

described elsewhere.⁵ During the OPT, an anaphylaxis occurred at a cumulative dose of 36.1 mg celecoxib (actual doses administered were 0.1, 1, 10, and 25 mg over a 3-hour period) with generalized pruritus, rhinoconjunctivitis, and gastrointestinal pain, rapidly followed by tachycardia (heart rate, 148 bpm) and a drop of 65 mm Hg in systolic blood pressure. The shock subsided after 2 consecutive intramuscular injections of 0.25 mg epinephrine together with 100 mg intravenous methylprednisolone and 5 mg dexchlorpheniramine.

Six weeks later, a second OPT was performed with rofecoxib to find an alternative treatment to celecoxib. No symptoms occurred after the full therapeutic dose administration. Because of the sulfonamide structure of celecoxib,³ we performed a third OPT with cotrimoxazole (sulfamethoxazole + trimethoprim). There was no reaction.

Cases of anaphylaxis to celecoxib have been described^{1-4,6,7} but appear to be rare. Indeed, a recent postmarketing surveillance study was undertaken in England,⁶ and only 2 episodes of anaphylaxis have been reported in a cohort of 17,458 patients (0.01%). Drug responsibility was proven by OPT in 1 case only² and by clinical history in the other cases.^{1,3,4,6} In another case,⁷ a patient with 3 episodes of anaphylaxis to diclofenac underwent an in-hospital open challenge to rofecoxib. This patient experienced an isolated drop in blood pressure 40 minutes later, which was more likely a vasovagal reaction.⁸ Allergic mechanisms were proven by using lymphocyte transformation tests in 2 cases,^{2,4} but apparently not IgE-mediated, as demonstrated by negative skin tests results^{2,4} (including our case) and ELISA.¹ Cross-reactions between sulfonamides and the sulfur moiety of celecoxib have been suggested in 1 case⁴ but this seems to be an independent and coincidental sensitization to the 2 drugs. Our case report excludes cross-reactions between celecoxib and sulfamethoxazole and also between celecoxib and rofecoxib. Therefore, it underlines the importance of a thorough drug allergy work-up, allowing the reintroduction of other coxibs.

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Exploration des Allergies

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IgE-mediated asthma associated with a unique allergen from Angelim pedra (*Hymenolobium petraeum*) wood

To the Editor:

Angelim pedra (*Hymenolobium petraeum*) is a tree found in the Amazon basin belonging to the Fabaceae family and is harvested for its timber. It can grow as tall as 60 m, and its wood is used in construction, furniture, and carpentry.¹

Exposure to sawdust from a variety of woods has been shown to cause occupational asthma and contact urticaria, according to published scientific reports.^{2,3}

The following is a description of a case of occupational asthma caused by Angelim pedra in a 38-year-old male carpenter who was asymptomatic when harvesting Angelim pedra wood in Brazil for 20 years. He has lived in Spain since 1998. In 2000, he began to have cough, rhinorrhea, wheezing, dyspnea, and ocular itching within a few minutes of each new exposure on initiating new work with this imported wood in Spain in 1999. He reported no symptoms with other woods.

Skin prick tests were performed by using the extracts of a variety of wood sawdust (iroko, mansonia, oak, cedar, pine, teak, obeche), which were extracted (10% wt/vol) in PBS and shaken for 24 hours at room temperature. The suspension was centrifuged at 8000 rpm for 30 minutes, the pellet was discarded, and the remaining solution was filtered through a 0.22- μ m pore size membrane. All skin tests with extracts of various kinds of woods were tested in 3 atopic and nonatopic unexposed carpenters.

Nonspecific bronchial challenge testing with methacholine was performed 24 hours before bronchial challenge with Angelim pedra wood. Bronchial challenge with Angelim pedra sawdust was performed in a 3-m³ challenge chamber. The wood dust aerosol was generated by asking the patients to tip the wood dust from 1 tray to another for increasing periods (1, 5, 15 minutes) as previously described.⁴ The concentrations of total dust particles during the challenges were measured. A maximum concentration of 2.5 mg/m³ was not exceeded. The patients wore protective clothing and vinyl gloves during the challenge. On a control day, the subject was challenged with formaldehyde to ensure that fluctuations of FEV₁ were <10% and to exclude a sensitization to formaldehyde. Bronchial challenge with formaldehyde

