ORIGINAL ARTICLE

Drug Challenge Tests With General Anesthetics: Predictive Value of Skin Tests

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Abstract

Background: The study of perioperative drug reactions remains a major challenge for both diagnosis and therapy.
The lack of a standard assessment of allergy to general anesthetics and of data establishing the true value of skin tests for most drugs used in induction and maintenance of anesthesia, as well as the lack of commercially available reagents for in vitro tests, renders the study of these reactions problematic.
The aims of this study were to provide a diagnostic protocol for drug challenge testing with general anesthetics, to establish an etiological diagnosis that is as specific as possible, and to determine the predictive value of skin tests.
Methods: Twenty-nine patients with perioperative drug reactions were included in the study from November 2008 to December 2018.
Results: We confirmed the high negative predictive value of the tests (96%-100%) in the case of propofol, rocuronium, and fentanyl. To our knowledge, this is the first study to describe drug challenge testing with general anesthetics and, therefore, to establish the true negative predictive value of skin tests, which leads to a definitive diagnosis and safer surgery.
Conclusions: After assessing risks and benefits and considering the importance of this group of drugs, we conclude that drug challenge testing with general anesthetics is necessary. We propose a protocol for perioperative drug reactions that enables us to make a highly accurate etiological diagnosis with minimum risk for the patient.

Key words: Drug challenge test. General anesthetics. Perioperative drug reactions. Predictive value. Skin tests.

Resumen

Antecedentes: La ausencia de estandarización del estudio de alergia a anestésicos generales y ausencia de verdaderos datos sobre el valor de las pruebas cutáneas en la mayoría de los fármacos empleados en anestesia general, así como la ausencia de reactivos disponibles comercialmente para poder realizar tests in vitro, continúa suponiendo un dilema para estudiar las reacciones perianestésicas.
El objetivo de este estudio fue aportar un protocolo de pruebas de provocación con anestésicos generales para poder establecer un diagnóstico etiológico lo mas especifico posible, y determinar el valor predictivo de las pruebas cutáneas.
Métodos: Desde noviembre de 2008 a diciembre de 2018, fueron estudiados 29 pacientes con reacciones perioperatorias a medicamentos.
Resultados: Con este estudio, confirmamos el alto valor predictivo negativo (VPN) de las pruebas cutáneas (96-100%) en el caso del propofol, rocuronio y fentanilo. En nuestro conocimiento, este es el primer trabajo que describe pruebas de provocación con anestésicos generales, y en aportar el verdadero VPN de las pruebas cutáneas, lo que permite llegar a un diagnóstico más definitivo, y a una mayor seguridad en futuras cirugías.
Conclusiones: Valorando riesgos /beneficios y considerando la importancia de este grupo de medicamentos, concluimos que las pruebas de provocación controlada con anestésicos generales, son necesarias. Proponemos un protocolo diagnóstico de las reacciones perioperatorias por fármacos, que permita alcanzar un diagnóstico etiológico lo más certero posible, con el menor riesgo para el paciente.

Palabras clave: Anestésicos generales. Pruebas cutáneas. Pruebas de provocación controlada. Reacciones perioperatorias. Valor predictivo.

Introduction

The study of perioperative drug reactions (PODRs) remains a major challenge for both diagnosis and therapy. The possible causes of PODRs include not only general anesthetics, but also other agents and drugs used during induction, maintenance, and recovery.

Etiological diagnosis of these reactions is essential. An error can lead to re-exposure to the causative drug, which could prove fatal. It could also lead to the prohibition of drugs that may be necessary for the patient in the future or the choice of a less effective alternative with second-line drugs [1]. Therefore, we consider it essential to establish measures and protocols that enable a highly accurate etiological diagnosis to be established. In the case of hypnotic drugs and neuromuscular blocking agents (NMBAs), the only currently available tools for establishing an etiological diagnosis are skin tests and, in very specific cases, in vitro tests, which are used to determine specific IgE to certain antigens. However, these may provide false-negative results, with the consequent risk for the patients. Moreover, they are only available for some drugs [2-6].

