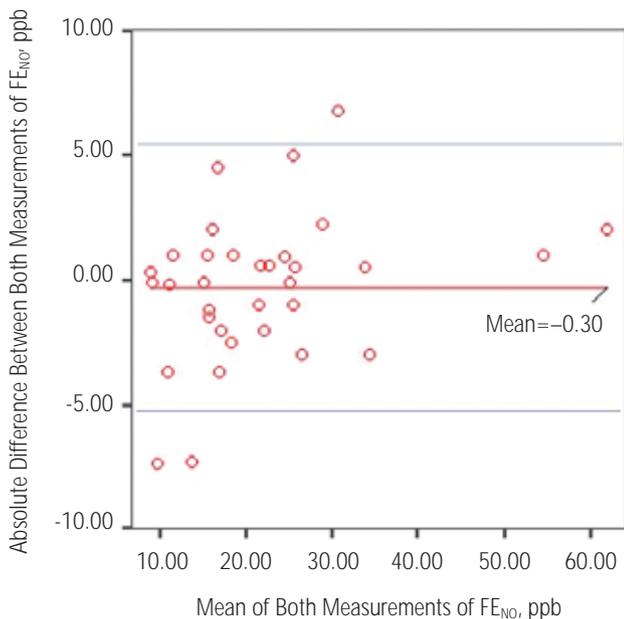


Figure. Analysis of agreement between the 2 measurements.

measurements ranged from 6 ppb to 63 ppb. Agreement was excellent between both measurements, with an average difference of -0.30 ppb (range, -7.4 to 6.80), as shown in the Figure. These differences followed a random distribution and were not correlated with FE_{NO} levels.

We found the degree of agreement between the measurements made with both devices in control subjects to be excellent. However, this agreement should be verified in asthmatic subjects with higher levels of FE_{NO} .

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Hypersensitivity to Pollen Panallergens (Profilin and Polcalcin) Detected In Vitro and In Vivo: a Comparative Analysis

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Key words: Profilin. Calcium-binding protein. Allergens. Pollen.

Palabras clave: Profilina. Proteína de unión a calcio. Alérgenos. Polen.

Profilin and polcalcin are plant panallergens. Profilin can cause cross-reactivity between pollen and vegetable foods [1,2]; polcalcins are cross-reacting pollen allergens [3,4]. Polcalcin and profilin hypersensitivity affects between 10% and 30% of pollen-allergic patients [5]; sensitized individuals react to several botanically unrelated sources. Recombinant profilins and polcalcins are now available for routine in vitro diagnosis of allergy, and profilin- and polcalcin-enriched natural pollen extracts for skin prick tests (SPT) have recently been produced. This study compared in vivo and in vitro tests for profilin and polcalcin.

We studied 59 patients (age, 12-72 years) with seasonal respiratory symptoms and positive SPT results to more than 4 extracts from among the following: grass, mugwort, ragweed, pellitory, plantain, birch, olive (50 000 SBU/mL; Allergopharma, Reinbeck, Germany), *Platanus*, and cypress (30 HEP; ALK-Abelló, Madrid, Spain). Fifty-seven and 48 were assessed for profilin and polcalcin hypersensitivity, respectively, both by SPT (ALK-Abelló, see below) and in vitro (measuring immunoglobulin [Ig] E to grass profilin or polcalcin, Phl p 12 and Phl p 7).

To prepare profilin-enriched SPT, Pho d 2 was purified from date palm pollen using affinity chromatography [5]; purity was checked using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS PAGE), mass spectrometry, and amino acid analysis. The final concentration of Pho d 2 was adjusted to 50 $\mu\text{g/mL}$. Polcalcin-enriched SPT was obtained from the same extract after Pho d 2 purification. Protein identity was assessed using SDS-PAGE. The final concentration of polcalcin was 1 $\mu\text{g/mL}$ by inhibition assay using the ADVIA-Centaur

platform (Siemens Healthcare Systems, Madrid, Spain). IgE was measured using FEIA ImmunoCAP (Phadia, Uppsala, Sweden); levels greater than 0.35 kU_A/L were considered positive.