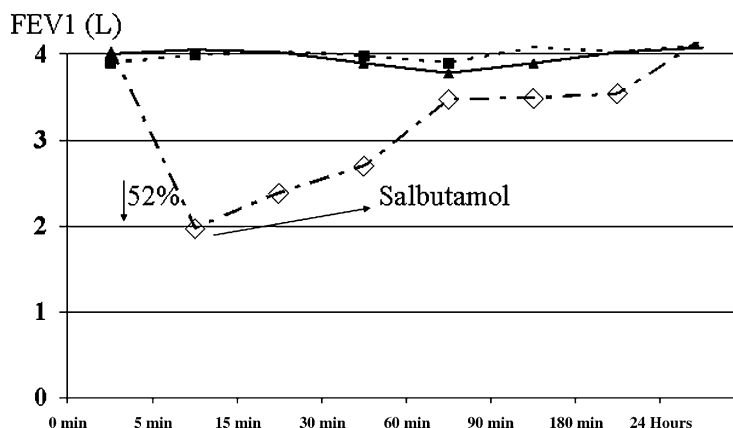


FIG 1. Bronchoprovocation with Angelim pedra wood (◇), chestnut wood (■), and formaldehyde (▲).

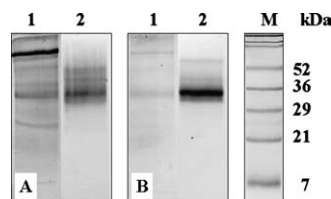


FIG 2. Ethanol fractionation of Angelim pedra extract. **A**, Pellet obtained after a 50% to 90% ethanol fractionation. **B**, Pellet obtained in a citrate-phosphate buffer (pH 4) and 50% ethanol. Lanes 1, SDS-PAGE. Lanes 2, Immunoblotting with the serum of the patient. **M**, Standards.

was performed in a 3-m³ challenge chamber to clean air containing formaldehyde vapor at levels of 0.2 mg/m³. The patient was exposed for 15 minutes. Bronchial challenge with Angelim pedra sawdust was tested in an atopic unexposed carpenter.

In vitro tests were performed by using a different extract: 1 g Angelim pedra sawdust was mixed with 20 mL PBS and shaken for 24 hours at room temperature. The mixture was centrifuged for 15 minutes at 4500g, and the pellet was discarded. The supernatant was subjected to ethanol fractionation. Ten milliliters of the supernatant was mixed with an equal amount of absolute ethanol and left for 30 minutes at room temperature (50% vol/vol). Thereafter, the mixture was centrifuged as described, and the pellet was discarded. The supernatant was remixed with 80 mL absolute ethanol (90% final ethanol concentration). After 30 minutes, the mixture was centrifuged, and the pellet obtained was resuspended in 0.5 mL PBS (20× concentration). For a further purification, the extract obtained was mixed with different amounts of 0.1 mol/L citric acid and 0.2 mol/L disodium hydrogen phosphate, obtaining different pHs between 3 and 8, and equal amounts of absolute ethanol (50% vol/vol). After centrifugation, the resulting pellets were resuspended in a solution of 1/5 of their volume in a sample buffer and boiled for 5 minutes for SDS-PAGE and blot analyses.

SDS-PAGE was performed in 16% polyacrylamide minigels and stained with Coomassie Brilliant Blue (Bio-Rad Laboratories, Hercules, Calif). Immunoblotting was performed after an overnight transfer to nitrocellulose by using a diffusion method followed by an incubation step of 30 minutes in 3% Nonidet P-40. Nitrocellulose was also incubated in serum of the patient. Bound IgE was detected by using a monoclonal anti-IgE (Ingenasa, Madrid, Spain) at a 1/1000 dilution for 3 hours and an alkaline phosphatase-labeled goat antimouse antibody (Biosource International, Camarillo, Calif) at a 1/4000 dilution for 1 hour, as previously described in depth.⁵ Purified protein was transferred to a Sequi-Blot polyvinylidene difluoride membrane (Bio-Rad Laboratories), and N-terminal amino acid sequence was determined by Edman degradation performed at Proteomics Laboratory (Centro Nacional de Biotecnología, Universidad Autónoma, Madrid, Spain).

Skin prick tests were positive only to the Angelim pedra wood extract. Nonspecific bronchial challenge testing with methacholine revealed bronchial hyperresponsiveness with a PC₂₀ value of 2.6 mg/mL. Bronchial challenge with Angelim pedra wood demonstrated immediate type response, as shown in Fig 1. Skin tests results were all negative in 3 atopic and nonatopic unexposed carpenters. Bronchial challenge with Angelim pedra sawdust was negative in the control subject with asthma.

