Chronic Desensitization to Quinolones in Fixed Drug Eruption

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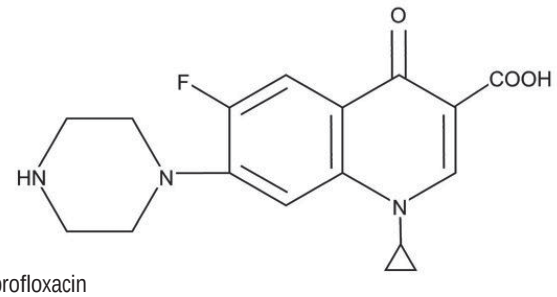
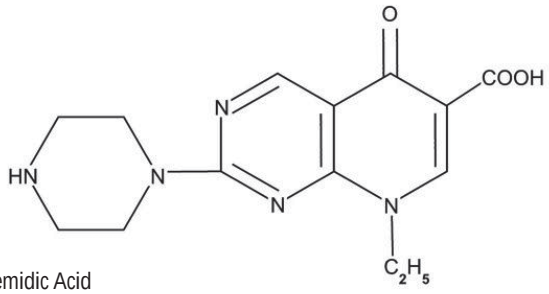
Palabras clave: Exantema fijo medicamentoso. Desensibilización crónica. Alergia a quinolonas. Alergia a ciprofloxacino.



Ciprofloxacin



Pipemidic Acid

Figure. Chemical structure of ciprofloxacin and pipemidic acid.

Successful desensitization protocols have been reported in patients with fixed drug eruption (FDE) [1-3]. In chronic diseases, it would be desirable to sustain the tolerance achieved after desensitization. Maintained tolerance has been reported in immunoglobulin (Ig) E–mediated hypersensitivity reactions [4,5], but not in FDE.

We report the case of a 28-year-old female with cystic fibrosis who developed several erythematous plaques on both hands while being treated with ciprofloxacin 10 years previously. In order to offer the patient an alternative drug, we performed a gradual dose challenge with levofloxacin. Two hours after receiving the full dose (500 mg), the lesions reappeared at the same sites, confirming the diagnosis of FDE and cross-reactivity between the 2 drugs.

Ciprofloxacin was the first choice for her disease, so we proposed a slow desensitization regimen, as described elsewhere with cotrimoxazole in FDE [3]. She could not delay administration of ciprofloxacin for long and agreed to receive progressive oral doses of ciprofloxacin over a period of 3 days 4 months after the positive challenge test with levofloxacin. On the second day, the lesions reappeared on her hands but she decided to continue with administration and received 750 mg twice daily until she completed a 21-day course. Her condition worsened initially, with intense itching and desquamation of the plaques. The lesions improved after 14 days and disappeared before concluding treatment with ciprofloxacin.

She was then treated with daily doses of pipemidic acid, a first-generation quinolone. After 6 months of maintenance therapy with this agent, a new therapeutic course of ciprofloxacin was administered. Mild nonpruritic lesions that vanished in only 24 hours without desquamation reappeared at the same sites. The patient has been receiving a twice-daily maintenance dose of 400 mg of pipemidic acid since then and, for the last 2 years, she has been able to tolerate several subsequent courses of ciprofloxacin, approximately every 2 months, with very few or no lesions after each course of therapy.

We aimed to maintain indefinitely the tolerance she had acquired after a full therapeutic course of ciprofloxacin with a daily dose of pipemidic acid, based on supposed cross-reactivity between these 2 quinolones. Cross-reactivity between quinolones has been widely reported [6-8]. Ciprofloxacin and pipemidic acid share a very similar structure (Figure), although pipemidic acid is not active against *Pseudomonas* species and has low tissue penetration. Cross-reactivity between levofloxacin and ciprofloxacin was demonstrated in this patient. The clinical course did not allow us to study cross-reactivity with other quinolones or to perform patch tests at the affected and unaffected sites before starting treatment with pipemidic acid.

Although a refractory period of days [9], weeks, or months [10] has been described in FDE, this does not explain how the patient tolerated ciprofloxacin, as the time between the courses of therapy was quite long (6 months between the first 2 courses) and longer than the interval between the challenge test with levofloxacin and the first therapeutic course with ciprofloxacin, both of which triggered severe lesions.

In conclusion, our case report demonstrates that desensitization to ciprofloxacin can be achieved in FDE and suggests that maintenance therapy with a similar compound may induce long-term tolerance that would allow the safe use of the drug in subsequent courses of therapy.