Altogether, 50/57 (88%) patients were profilin reactors. The results of in vivo and in vitro tests were consistent

Table. In Vivo and In Vitro Findings in Patients Showing Discrepancies Between Skin Prick Test and CAP

No.	IgE ^a to Phl p 12	Profilin SPT ^b	IgE to Phl p 7	Polcalcin SPT
2	1.95	0		
3	0.05	4	0.07	3
5			0.08	4
8	0.17	4		
13	0	3		
40	0.22	4		
44	0.22	4		
49	0.35	4		
51	0	3		
52			0	3
59	0.46	0		

Abbreviations: Ig, immunoglobulin; SPT, skin prick test.

^aIgE levels are expressed in kU_A/L (negative if <0.35)

^bSkin reactivity to purified date palm profilin and polcalcin is expressed as a function of the SPT induced by a positive control (histamine 10 mg/mL): 0, SPT negative; 2, mean diameter of the wheal at least half that of the control wheal; 3, equivalent to the diameter of the control wheal; 4, mean diameter of the wheal exceeding that of the control wheal.

in 48/57 (84%) cases: negative in 7 patients and positive in 41 patients. In 9 patients, the results were discordant (Table): 7 patients were SPT+/ImmunoCAP-, whereas 2 were SPT-/ImmunoCAP+. Polcalcin hypersensitivity was detected in 15/48 (31%) patients. The results of in vivo and in vitro tests were consistent in 45/48 patients (94%): negative in 33 cases, positive in 12. In 3 patients, the tests produced discordant results (Table); all 3 were SPT+/ImmunoCAP-. SPT specificity was checked by testing with 100 single-pollen reactors (44, grass, 33, ragweed, 16 birch, 4 pellitory, 3 cypress) and 30 patients with chronic urticaria but no respiratory allergy with both extracts; no positive SPT was recorded. The specificity of in vitro tests was checked using sera from 30 single-pollen reactors (10 grass, 10 ragweed, 6 birch, 2 cypress, and 2 pellitory); no positive results were recorded. Thus, the sensitivity of SPT and ImmunoCAP was, respectively, 96% (48/50) and 86% (43/50) for profilin and 100% (15/15) and 80% (12/15) for polcalcin. These differences were not statistically significant.

This study confirms that SPT with natural extracts enriched in pollen panallergens are useful diagnostic tools for the allergologist [6]. They are less expensive and time-consuming than in vitro assays and produce results within minutes in the office. When negative, they detect cosensitization to different pollen sources; when positive, they detect corecognition of cross-reacting allergens and prompt in vitro investigations. Although the number of polcalcin reactors (n=15) was too low to draw definitive conclusions, it seems that the sensitivity of these SPT may slightly be even superior (though not significantly) to ImmunoCAP; in fact, although reactivity to specific date pollen allergens cannot be ruled out, no control patients reacted to the

extracts, suggesting that SPT+/ImmunoCAP- patients were sensitized to 1 of the 2 panallergens. We could speculate that some patients reacted to isoforms other than those present in the rPhl p 7 and rPhl p 12 used in ImmunoCAP. Furthermore, recombinant profilins from different sources may show significant differences in sensitivity [7].

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Immediate Type 1 Hypersensitivity to Apomorphine: A Case Report

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Key words: Apomorphine. Hypersensitivity. Parkinson disease.

Palabras clave: Apomorfin. Hipersensibilidad. Enfermedad de Parkinson.