One allergen with an estimated molecular weight of 35 kd was detected after ethanol fractionation of an Angelim pedra sawdust extract. Lane B2 of Fig 2 shows the allergenic activity of the protein purified and concentrated at pH 4. After SDS-PAGE, this band of protein was transferred to a polyvinylidene difluoride membrane and excised, and finally, the N-terminal amino acid sequence of the 10 final residues was determined. No homologies to other known proteins were found in the FASTA and SWISS-PROT databases.^{6,7}

The immunologic studies performed suggest that the pathogenic mechanism responsible for the development of respiratory symptoms in this worker who inhales Angelim

pedra dust is IgE-mediated. This is the first case of occupational asthma by Angelim pedra reported and the first wood allergen in which the N-terminal amino acid composition is known.

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SPINK5 polymorphism is associated with disease severity and food allergy in children with atopic dermatitis

To the Editor:

Serine protease inhibitor Karzal type 5 (SPINK5) is a protease inhibitor protein and is encoded by the gene *SPINK5*.¹ Several mutations in the *SPINK5* gene can cause Netherton syndrome, a rare autosomal recessive disorder characterized by defective cornification of the skin and T_H2-skewed immunologic alterations resembling atopic dermatitis (AD).² SPINK5 regulates proteolysis in epithelia formation and keratinocyte terminal differentiation, and its defects lead to overdesquamation of corneocytes and skin barrier dysfunction.³ SPINK5 is also expressed in the thymus, and its defects have been suggested to cause abnormal maturation of T lymphocytes and lead to T_H2 responses, such as increased IgE levels and eosinophilia.²

Walley et al⁴ recently reported an association between AD and the G1258A (Glu420Lys) polymorphism in *SPINK5* in a white population, thus establishing a link between a rare and a common skin disease. Thereafter, the association of this polymorphism with AD in 2 independent Japanese populations^{5,6} and with bronchial asthma (BA) in a German population⁷ has been reported. However, there have been no reports as to whether the single nucleotide polymorphism (SNP) is associated with the severity of AD. We therefore aimed to determine the association of the G1258A (Glu420Lys) polymorphism in *SPINK5* with AD severity and other allergic diseases in children with AD.

Japanese children more than 5 years of age with AD (n = 118), whose symptoms started in infancy and who are still being followed up at our clinic, were enrolled in the study. The diagnosis of AD was made according to the criteria set out by Haniffin and Rajka.⁸ After written informed consent was obtained, blood was collected for serum IgE measurement, eosinophil counts, CAP-RAST score of 10 selected allergens, and DNA extraction to genotype the study population for the G1258A (Glu420Lys) polymorphism in *SPINK5*, as described elsewhere.⁴ The study was approved by the ethics committee of the Graduate School of Kyoto University. The severity of AD (mild, moderate, severe, or most severe) was determined on the basis of the guidelines established by the Study Group founded by the Japanese Ministry of Health, Labour, and Welfare. The prevalence and severity of BA was determined on the basis of the guidelines established by the Japanese Society of Pediatric Allergy and Clinical Immunology. The details of the severity determination of both AD and BA can be provided on request. Food allergy was defined as an episode of immediate allergic reaction (skin, oral, respiratory, and/or gastrointestinal symptoms) within 1 hour after eating at least one causative food, which was confirmed on the basis of positive CAP-RAST results.

Genomic frequencies of the *SPINK5*/1258 polymorphism site were 41 (34.7%) for AA, 51 (43.2%) for AG, and 26 (22.0%) for GG. Distribution of age, IgE level, eosinophil count, and number of CAP-RAST-positive allergens did not differ significantly among genotypes (data not shown).

A comparison of the distributions of mild-to-moderate and severe to most severe cases indicates that both the AA and AG groups showed significantly higher rates of more than severe cases (Table I; odds ratio, 95% CI, and *P* values of 4.00, 1.26-12.65, and .02 for AA and 3.45, 1.13-10.58, and 0.03 for AG, respectively) than did the GG group. When the distributions of mild-to-severe cases and most severe cases were compared, the AA group proved to have significantly higher rates of most severe cases (Table II; odds ratio, 95% CI, and *P* value of 6.22, 1.28-30.2, and .02, respectively) than did the GG group. These data clearly show that the polymorphism is associated not only with disease occurrence but also with disease severity in children with AD. It has been well established that AD is a multifactorial disease and that not only its atopic status