The basophil activation test (BAT) can be used to detect the causative drug, although it is not currently validated and its positive and negative predictive values have not yet been established [7,8]. The most recent findings on this test indicate that it is a promising tool for diagnosis [9].

For these reasons, drug challenge testing (DCT) with general anesthetics is very useful and even essential in some cases. Nevertheless, the most suitable approach remains undetermined. While DCT is the gold standard for diagnosis of drug-induced hypersensitivity reactions [9,10], the complexity and the potential risks inherent to this approach prevents it from being performed with general anesthetics, and there are no published protocols on their use.

Unlike the agents used in other DCTs, hypnotics and NMBAs can only be administered in the operating room or in a postanesthesia care unit (PACU), with the consequent need for coordination between the Anesthesiology and Allergy Services and appropriate infrastructure. According to the recommendations of recent management guidelines on PODRs published by the Drug Allergy Committee of the Spanish Society of Allergology and Clinical Immunology (SEAIC) [11], DCT with general anesthetics should always be performed after assessment of the risk-benefit ratio under strict patient monitoring and with adequate infrastructure.

As DCTs are not performed with anesthetics, the positive predictive value (PPV) and negative predictive value (NPV), sensitivity, and specificity of skin tests with general anesthetics are unknown. The only available data are from a series of cases reviewed after re-exposure to general anesthetics [12,13].

Assessment of these reactions is rendered problematic owing to the lack of standardization in the study of allergy to general anesthetics, the absence of data establishing the true value of skin testing for most drugs used in induction and maintenance of anesthesia, and the lack of commercially available reagents to perform in vitro tests. The aim of this study was to perform challenge testing with general anesthetics in order to establish a specific etiological diagnosis and to determine the predictive value of skin tests with general anesthetics.

Table. Concentrations Used for Skin Tests and Challenge Tests With General Anesthetics

Drug	Skin Tests	Drug Challenge Test (Intravenous)
Propofol	– Prick 10 mg/mL – IDT: 1 mg/mL	150-200 mg
Rocuronium	– Prick: 10 mg/mL – IDT: 0.01 mg/mL	0.6 mg/kg
Cisatracurium	– Prick: 2 mg/mL – ID: 0.02 mg/mL	0.15 mg/kg
Sugammadex	– IDT: 0.1 mg/mL and 1 mg/mL	2-4 mg/kg
Remifentanil	– Prick: 5 mg/mL – IDT: 0.05 mg/mL	0.1-2 µg/kg
Fentanyl	– Prick: 0.05 mg/mL – IDT: 0.005 mg/mL	50 µg

Abbreviation: IDT, intradermal test.

Materials and Methods

The study population comprised 29 patients with PODRs, who were included between November 2008 and December 2018. Ethics committee approval (ALE-ANES/20). The data collected from each patient were age, sex, personal history of allergy, previous exposure to general anesthetics, type of reaction, time to performance of the PODR study, and the drugs involved. All the culprit drugs used during the anesthetic procedure were included. Clinical reactions were classified according to the Brown criteria [14], as modified by Ring and Messmer [15], into 3 grades: mild (skin symptoms), moderate (edema of the glottis or 2 or more organs affected without changes in vital signs), and severe (more than 2 organs affected with changes in vital signs).

In addition to studying the drugs involved, tests with other agents implicated in the reaction, such as latex and antiseptics (chlorhexidine and povidone iodine), were documented. A standard allergological study was performed with skin tests and/or specific IgE determination and/or latex use test and/or topical application of chlorhexidine and povidone iodine.