Injectable apomorphine is commonly used as rescue therapy for intractable off periods in Parkinson disease [1]. It is administered as an intermittent subcutaneous rescue injection to reverse drug-refractory off periods and as a continuous diurnal subcutaneous apomorphine infusion [2], which typically provides a clinical benefit within 10 minutes [1]

A 56-year-old man experienced episodes of raised itchy wheals on the underarms, groin, chest, lower back, and buttocks approximately 20-25 minutes after subcutaneous administration of 4-6 mg apomorphine (Figure). The symptoms disappeared 30 minutes later with no residual lesions when the effects of the drug had worn off. The patient showed no clinical signs of mastocytosis, either as a result of massive release of mast cell mediators following chronic release of mast cells or as a result of tissue infiltration. He had no history of idiopathic or nonsteroidal anti-inflammatory drug (NSAID)-related anaphylactic reactions or life-threatening vascular collapse, and NSAIDs (eg, ibuprofen, aspirin) to treat a herniated disc were well tolerated. Apart from the medication prescribed for Parkinson disease and occasional NSAIDs (metamizole), all of which he tolerated well, the patient was taking no antihypertensive medication (angiotensin-converting enzyme inhibitors, β -blockers, or angiotensin receptor blockers). On one occasion he was prescribed tramadol. Although ingestion of morphine and opioid derivatives can produce nonspecific release of mast cell mediators, no such release of histamine occurred in our patient following ingestion of tramadol. Skin prick test (SPT) responses were negative with aeroallergens and foods. SPT with apomorphine 10 mg/mL and intradermal tests with diluted apomorphine at concentrations of 1:1000 and 1:100 were also negative. An intradermal test at a dilution of 1:10 resulted in a 6-mm papule in our patient and a negative response in 14 control subjects. Patch testing on our patient with apomorphine 10 mg/mL diluted in water to 0%, 0.05%, and 1% was negative at 48 hours and 96 hours. A single-



Figure. Raised wheals on underarms, groin, chest, sacrum, and buttocks.

blind placebo-controlled provocation test with subcutaneous apomorphine 10 mg/mL produced a positive response after approximately 20 minutes, with scattered papules measuring 4 to 5 cm in diameter and erythematous lesions on the lower back, buttocks, chest, underarm, and penis, which disappeared 30 minutes later. As the commercial preparation of apomorphine contains 0.093% sodium bisulphite, a known trigger for contact dermatitis, our patient underwent a double-blind placebo-controlled trial with sodium metabisulphite in 50 mg, 100 mg, and 150 mg doses; the results were negative. Our findings for total immunoglobulin (Ig) E and specific IgE values (Hytec, Hycor Biomedical Ltd, Penicuik, UK) were not significant.

Adverse skin reactions to apomorphine have been described in less than 1% of patients [3]. Sodium metabisulphite has been identified as a cause of contact dermatitis [4] and of allergic reactions. In our study, SPTs with aeroallergens and the sodium metabisulphite provocation test produced negative responses. The positive response by our patient to the single-blind placebo-controlled provocation test with apomorphine 10 mg/mL suggests an IgE-mediated mechanism that we are unable to contrast with others due to the paucity of related studies in the literature. To our knowledge, this is the first report of a type I hypersensitivity reaction to apomorphine.

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Identification of Allergens in Chicken Meat Allergy

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Key words: Allergy. Chicken meat. MLC. Myosin. Parvalbumin.

Palabras clave: Alergia. Carne de pollo. CLM. Miosina. Parvalbúmina.

Chicken meat is widely consumed. Most cases of chicken meat allergy are associated with hypersensitivity to egg and/or feather, thus prompting the so-called bird-egg syndrome, with α -livetin (Gal d 5) as the most frequent cross-reacting protein [1]. Few cases of chicken meat allergy without egg hypersensitivity have been published, and its profile of allergen sensitization has seldom been investigated [2,3], although α -parvalbumin was recently identified as the allergen implicated in a case of poultry meat allergy [4].

A 20-year-old man experienced oropharyngeal and palmar itching, facial hives, lip swelling, dysphagia, dyspnea, and heartburn 15 minutes after eating chicken. He tolerated turkey, but did not eat any other poultry meat or meats such as veal, pork, and rabbit. He tolerated eggs and had no contact with birds.

