

General anesthetics drug challenge tests: predictive value of skin tests

Drug challenge test with general anaesthetics

Tornero Molina P^{1,3}, Rojas-Perez-Ezquerria P^{1,3}, Noguerado-Mellado B^{1,3}, Baeza Ochoa de Ocáriz ML^{1,3}, Garrido Sánchez A^{2,3}, Alonso Mateos M^{2,3}, Zubeldia Ortuño JM^{1,3}.

¹Allergy Department, University Hospital Gregorio Marañón, Madrid, Spain

²Anesthesiology Department, University Hospital Gregorio Marañón, Madrid, Spain

³Gregorio Marañón Health Research Institute, Madrid, Spain

Corresponding:

Patricia Rojas-Perez-Ezquerria

Allergy Department. Hospital General Universitario Gregorio Marañón

Dr. Esquerdo, 46. 28007 Madrid, Spain.

E-mail: patricia.rojas@salud.madrid.org/ projasperezezquerria@gmail.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi:

10.18176/jiaci.0402

Summary

Background: The study of perioperative drug reactions remains a major challenge both for diagnosis and therapeutic management. Lack of standardization of the study of allergy to general anesthetics and nonexistence of data establishing the true value of skin tests for the majority of drugs used in anesthesia induction and maintenance, as well as the lack of commercially available reagents to perform in vitro tests, is a continuous dilemma in the study of these reactions.

Objective: The aim of this study was to provide a diagnostic protocol for drug challenge test with general anesthetics to establish an etiological diagnosis as specific as possible and to determine the predictive value of skin tests.

Material and Methods: Twenty-nine patients with perioperative drug reactions were included in the study from November 2008 to December 2017.

Results: With this study, we have confirmed the high negative predictive value (NPV) 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 test with general anesthetics, and therefore the true NPV of skin tests, which gives a definitive diagnosis, and better safety in later surgical needs.

Conclusions: After assessing risks and benefits and considering the importance of this group of drugs, we conclude that drug challenge test with general anesthetics are necessary. We propose a diagnostic protocol for perioperative drug reactions that allows to reach an etiological diagnosis as accurate as possible with the minimum risks for the patient.

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

Resumen

Introducción: 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.

Objetivo: El objetivo de este estudio fue aportar un protocolo de pruebas de provocación con anestésicos generales para poder establecer un diagnóstico etiológico lo más específico posible, y determinar el valor predictivo de las pruebas cutáneas.

Material y Métodos: Desde Noviembre de 2008 a Diciembre de 2017, 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.

Conclusión: 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 (PODR) remains a major challenge both for diagnosis and therapeutic management. In PODR, not only general anesthetics but also other agents and drugs used during the procedure, either during the induction phase of general anesthesia or during maintenance or recovery, are possible causes of the clinical adverse reaction.

Etiological diagnosis of these reactions is essential. An error can lead to re-exposure to the causative drug which could result in a fatal outcome, or the prohibition of drugs necessary for the patient in the future, or the choice of a less effective treatment alternatives with second-line drugs [1]. Therefore, we consider it essential to establish measures and protocols allowing an etiological diagnosis as accurate as possible to be established. In the case of hypnotic drugs and NMBAs, skin tests (ST), and in some very specific cases, *in vitro* tests to determine specific IgE to certain antigens, are currently the only available tool in routine clinical practice for etiological diagnosis. However, these may provide false negatives results, with the consequent risk for the patients. Moreover, they are only available for some of the drugs [2-6].

The basophil activation test (BAT) could detect the causative drug but currently is not validated and its positive and negative predictive values have still not been established [7, 8]. But, the latest published studies on this test found that it may be a promising tool for diagnosis [9].

For these reasons the drug challenge test (DCT) with general anesthetics is very useful and even essential in some cases. Nevertheless, this is one of the main issues that remains today unresolved yet. DCT is the *gold standard* for diagnosis of drug-induced HSR [9,10], but with general anesthetics due to their complexity and the potential risks

inherent to these tests, they are not performed and there are no published protocols on their use.

Unlike other DCT, hypnotics and NMBAs can only be administered in the operating room or in a post-anesthesia care unit (PACU), with the consequent need for coordination of the Anesthesiology and Allergy Services and with an adequate infrastructure. In this regard, in a recent management guide on PODR published by the Drug Allergy Committee of the Spanish Society of Allergology and Clinical Immunology (SEAIC) [11], the recommendations on DCT with general anesthetics established that they should always be done after risk benefit assessment under strict patient monitoring and with an adequate infrastructure.