Skin Tests

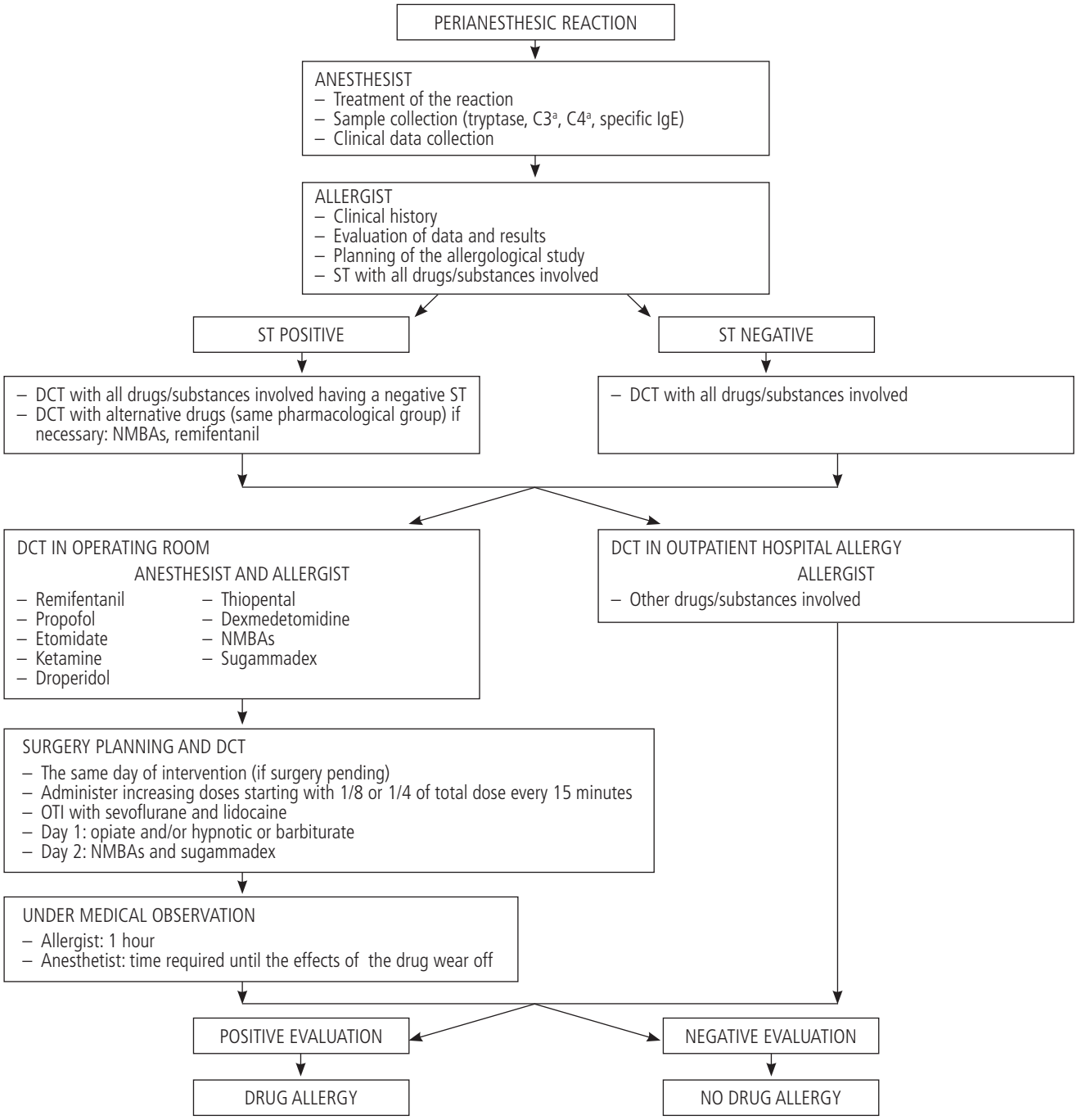
Skin tests were performed with all the drugs involved in each reaction at the Drug Allergy Unit of the Allergy Service according to the protocols of the European Network for Drug Allergy (ENDA) of the European Academy of Allergy and Clinical Immunology [16] (Table).

In the case of a positive skin test result to any of the drugs involved, skin tests were performed with other drugs belonging to the same pharmacological group to determine the presence of cross-reactivity and to confirm tolerance to alternative drugs.