Skin prick tests (SPT) to commercial meat extracts, egg proteins, and a feather mix extract were performed. Prick-by-prick tests were also carried out with raw and boiled poultry meats (Table). Protein extracts from raw and boiled chicken, turkey, duck, quail, and ostrich meat were prepared following a standard protocol (homogenization in phosphate-buffer-saline, dialyzation, and lyophilization) and administered as SPTs (Table). The results of serum specific immunoglobulin (Ig) E against the commercial meat extracts (Phadia CAPsystem) and

Table. Results of Skin Test and Specific Immunoglobulin E Determinations

	Skin Tests			Specific IgE	
	Commercial SPT	Prick-by-Prick	Extract SPT, 10 mg/mL	Phadia CAP system, KU _A /L	EAST technique, KU _A /L
Chicken	0	NP	NP	<0.35	NP
Veal	0	NP	NP	<0.35	NP
Pork	0	NP	NP	<0.35	NP
Lamb	0	NP	NP	<0.35	NP
Chicken, raw	NP	4	4	NP	<0.35
Chicken, boiled	NP	3	5	NP	0.6
Turkey, raw	NP	4	5	NP	<0.35
Turkey, boiled	NP	7	11	NP	0.6
Duck, raw	NP	5	7	NP	<0.35
Duck, boiled	NP	5	5	NP	0.4
Quail, raw	NP	0	8	NP	<0.35
Quail, boiled	NP	3	9	NP	0.6
Ostrich, raw	NP	NP	4	NP	<0.35
Ostrich, boiled	NP	NP	4	NP	0.4
White	0	NP	0	<0.35	<0.35
Yolk	0	NP	0	<0.35	<0.35
Ovoalbumin	0	NP	NP	<0.35	NP
Ovomucoid	0	NP	NP	<0.35	NP
Chicken feathers	0	NP	NP	<0.35	<0.35
Histamine	6				
Saline solution	0				
Total IgE				36.2 IU/mL	

Abbreviations: Ig, immunoglobulin; NP, not performed; SPT, skin prick test.

sIgE determinations against the poultry meat extracts prepared (EAST technique) are shown in the Table. The patient declined an oral challenge test with duck, quail, and ostrich.

Potential allergenic components of all these extracts were detected by IgE-immunodetection after separation using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) [5]. SDS-PAGE IgE immunoblotting assays were carried out and revealed reactivity to bands of 16 and 27 kDa in boiled chicken extract, 16 and 28 kDa in boiled duck extract, and 16 kDa in boiled turkey extract (data not shown). Complete inhibition of the IgE-binding bands in boiled extracts of duck and turkey was observed when these were preincubated with boiled chicken extract (data not shown). To identify these IgE-binding proteins, the 16- and 27-kDa bands from the boiled chicken extract were manually excised, digested with trypsin, and analyzed by mass spectrometry in tandem (MS/MS) [5]. Proteins were identified using a nonredundant protein sequence database (National Center for Biotechnology Information). The analysis of the resulting peptides by mass spectrometry or MS/MS identified the 16-kDa band as α -parvalbumin and the 27-kDa band as myosin light chain 1 (MLC).

α -Parvalbumin is abundant in the muscle of fish and amphibians, rather less so in birds and mammals, and is not generally described as allergenic, except for a case of allergy to frog meat [6] and a case of allergy to poultry meat [4]. β -Parvalbumin, which does not usually cross-react with α -parvalbumin [7], has been described as a major allergen and as the most important allergen in many fish species. Parvalbumins are believed to be potent food allergens due to their thermal stability and resistance to digestion [7]. Myosins are a large superfamily of motor proteins that move along

actin filaments while hydrolyzing adenosine triphosphate. Two light chains of muscle myosin, each measuring 20 kDa, wrap around the neck region of the 2 myosin heavy chains [8]. Although shrimp MLC (Lit v 3) has been identified as a new major shrimp allergen [8], MLC has never been described as an allergen in chicken meat.

We present a patient with IgE-mediated allergy to chicken meat and no sensitization to egg proteins. α -Parvalbumin and myosin were identified as the relevant allergens. IgE binding to these proteins has also been identified in turkey and duck meat. This is the first report of MLC as a potential allergen in a case of chicken meat allergy.