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The authors have no conflicts of interest to declare.

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Urticaria and Angioedema Due to Ingestion of Carob Gum: A Case Report

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Palabras clave: Goma garrofin. E-410. Semilla de algarroba. Urticaria. Alergia.

Carob bean gum (E410) is extracted from the seeds of the carob tree, *Ceratonia siliqua*, a member of the legume family. The gum is used as a thickening and gelling agent and as an egg substitute in food product manufacturing [1].

A 59-year-old woman who worked as a cook complained of nasal hydrorrhea and sneezing while handling powder to prepare crème caramel. A few minutes after ingesting this dessert, she developed urticaria and lip edema. She did not report symptoms with other foods, including nuts, or other legumes.

Skin prick tests (SPTs) with each component of the powder diluted in saline (corn starch, vanilla, carob gum, carrageenan, tartrazine, and yellow colorant) were positive for carob gum (11 mm).

SPTs with a panel of aeroallergens and food extracts were positive for almond, hazelnut, peanut, and lentil. SPTs with other thickenings, such as guar gum, gum Arabic, and tragacanth were all negative.

SPTs with carob gum at 25, 15, and 5 mg/mL induced wheals of 9, 8, and 6 mm, respectively. SPT were also positive for raw carob gum (14 mm), boiled carob gum (9 mm), and carob bean extract (20 mm).

Control SPTs with carob gum and carob bean extract were negative in 10 nonatopic individuals.

Serum specific immunoglobulin (Ig) E by enzyme allergosorbent test to carob gum, carob bean, and guar gum were 88.8 kU_A/L, >100 kU_A/L, and 1.7 kU_A/L, respectively. Using CAP (Pharmacia, Uppsala, Sweden), positive results were obtained with almond (1.4 kU_A/L), hazelnut (3 kU_A/L), peanut (18.7 kU_A/L), and lentil (6.4 kU_A/L).

Sodium dodecyl sulfate polyacrylamide gel electrophoresis immunoblotting according to the Laemmli procedure with carob gum (raw and cooked) revealed 2 high-molecular-mass IgE binding bands (>97 kDa), a series of bands from 45 to 30 kDa, and 2 bands of 29 and 25 kDa. Guar gum (raw and cooked) showed bands of 60, 55, and 40 kDa. Neither carob gum nor guar gum lost its IgE binding capacity after exposure to 2-mercaptoethanol. Carob bean extract showed an IgE binding area from 25 to 70 kDa, under reducing conditions (Figure).

We report a case of urticaria and angioedema after ingestion of crème caramel containing carob bean gum. Positive SPT

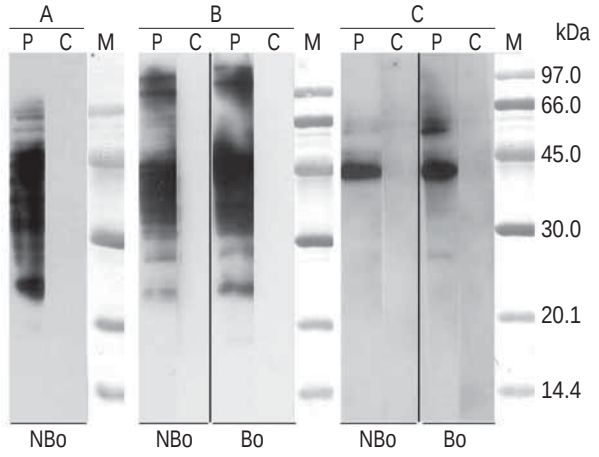

Figure. Results of sodium dodecyl sulfate polyacrylamide gel electrophoresis. A, Protein extract from carob been. B, Carob bean gum. C, Guar gum. Lane P, patient's serum; Lane C, control serum (pool from non atopic subject sera); Lane M, molecular mass marker. Bo indicates boiled; NBo, not boiled.

results, high titers of serum specific IgE to carob bean and carob gum demonstrate an IgE-mediated mechanism. Furthermore, IgE immunoblotting revealed a broad IgE binding area for carob gum in both raw and cooked forms.

Vegetable gums are known causes of IgE-mediated allergy. Because carob gum is extracted from a Leguminosae seed, some authors have suggested cross-reactivity with other legume-based gums (tragacanth, gum Arabic, and guar gum [1]) and protein extracts from legume seeds (soy bean [1] and peanut [2]). The results of testing with these vegetable gums were negative in our patient, except for guar gum (obtained from *Cyanopsis tetragonobus*), and positive for others such as peanut or lentil.