Drug Challenge Test Requirements

The requirements for performing DCT with general anesthetics, in addition to those necessary for other drugs, included a number of extraordinary conditions such as:

– Collaboration and coordination with the Anesthesiology Service, since the patient must be intubated and the therapeutic effects of the general anesthetics monitored.
– Acceptance of 2 different informed consents specifying the risk of each of these techniques, owing to the additional risk inherent to anesthesia.
– Administration in the operating room/PACU of drugs causing respiratory depression (eg, etomidate, ketamine, propofol, remifentanil, NMBAs, barbiturates).
– After completing the DCT, patients had to remain under observation in the PACU for at least 1 hour. They could not be discharged until the anesthesiologist considered



Abbreviations: DCT indicates drug challenge text; NMBA, neuromuscular blocking agent; OTI, orotracheal intubation; ST, skin test
[a]Only in cases of isolated angioedema

Figure. Diagnostic algorithm.

that the effects of the drugs used in the procedure had worn off.

Increasing doses of the drug were administered every 20-30 minutes, starting with 1/8 or 1/4 of the therapeutic dose, depending on the severity of the initial reaction.

The patient was intubated during the DCT with remifentanil and NMBAs, as well as in cases of severe PODR with bronchial symptoms, edema of the glottis, or need for cardiopulmonary resuscitation, since in these cases the patient could be ventilated more effectively. Endotracheal intubation was performed after inhalational induction with sevoflurane and local airway anesthesia with lidocaine.

DCT with propofol did not require the patient to be intubated, except when decided otherwise owing to the severity of the previous reaction. Although the dose of propofol administered causes respiratory depression and apnea, the patient can be manually ventilated until its effect has worn off, since it has a very short half-life (3-5 minutes).

The DCT was performed with 2 different drugs on the same day, with an interval of 1 hour between them. With this procedure, the total study time was significantly shortened in the operating room. In cases where the patient was scheduled to undergo a procedure with general anesthesia, the process was coordinated with the surgeon so that if the DCT was negative, the procedure could be performed immediately after the test, as the patient was already anesthetized.

Some of the DCTs to rule out hypersensitivity to the drugs used in the surgical procedure can be safely performed in the Drug Allergy Unit. DCTs with these drugs or agents which, in our study, included ß-lactam antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, opioids, local anesthetics, antiseptics, and latex, were performed following the standard clinical protocols [17].

In the case of remifentanil, an ultrashort-acting fentanyl derivative (<3 minutes) with high risk of respiratory depression, we followed the recommendations of the anesthesiologists and performed the DCT in the operating room/PACU by administering increasing doses every 30 minutes until a total cumulative dose of 0.05 mg was reached. The observation period at the end of the test was 60 minutes. In all cases, a challenge with intravenous fentanyl was subsequently performed in the operating room/PACU.

The Figure shows the diagnostic algorithm used in this study.

Results

The study population comprised 29 patients (20 women [69%], 9 men [31%]), with a mean age of 51.7 years (range, 21-80). Only 31% had a personal history of atopy (Appendix 1). All patients except 1 had previously undergone a procedure with general anesthetics without incidents.

All procedures were carried out at least 6 weeks after the initial reaction in accordance with current guidelines [9,18]. The mean (SD) time from the reaction to performance of the study was 19.5 (38.9) months.

According to severity, the initial reactions were mild (65%: 11 generalized urticaria, 2 urticaria-angioedema, 6 generalized erythematous macular rash); moderate (13%: 1 angioedema of the glottis, 3 bronchospasm); and severe (21%: 6 anaphylactic shock, 1 cardiopulmonary arrest).

Our procedures included the following:

Hypnotic drugs

Propofol was involved in all cases (n=29), and the skin test results were negative in all patients (100%). DCT were performed in 28 patients. The result was negative in 27 patients and positive in 1 patient, who developed redness in face, neck, back, and arms 5 minutes after administration of 50 mg of propofol. This remitted with intravenous hydrocortisone and dexchlorpheniramine in less than 1 hour. The NPV of the skin test was 96% (95%CI, 78.05%-99.9%).