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Effect of Alcohol Consumption and Cessation on Serum Total Immunoglobulin E Concentrations

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Key words: IgE. Alcohol. T_H2

Palabras clave: IgE. Alcohol. T_H2

Alcohol consumption influences many aspects of immunity [1], including a shift towards type 2 helper T cell (T_H2) responses [1,2]. Observational evidence in humans indicates that alcohol consumption, particularly heavy consumption, is associated with increased serum total immunoglobulin (Ig) E concentrations [3,4]. However, confounding factors hamper the inference of causation in observational studies. Alcohol consumption is associated with a number of factors (age, gender, smoking, nutrition, infection, and liver disease) that affect IgE concentrations. Although the effect of alcohol seems independent of these factors [4], additional uncontrolled confounders may exist. Temporal ambiguity is a drawback of cross-sectional studies showing an association between alcohol consumption and serum IgE [4]. Additional evidence for causality includes the reversibility of the effect if the potential cause is removed. The present study investigated the effect of alcohol consumption and the short-term effect of cessation of consumption on serum total IgE concentrations.

The cohort comprised 270 individuals (age, 27-83 years; 64% men) attending a thermal spa in northern Portugal that is officially recognized as complementary therapy for hepatobiliary and metabolic diseases [5]. During a standard 14-day stay, individuals follow a supervised diet, drink local mineral waters, and voluntarily abstain from alcohol consumption. Blood samples were provided by all participants on admission and by 211 individuals at the end of the stay. Alcohol consumption was recorded as the number of standard drinking units consumed weekly (glasses of wine, beers, and spirits, each containing about 10 g of alcohol). Occasional alcohol consumers (<1 unit/week) and abstainers were grouped together; regular alcohol consumers were classified as light-to-moderate drinkers (1-28 units/week) or heavy drinkers (>28 units/week) and were grouped separately. Determinations included serum total IgE (Immulite, Siemens, UK) and γ -glutamyltransferase (GGT, Olympus Analyzer, Olympus, Germany), a marker of alcohol consumption. Written consent was obtained from all participants.

Serum IgE concentrations were higher in heavy and light-to-moderate drinkers than in occasional drinkers/abstainers ($P=.01$ and $P<.001$, respectively; Mann-Whitney test)