In a study of peanut-allergic individuals, Fiocchi et al [2] observed that heat processing of carob bean abolishes the IgE binding to carob bean proteins detected under native conditions. Therefore, peanut-allergic individuals could tolerate the cooked carob seed, but not the raw one. In our patient, in vivo and in vitro testing revealed no allergenic differences between raw and boiled gum samples. In spite of the positive prick tests obtained with other members of the Leguminosae family and various nuts, our patient tolerated ingestion of all of them.

Occupational asthma due to carob bean gum has been described in a jam factory worker [3] and an ice-cream manufacturer [4]. Our patient suffered rhinitis while handling the powder used to prepare crème caramel and subsequently developed urticaria upon ingestion. We only found one other case of ingestion-related urticaria in a patient who also experienced vomiting and flushing after taking an antiregurgitation formula [5].

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Occupational Asthma Caused by Acrylates in Optical Laboratory Technicians

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Key words: Acrylates. Occupational asthma. Rhinitis. Induced sputum.
Palabras clave: Acrilatos. Asma ocupacional. Rinitis. Esputo inducido.

Acrylates are well known causative agents of occupational rhinitis, asthma [1,2], and nonasthmatic eosinophilic bronchitis [3]. However, acrylates contained in eyeglass lenses have not been previously reported as an etiological agent of occupational asthma. We report 2 cases of optical laboratory technicians with work-related rhinitis and asthma symptoms.

A 54-year-old nonsmoking woman had worked as an optical laboratory technician for 23 years. Her job involved grinding and polishing eyeglasses made of polycarbonate and polymethyl methacrylate (PMM). During the last 2 years, she

began to experience nasal congestion, sneezing, persistent dry cough, dyspnea, and wheezing while at work and after her shift. Her symptoms developed upon exposure to the dust generated by grinding the lenses. She was placed on treatment with terbutaline as needed. These symptoms subsided markedly during vacations. Her respiratory symptoms had worsened progressively over the previous few months, and she required treatment for severe dyspnea and cough in the emergency department.

A chest X-ray showed no abnormalities. The results of skin prick tests with common aeroallergens were negative. Serial peak expiratory flow monitoring was consistent with occupational asthma. Pulmonary function tests showed normal spirometry values (forced vital capacity [FVC], 126% predicted; forced expiratory volume in the first second [FEV_1], 125%; FEV_1/FVC, 83%), and the methacholine challenge test was negative (up to 16 mg/mL) both at work and away from work. The fraction of exhaled nitric oxide (FE_{NO}) at baseline was 11 ppb. A specific inhalation challenge (SIC) was performed in a 7-m^3 challenge chamber (1) with PMM powder at a concentration of 0.3 mg/m^3 for 30 minutes, and an isolated late asthmatic reaction was observed (21% fall in FEV_1 7 h after the SIC). A second SIC was performed with PMM at a concentration of 2 mg/m^3 for 30 minutes, and, once again, a late asthmatic response was observed. The methacholine challenge test remained negative and FE_{NO} (15 ppb) did not change after the positive SIC. A sham exposure with polycarbonate dust caused no reaction. Induced sputum analysis [4,5] showed a significant increase in eosinophils at work (14%), and the count returned to normal values after 1 month of sick leave (2.5%), thus supporting the diagnosis of occupational asthma [6].

Three months after her sick leave she was totally symptom-free, and 6 months later she was on permanent occupational disability, remaining asymptomatic since then.

A 50-year-old nonatopic woman had worked in an optical laboratory for 34 years in the production of glass lenses. Organic lenses made of PMM were introduced in her workplace 15 years ago. In the last 10 years, she had experienced work-related respiratory symptoms consisting of nasal stuffiness, rhinorrhea, dry cough, and shortness of breath. The asthma symptoms had worsened over the last year. She was placed on treatment with salmeterol/fluticasone 50/500 µg twice daily. One year before consulting us she had had a severe asthma attack that was treated in the emergency department. She has been on sick leave since then. A chest X-ray was normal. Pulmonary function tests showed normal spirometry values (FVC, 101% predicted; FEV_1, 88%; FEV_1/FVC, 73%), and the methacholine challenge test was positive (PC_{20}, 0.7 mg/mL). Baseline FE_{NO} was 7 ppb. Induced sputum analysis could not be performed in this patient. An SIC performed with PMM powder at a concentration of 2 mg/m^3 for 30 minutes elicited rhinitis symptoms and a dual asthmatic reaction (18% fall in FEV_1 during the first hour, 25% drop in FEV_1 18 h after the challenge). FE_{NO} at 24 hours after the SIC was 6 ppb. No response was observed during sham exposure. She was removed from exposure and 2 months later was awarded long-term disability. After 6 months, her asthma symptoms had subsided and she needed salbutamol once or twice a week.

