Original Article

Cocaine Allergy in Drug-Dependent Patients and Allergic People

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What is already known about this topic? Adverse reactions to local anesthetics, especially esters, are not uncommon, but true allergy is rarely diagnosed. To our knowledge, currently there is no reliable method of determining IgE-mediated hypersensitivity to local anesthetics and cocaine.

What does the article add to our knowledge? Cocaine might be an important allergen. Drug abusers and patients sensitized to local anesthesia and tobacco are at risk. Both prick tests and specific IgE against coca leaf extract detected sensitization to cocaine. The highest levels were related to severe clinical profiles.

How does this study impact current management guidelines? Cocaine can provoke life-threatening allergic attacks and should be considered in patients at risk of abusing drugs who have poorly controlled asthma and in candidates for local surgery and persons in occupational contact with cocaine derivatives. Cocaine hypersensitivity may be tested with a simple and reliable method such as prick tests and IgE determination to coca leaf extracts.

BACKGROUND: Adverse reactions to local anesthetics (LAs), especially esters, are not uncommon, but true allergy is rarely diagnosed. To our knowledge, currently there is no reliable method of determining IgE-mediated hypersensitivity to LAs and cocaine.

OBJECTIVE: To assess the clinical value of allergy tests (prick, IgE, challenges, and arrays) in people suffering hypersensitivity reactions (asthma and anaphylaxis) during local anesthesia with cocaine derivatives and drug abusers with allergic symptoms after cocaine inhalation.

METHODS: We selected cocaine-dependent patients and allergic patients who suffered severe reactions during local anesthesia from a database of 23,873 patients. The diagnostic yield (sensitivity, specificity, and predictive value) of allergy tests using cocaine and coca leaf extracts in determining cocaine allergy was assessed, taking a positive challenge as the criterion standard.

RESULTS: After prick tests, specific IgE, and challenge with cocaine extract, 41 of 211 patients (19.4%) were diagnosed as sensitized to cocaine. Prick tests and IgE to coca leaves (coca tea) had a good sensitivity (95.1% and 92.7%, respectively) and specificity (92.3 and 98.8%, respectively) for the diagnosis of cocaine allergy and LA-derived allergy.

CONCLUSIONS: Cocaine may be an important allergen. Drug abusers and patients sensitized to local anesthesia and tobacco are at risk. Both prick tests and specific IgE against coca leaf extract detected sensitization to cocaine. The highest levels were related to severe clinical profiles. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Cocaine; Anaphylaxis; Drug abusers; Anesthesia*

Cocaine, derived from the shrub *Erythroxylon*, of which more than 200 species are known, is the main alkaloid present in *Erythroxylon coca*, which grows in South America (mainly Colombia, Bolivia, and Peru) and other tropical regions. Cocaine is obtained from an extract of the leaves, which is then hydrolyzed and esterified with methanol and benzoic acid to produce the hydrochloride salt of cocaine.[1]

Cocaine, which was used as a cure for morphine and alcohol addiction, was discovered to be a local anesthetic (LA) by Koller

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Abbreviations used
CRD- Component-resolved diagnosis
ED- Emergency department
LA- Local anesthetic
LTP- Lipid transfer protein

(1884) and was the first effective treatment for nasal congestion associated with seasonal allergies. Nevertheless, bronchospasm occurred in patients smoking cocaine,[2] often in patients with a history of asthma. Reports suggested that these side effects were not likely to be mediated by the immune system. However, hypersensitivity pneumonitis to cocaine has been described and is associated with elevated IgE levels.[2] Cases of severe angioedema after cocaine inhalation are reported.[3]

Cocaine is used as an LA to rapidly numb the lining of the mouth, nose, and throat (mucous membranes) before medical procedures (eg, biopsy and stitches) because it rapidly numbs the area of application after 1 to 2 minutes. Cocaine also causes blood vessels to narrow, which may decrease bleeding and swelling.[2] The incidence of systemic toxicity to LAs has significantly decreased in recent years, from 0.2 to 0.001, probably because of the large shift in preference from the use of amides to the use of LAs.[4]

Cases of anaphylaxis after LAs have been described,[5] but real allergy to LAs is very rare, with some authors suggesting that most adverse reactions are psychogenic or vasovagal.[6]

The true incidence of allergic reactions to LAs is unknown, and most adverse events are attributed to toxicity. LAs of the ester group (cocaine, benzocaine, procaine, tetracaine, and chloroprocaine) have more frequently been associated with allergic reactions than LAs from the amide group.