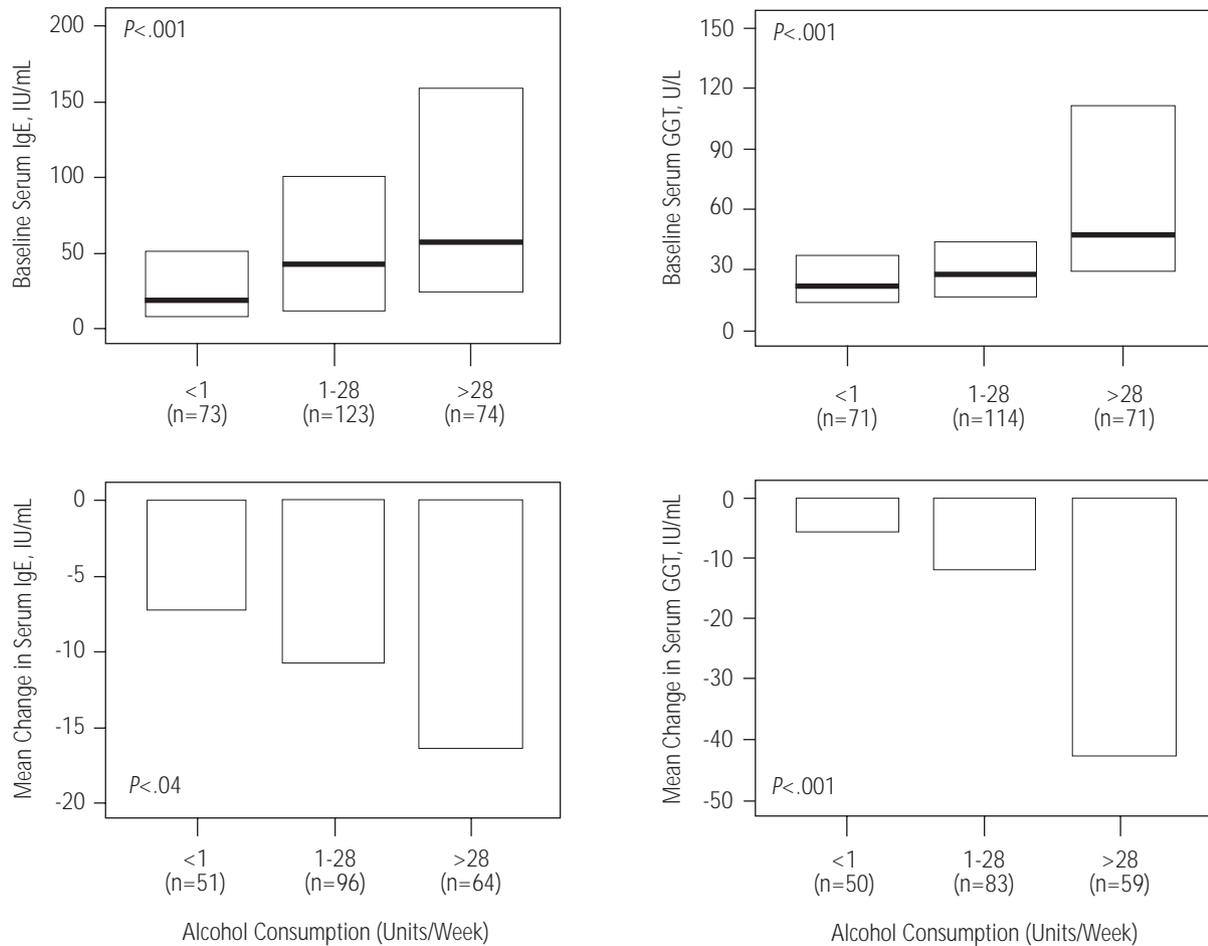


Figure. Upper panels, Baseline serum concentrations of serum total IgE and GGT in relation to alcohol consumption. Bars represent the interquartile range; horizontal lines represent the median. Lower panels, Mean change in serum concentration of IgE and GGT after 14 days' cessation of alcohol consumption in the corresponding groups. *P* values were obtained after comparison of the 3 groups using the Jonckheere-Terpstra test for trend. GGT indicates γ -glutamyltransferase; Ig, immunoglobulin.

(Figure). Multivariate analysis (linear regression) revealed alcohol consumption (in units/week) to be positively associated with IgE concentrations after adjusting for age, gender, and smoking ($P=.001$, data not shown). Serum IgE concentrations tended to decrease after 14 days in parallel with baseline alcohol consumption (Figure). The decrease in serum IgE after cessation of alcohol consumption was statistically significant in light-to-moderate drinkers and in heavy drinkers ($P<.001$ in both cases, Wilcoxon test). Variations in serum IgE paralleled those of serum GGT (Figure).

These results support the notion that alcohol consumption increases serum total IgE levels. According to the classic criteria for causality, there is experimental evidence in animals [2], consistency among studies, strength of association, a dose-response effect, independence of confounders [4], and a trend toward reversal shortly after elimination of the cause, as shown here. The short half-life of serum IgE [6] allows changes to be observed over a short period. A similar trend has been reported in small samples of alcoholics admitted to the hospital [3,4], but not in drinkers from the general population. Furthermore,

the association between alcohol consumption and high IgE levels has biological plausibility. Alcohol consumption induces changes in cytokine balance with increased production of T_H2 cytokines, which correlates with elevated IgE levels in alcoholics [4] and in animal models [2]. Some of these effects could be mediated by intestinal absorption of endotoxin [7]. For unknown reasons, drinkers are specifically at risk of sensitization to cross-reactive carbohydrates [8,9].

In summary, regular alcohol consumption (even light-to-moderate drinking) is associated with increased serum total IgE concentrations, which tend to normalize shortly after abstinence. Alcohol consumption should be considered when interpreting total serum IgE levels.

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