Opioids

Fentanyl was involved in 23 cases, all of which had negative skin test results (100%). Of the 23 DCTs performed, only 1 was positive (urticaria on the chest and upper extremities). Skin testing with remifentanil was negative in the 5 cases in which it was involved, and all patients underwent challenge testing. Patient 21, ie, the patient who had a positive DCT with fentanyl, also developed urticaria during the DCT with remifentanil. Both reactions resolved in less than 1 hour with intravenous dexchlorpheniramine and methylprednisolone. The NPV of the skin test was 96% for fentanyl (95%CI, 78.05%-99.9%). Given that our series was small, we were unable to calculate a predictive value for remifentanil.

Neuromuscular blocking agents

The only NMBA involved in the present series was rocuronium in 22 patients. In the remaining cases, NMBAs were not used during the procedure when the reaction occurred. The skin test results were negative in 100% of cases. DCTs were performed with rocuronium in 21 patients, with a negative result in all cases. The NPV of the skin test was 100% (95%CI, 83.9%-100%).

Sugammadex

Sugammadex was involved in 3 patients, and all skin test and DCT results were negative. We tested the drug at 0.1 mg/mL, which is the concentration recommended by other authors [11]. However, given the negative results, we also performed skin tests at 1 mg/mL; these all yielded negative results. Ten healthy controls exposed to sugammadex with no symptoms had negative skin test results at this concentration. The small number of cases prevented us from determining a predictive value.

Other drugs

Antibiotics were involved in 14 patients (10 cefazolin, 3 amoxicillin-clavulanate, 1 piperacillin-tazobactam). Hypersensitivity to antibiotics was confirmed in 7 patients (by skin test in 6 and by DCT in 1). The causative drugs were cefazolin in 5 patients and amoxicillin in 2 patients.

Two of the 4 patients who received NSAIDs during surgery (1 metamizole, 3 metamizole + dexketoprofen) were diagnosed with selective allergy to NSAIDs by positive skin test results. Metamizole was the causative drug in both cases.

Latex and antiseptics

Latex allergy was confirmed by skin test and by specific IgE testing (CAP-FEIA; Phadia) in 1 patient and ruled out in the remaining 28 patients. Chlorhexidine allergy was ruled out in 26 patients and povidone iodine allergy in 3 patients.

All patients underwent DCT with the general anesthetics involved in the reaction, except patient 5, who experienced an anaphylactic shock with cardiopulmonary arrest during the anesthetic procedure. The results of skin tests were negative for all general anesthetics involved. However, DCTs were only performed with fentanyl, midazolam, lidocaine, latex, and chlorhexidine. No challenge test was performed with propofol or rocuronium, although the DCT with cisatracurium was negative.

In summary, the diagnosis of drug allergy was confirmed in 12 cases (41%) (n=12): 1 case of sensitization to propofol (8%), 1 case of allergy to opioids (8%), 7 cases of sensitization to antibiotics (cefazolin and amoxicillin [59%]), 2 cases of allergy to pyrazolones (17%), and 1 case of allergy to latex (8%).

The incidence of allergic reactions to general anesthetics during the DCT in our study was 4% (1 case with propofol, 1 case with fentanyl, and 1 case with remifentanil [both opioids in the same patient]). All were mild and could be managed with intravenous antihistamines and corticosteroids, without the need for administration of epinephrine.

However, 2 nonallergic reactions were observed during the study; these consisted of hypoxia due to severe irritative bronchospasm secondary to manipulation of the airway.

The patients presented isolated bronchospasm as the initial reaction. Allergy was ruled out using during the challenge test with fentanyl, sevoflurane, and lidocaine.

Discussion

The incidence of PODR during anesthesia varies by country from 1/5000 to 1/20 000 anesthetic procedures, with an associated mortality of 3%-9% [19]. The reactions are IgE-mediated in up to 70% of cases [20].

The most frequently involved drugs in PODRs can also vary by country and population group. Whereas NMBAs are the main cause of reactions (50%-70% according the series reported) in France [6,20], Norway [21], Denmark [22], Australia [23], and the United Kingdom [24,25], antibiotics are responsible for 50% of these reactions in the United States [26] and Spain [27].

