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ORIGINAL ARTICLE

Utility of opium seed extract tests in preventing hypersensitivity reactions during surgery

A. Armentia[a,*], F. Pineda[b], R. Palacios[b], F.-J. Martín-Gil[c], A.S. Miguel[c], J.J. Arenal[d], J. Tejedor[e], B.M. Tef[f]

[a] *Allergy Unit, Rio Hortega University Hospital, UMDAI, Valladolid, Spain*
[b] *DIATER Laboratories, Madrid, Spain*
[c] *Clinical Chemistry Service, Hospital Universitario Rio Hortega, Valladolid, Spain*
[d] *Surgical Service, Hospital Universitario Rio Hortega, Valladolid, Spain*
[e] *Health Area Director, Delegacion del Gobierno de Castilla y León, Spain*
[f] *Research Unit, IEN, Rio Hortega University Hospital, Valladolid, Spain*

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Abstract
Background: Anaphylaxis during anaesthesia is fatal in 3–9% of patients and analgesics, including opioids, and is the second most common medicament-related cause, although the prevalence is underestimated. We recently found that patients may generate IgE antibodies to opium seeds.
Objectives: To determine the diagnostic accuracy of specific antibodies to morphine, codeine, rocuronium and oil body and aqueous fractions of *Papaver somniferum* seeds in the diagnosis and prevention of allergy to opioids.
Methods: Patients with hypersensitivity reactions during surgery, and severe clinical allergy (pollen, tobacco), and illicit heroin users were selected. The sensitivity, specificity and predictive values of in vivo and in vitro diagnostic techniques including oil body and aqueous fractions of *P. somniferum* seeds were measured.
Results: We studied 203 patients, with mean age 35.1 ± 17.1 and 200 healthy controls. Patients sensitised to heroin or with hypersensitivity reactions during surgery responded to *P. somniferum* seed tests. Of patients not known to be sensitised to opioids, the highest positivity was in patients sensitised to tobacco ($p < 0.001$). Opium seed skin tests and IgE, especially the oil body fraction, were more sensitive (64.2%) and specific (98.4%) than morphine, codeine and rocuronium tests for opioid sensitivity. Pollen allergy was not a risk factor for sensitisation to morphine.

Abbreviations: NMBA, neuromuscular blocking agents; PBS, phosphate buffered saline; SDSPAGE, dodecyl sulphate polyacrylamide gel.

* Corresponding author.
E-mail address: aliciaarmentia@gmail.com (A. Armentia).

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Conclusions: Sensitivity to opioids and intraoperative anaphylaxis can be diagnosed by routine tests. IgE and skin tests for the oil body fraction of *P. somniferum* had the highest sensitivity for sensitisation to opioids.

Introduction

Anaphylaxis during anaesthesia is a serious clinical condition that may be fatal.[1] General anaesthetics include hypnotics, analgesics, muscle relaxants and other substances, such as anticholinergics, benzodiazepines and cholinesterase inhibitors, which reverse the effect of muscle relaxants.

Analgesics include natural (morphine) and synthetic (fentanyl, meperidine, alfentanil and remifentanil) opioids, and morphine-related compounds. Muscle relaxants include neuromuscular blocking agents (MBAL), which have a quaternary ammonium ion structure and contain a hydrophobic ring skeleton and a hydrophilic tertiary amine similar to the structure of morphine.[2]

Fifty to seventy per cent of anaphylactic reactions during anaesthesia are due to opioids and MBALs.[1] Therefore, identification of hypersensitivity to these agents may be life-saving. However, making an aetiological diagnosis of allergy in a patient under anaesthesia is difficult because skin reactions are hidden by surgical drapes, anaesthetised patients cannot complain of itching or asthma, and multiple drugs are used. A method of preventing adverse drug events due to widely used drugs such as opioids would be a major advantage in the prevention of adverse reactions to these drugs and have a great health and social impact.

In vivo skin tests (prick test and intradermal) are not sure in confirming clinical allergic reactions to MBALs and opioids.[3]

In vitro methods, based mainly on the quantification of specific immunoglobulin E (IgE) in serum against MBALs is another commonly used diagnostic alternative and has shown the presence of specific serum IgE against alcuronium, D-tubocurarine, pancuronium and analogues, vecuronium, succinylcholine, decamethonium and gallamine in patients allergic to these MBALs, but their clinical utility is not clear.[4]

In a recent study of heroin addicts, we found that *Papaver somniferum* (opium seed extracts) provided a higher diagnostic yield.[5] Opium is one of the most important plants cultivated for the pharmaceutical industry, as it is the only source of alkaloids such as morphine, codeine and thebaine, which are widely used in medicine as analgesics, anaesthetics, antitussives and antispasmodics.

Here we hypothesised that the oil body (liposoluble) and aqueous (hydrosoluble) fractions of *P. somniferum* seed extracts could have a better diagnostic yield in the diagnosis of sensitivity to opioids, because the seeds contain the whole proteome of the future plant. The objective of this study was to compare the clinical utility of specific antibodies to morphine, codeine, rocuronium and protein and lipid-soluble seed opium (*P. somniferum*) in the diagnosis and prevention of allergy to opioids in a large series of patients.

Patients and methods

We designed a retrospective–prospective study. We selected patients with a possible severe risk of allergic reaction to opioids given as aesthesia or analgesia from a large database of allergic patients.

Patients

From the records of the 23,873 patients seen in the last 23 years by the Allergy Unit, University Hospital Rio Hortega, we selected: 40 randomly selected patients of both sexes with the most-frequently seen severe allergy in our area: asthma due to *Lolium perenne*. Asthma due to pollen was defined as (a) $\geq$1 positive skin-prick test for pollen, (b) CAP (IgE) positive >0.35 IU/mL for pollen, (c) positive specific challenge.

From the same records, due to the infrequency of these reactions, we selected all 80 patients with anaphylaxis during surgery or severe reactions to opioids (asthma, urticaria, anaphylaxis, angio-oedema, vomiting, angina, and rash). The suspected agents involved included tramadol, rocuronium fentanyl, propofol, morphine, codeine, algidol, and atracurium.

In addition, 42 habitual heroin consumers (of whom 31 were severely dependent) were recruited from the Castile-Leon Association for the Help of Drug Addiction (ACLAD).

We also recruited all 25 patients allergic to tobacco (defined as skin test CAP (IgE) >0.35 IU/mL and positive bronchial challenge); all 16 patients with anaphylaxis due to codeine (diagnosed according to clinical criteria); and ten patients with anaphylaxis during surgery due to penicillin (defined as positive skin test and IgE for the β-lactam antibiotic considered).

As control group we included 200 non-smoking, non-atopic healthy blood donors selected at random (Blood Donation Unit, SACYL) who were non-users of illicit drugs and had never consulted our Allergy Clinic.

All patients and controls gave written informed consent to participate in the study.

In addition, for in vitro techniques, we collected surplus blood from 20 cord blood samples of preterm infants.

The protocol was approved by the HURH Clinical Research Ethics Committee.

In vivo tests

Skin tests

Skin tests were performed with conventional prick tests in the case of commercialised tests, and according to the