In contrast, contact sensitization has been described via dibucaine-containing perianal medicaments[7,8] and benzocaine has been labeled as a notorious sensitizer.[9] Cases of "pseudoanaphylactic" reactions to intramuscular procaine penicillin G have been reported as Hoigne syndrome.[10]

Previously our group found IgE sensitization to *Cannabis sativa* diagnosed by prick tests, bronchial challenge tests, and specific IgE to cannabis extracts in patients suffering from asthma and anaphylaxis after using cannabis and/or heroine,[11] and after molecular analysis we found a recombinant lipid protein implicated in these reactions,[12-16] but were not able to find a reliable method of measuring specific IgE to cocaine. At that time, Phadia Laboratories (Uppsala, Sweden) had marketed an immunoassay, ImmnoCAP®Allergen c260 cocaine, that might be useful in cocaine and LA allergy diagnosis, but we have not found relevant results.

Until now, there are no efficient diagnostic techniques that demonstrate a hypersensitivity response mediated by IgE to cocaine-derived LAs. Previous studies that showed that cocaine-dependent patients responded positively to prick and IgE tests to coca leaf extracts led us to investigate the use of these tests in patients with hypersensitivity to cocaine-derived LAs.

We also used component-resolved diagnosis (CRD) based on microarrays to determine its sensitivity and sensibility for detecting different molecules of complex allergens, such as cocaine, which is often adulterated, or coca leaf extracts.

The aim of this study was to assess the clinical value of cocaine prick tests with different cocaine extracts, IgE determination (ImmunoCAP), and CRD by microarrays in allergic people who might have suffered hypersensitivity reactions during local anesthesia and in drug abusers with allergic symptoms after cocaine inhalation. Furthermore, we sought to determine the utility of antibody determinations as markers of clinical symptoms before local anesthesia.

METHODS

Patients

We carried out a cross-sectional study with patients and controls. We selected cocaine abusers and allergic patients who suffered severe reactions during local anesthesia from a database of 23,873 patients. These types of sensitization are infrequent, and therefore all patients attended over 30 years were included. We began with 268 selected patients and after providing information on the aim of the study, we finally included 21 patients who suffered anaphylaxis during local anesthesia and 42 drug abusers who presented allergic symptoms (asthma and anaphylaxis) after cocaine use. As controls, we included 33 patients sensitized to grass pollen, 25 patients sensitized to tobacco, 25 patients with allergy to cannabis, 21 patients who suffered allergic symptoms after handling cocaine products for work reasons (nurses, dentists, anesthetists), and 50 healthy nonatopic blood donors (Figure 1).

Drug abusers were recruited from the Association for the Aid of Drug Abusers (Asociación Castellano-Leonesa de Ayuda al Drogodependiente [ACLAD]). An epidemiological-clinical survey was carried out, including the characteristics and origin of dependence, possible adverse reactions (questioning of close friends or relatives), potential involvement of organs and systems, emergency department (ED) care, and treatment required.

Patients allergic to pollen were randomly selected from the registry of patients attended in the last years by the Allergy Clinic, Rio Hortega University Hospital of Valladolid. Pollen sensitivity was defined as (1) 1 or more positive skin test results for pollen, (2) Immunoassay ImmunoCAP® Allergen IgE positive level of more than 0.35 IU/mL for pollen, or (3) positive specific challenge.

Patients sensitized to tobacco were included because, in general, all cocaine abusers were smokers and tobacco was a risk factor in other studies on drug allergy.[11]

Cocaine consumption was self-estimated as nonconsumption, experimental, occasional, habitual, and dependence.

The 50 healthy blood donors (Blood Donation Unit, Health Department of Castile and Leon Community) were all nonsmokers and did not use illicit drugs. None had previously consulted the Allergy Clinic.

The protocol was evaluated and approved by the Clinical Research Ethics Committee of the Rio Hortega Hospital. Written consent was obtained from all patients and controls. The following tests were carried out in all patients and controls.

In vivo tests

Skin tests. Skin tests including allergens and illicit drugs were carried out as in previous studies.[12] In the case of the tobacco and cocaine used for testing, preliminary titration was done to determine the optimal concentration. Histamine 1/100 and physiological saline solution were used as positive and negative controls, respectively. The wheal area was measured after 15 minutes and traced for posterior measurement by planimetry. A wheal area of 19.62 mm^2 or more, corresponding to a diameter of 5 mm, was considered clearly positive. This area was specified as a cutoff point after study of the receiver-operating characteristic curves and was designed to exclude