We confirmed a diagnosis of drug allergy in 41% of patients. Of these, 75% had a positive immediate skin test result, which suggested an IgE-mediated mechanism. Consistent with other series, ß-lactams were the most frequently involved drugs (59%) [27]. We did not observe any sensitization to NMBAs among our patients, in contrast to data reported elsewhere [28].

Most immediate PODRs that occur in the operating room are IgE-mediated. Therefore, both etiological and allergological diagnosis are necessary if we are to guarantee the safety of these patients in future surgical procedures.

Diagnosis is hampered by the lack of standardization of the studies of allergy to general anesthetics and of data on the sensitivity, specificity, PPV, and NPV of skin tests for most drugs used during induction and maintenance of anesthesia. Diagnosis is also limited by the lack of commercially available reagents to perform in vitro tests. In most cases, the final diagnosis is based on the medical history and the result of skin testing, which is clearly inadequate.

Challenge testing is currently the only available procedure for confirming or ruling out PODRs and establishing the etiological diagnosis. In our study, the skin test results were negative in 100% of the reactions due to anesthetics, which could only be diagnosed by DCT.

The limitations for the performance of challenge tests with anesthetics are similar to those for other drugs. However, in addition, they require coordination with the Anesthesiology Service owing to the characteristics of anesthetics. Some of the procedures must be performed in the operating room, and the drugs must be administered by the anesthesiologist monitoring their therapeutic effects. Although this could be considered a significant disadvantage, it ensures that the procedure is safe. If the patient experiences a major adverse reaction, then appropriate action can be taken more quickly and efficiently. In the present study, only 10% of patients experienced allergic reactions during the DCT (1 propofol and 2 opioids). These were all mild, and the remaining agents could be ruled out and thus administered later if needed.

On the other hand, we did record 3 moderate-severe reactions, namely, bronchospasm and hypoxia caused by bronchial irritability secondary to manipulation of the airway. Knowledge of the real etiology of these conditions is very important. Otherwise, they might be attributed to an allergic mechanism, with the result that the avoidance of certain drugs or the use of alternatives will not prevent the recurrence of problems in subsequent anesthetic procedures. Reaching a specific diagnosis will enable measures to prevent or palliate these symptoms as much as possible in new procedures.

Published studies to date provide data on tolerance of general anesthetics in patients followed up after an allergological study based on skin and in vitro tests [28,29]. However, a diagnosis based on this approach requires long-term follow-up, is complex and, in our opinion, is subject to bias. Series are small, recommendations are based mainly on the use of drugs other than those involved in the reaction and whose skin test results were negative, without reaching a true etiological diagnosis. As a result, there is a potential risk of new reactions, since the degree of cross-reactivity between drugs from the same group and the predictive value of skin tests are unknown. Furthermore, in many cases, the procedures are performed years after the initial reaction, with the possibility that loss of immunological memory may alter the result. In some published series, recurrence of anaphylaxis was observed in subsequent surgical procedures, despite the recommendations made after the allergological study following a first episode; however, the cause of this recurrence could not be confirmed in all cases [13]. Our review of the literature yielded 1 study [12] in which an intravenous challenge test with propofol was applied in patients with suspected perioperative allergic reaction and possible food allergy.

Our study enabled us to confirm the high NPV of the tests (96%-100%) in the case of propofol, rocuronium, and

fentanyl. The NPV for sugammadex and remifentanil could not be determined owing to the small size of the sample. In a review of the literature, Tsur and Kalansky [31] reported only 10 cases of hypersensitivity to sugammadex confirmed by positive skin test results, although no challenge tests with the drug were reported.

To our knowledge, this is the first study to describe DCT with general anesthetics and therefore the true NPV of skin testing, which provides a definitive diagnosis and ensures safer surgery.

After assessing risks and benefits and considering the importance of this group of drugs, we conclude that DCT with general anesthetics is necessary.

We propose a diagnostic protocol for PODRs that makes it possible to reach as accurate an etiological diagnosis as possible with minimum risk for the patient.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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