These patients developed occupational asthma and rhinitis caused by methacrylate contained in organic eyeglass lenses as confirmed by SIC. It is noteworthy that patient 1 had occupational asthma despite the fact that bronchial hyperresponsiveness to methacholine was absent both before and after the challenge. Although this finding is uncommon, it has previously been reported with several occupational agents, including cyanoacrylate [7]. The pathogenesis of occupational asthma caused by acrylates is not fully understood; however, it is considered to be due to an immunologic mechanism not mediated by immunoglobulin E [1].

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Bilateral Posterior Subcapsular Cataracts After Inhaled Budesonide for Asthma: Have Patients Been Given Their Medications Correctly?

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Key words: Budesonide. Cataract. Child. Inhaled corticosteroids.
Palabras clave: Budesonida. Catarata. Niño. Corticoides inhalados.

Inhaled corticosteroids are currently the most effective anti-inflammatory medication for the treatment of asthma. The use of these agents is a known risk factor for the development of posterior subcapsular cataracts (PSC) in adults [1]. However, several controlled clinical trials have demonstrated that inhaled corticosteroids did not increase the risk of cataracts in infants and children [2,3].

We report the case of a 4-year-old boy with asthma who was examined by an ophthalmologist due to white reflex of the left pupil and decreased visual activity. The complaint persisted for approximately 1 month. Slit-lamp biomicroscopy showed a mature cataract on the left eye and a posterior subcapsular cataract on the right eye. Intraocular pressure was normal (15 mmHg in the left eye and 16 mmHg in the right eye). The evaluation revealed that the patient had been receiving 1000 μg/d of nebulized budesonide solution (Astra Zeneca, Södertälje, Sweden) to cure recurrent wheezing and cough since 4 months of age. During the 2 years prior to admission, the drug was intermittently nebulized directly onto his face without a facemask. Systemic treatment with corticosteroids was required twice for exacerbations of asthma. In addition, intranasal mometasone furoate (Schering-Plough, Tuas West Drive, Singapore) was started in response to complaints of nasal congestion after 2 months of treatment.

The family and prenatal and neonatal histories were unremarkable. His mental and motor development was consistent with his age. We did not observe any pathologic evidence except bilateral cataracts and mucosal hyperemia and conchal hypertrophy of the nasal cavity. Plasma electrolyte levels, kidney and liver function test results, screening for inborn errors of metabolism, urinalysis for reducing substances, and serology testing for congenital infections were all negative. Cataract surgery was planned first for the left eye and then the right eye. Lens aspiration with a Simcoe cannula and intraocular lens implantation were performed under general anesthesia.

Several controlled studies have shown that inhaled corticosteroids do not cause cataracts. However, some published case reports have found an association between the effects of inhaled corticosteroids and cataracts in children [2-4]. Published investigations of treatment have focused on the cumulative doses of inhaled corticosteroids and the modes of administration [5]. We suggest that inappropriate modes of administration alone may produce an adverse reaction, and that the cataract did not develop only because of the systemic effects of nebulized budesonide, but also as a result of inappropriate administration. The patient received the drug without a facemask over an extended period. Thus, droplets of the drug may have directly affected his eyes.

Several recent studies suggest that, without a facemask, the aerosol form of drugs might be deposited on the eyes and face. Design characteristics of the facemask and nebulizer, as well as the aerodynamic properties of the aerosol, can affect deposition of the drugs on the face and eyes [4,6]. Sangwan et al [6] showed that 0.09-1.78% of the nebulized charge entered into direct contact with the eye. The side effects of inhaled corticosteroids may take months or years to become evident [7]. The risk of cataract may be increased by topical contact with cumulative doses of nebulized budesonide over an extended period.

This is a dramatic example of how a drug deemed safe for specific treatment can be hazardous when applied in a different manner. Both patients and parents must be educated and warned of the possible adverse effects of the drug. Parents are always keen to give their children medications in easy and convenient ways, and may sometimes discover new methods. Doctors must be vigilant and evaluate carefully how their patients have been receiving their medication.

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