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

Study objectives

Lack of standardization of the study of allergy to general anesthetics and nonexistence of data establishing the true value of ST for the majority of drugs used in anesthesia induction and maintenance, as well as the lack of commercially available reagents to perform *in vitro* tests, is a continuous dilemma in the study of these reactions. The aim of this study was to perform challenge test with general anesthetics in order to establish an etiological diagnosis as specific as possible and to determine the predictive value of ST with general anesthetics.

Materials and Methods

Twenty-nine patients with PODR were included in the study from November 2008 to December 2018. Data records collected from each patient were: age, sex, personal history of allergy, previous exposure to general anesthetics, type of reaction, time to performance of PODR study and drugs/agents involved. All the culprit drugs/agents during the anesthetic procedure were included. Clinical reactions were classified according to Brown criteria [14] modified by Ring and Messmer [15] in 3 grades: (23) 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 just 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 had been performed with ST and/or specific IgE determination and/or latex use test and/or topical application of chlorhexidine and povidone iodine.

Skin tests

ST with all drugs involved in each reaction were performed at the Drug Allergy Unit of 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 1). In case of a positive ST to any of the drugs involved, ST were performed with other drugs belonging to the same pharmacological group to determine the presence of cross-reactivity and to confirm tolerance to other alternative drugs.

Drug challenge Tests 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 to perform the tests the patient must be intubated and the therapeutic effects of the general anesthetics monitored.
- Acceptance of two different informed consents, specifying the risk of each of these techniques, due to the additional risk inherent to anesthesia.
- Administration in the operating room/PACU of drugs causing respiratory depression (etomidate, ketamine, propofol, remifentanyl, NMBAs, barbiturates, etc.).
- After completing the DCT, the patients should remain under observation in the PACU for at least 1 hour. They should not be discharged until the anesthesiologist considers that the effects of the drugs used in the procedure have disappeared.

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

Endotracheal intubation (ETI) was performed during the DCT with remifentanyl, NMBAs, or in case of severe PODR, with bronchial symptoms, edema of the glottis, or need for cardiopulmonary resuscitation (CPR), since in these cases the patient could be ventilated more effectively. ETI was performed after the inhalational induction with sevoflurane and local airway anesthesia with lidocaine.

DCT with propofol did not require ETI, except when, decided otherwise due to the severity of the former reaction. Although the administered dose of propofol 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 one 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 it as the patient was already anesthetized.

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

In the case of remifentanyl, an ultrashort acting fentanyl derivate (<3 mins) with high risk of respiratory depression, we decide according with recommendations of the anesthesiologists, to perform the DCT in operating room/ PACU, administering increasing doses every 30 minutes until reaching a total cumulative dose of 0.05 mg. The observation period at the end of the test was 60 minutes. In all cases, fentanyl was later challenged intravenously in operating room/ PACU.

Figure 1 shows the diagnostic algorithm followed with the patients.

Results

Twenty-nine patients were studied, 20 were women (69%) and 9 were men (31%), with a mean age of 51.7 years (range: 21-80). Only 31% had a personal history of atopy (Appendix1). All patients except one had previously undergone some procedure with general anesthetics without incidents.

All procedures were done at least 6 weeks after the initial reaction in accordance with current guidelines (9,18, 29-30). The mean time elapsed from the reaction to performance of the study was 19.5 months (SD: 38.9).

The initial reactions according to severity grade were: 65% mild (11 generalized urticaria, 2 urticaria-angioedema, 6 generalized erythematous macular rash); 13% moderate (1 glottis angioedema, 3 bronchospasm); and 21% severe (6 anaphylactic shock, one with cardiopulmonary arrest [CPA]).

Our procedures included:

1. Hypnotic drugs:

Propofol was involved in all cases (n=29), and ST were negative in all patients (100%). DCT were performed in 28 patients. DCT were negative in 27 patients and positive in one patient, who 5 minutes after administration of 50 mg of propofol developed redness in face, neck, back and arms, which remitted with intravenously hydrocortisone and dexchlorpheniramine in less than one hour. The NPV of the ST was 96% (confidence interval (CI) 78.05% to 99.9%).

2. Opioids:

Fentanyl was involved in 23 cases and all had negative ST (100%). Twenty-three challenge tests were performed and only one was positive, who developed urticaria in chest and upper extremities. ST with remifentanil were negative in the 5 cases in which it was involved, and all patients were challenged. Patient n° 21, the same one who had a positive DCT with fentanyl, also developed urticaria during the DCT with remifentanil. Both reactions lasted less than 1 hour with intravenously dexchlorpheniramine and methylprednisolone. The NPV of the ST was 96% for fentanyl (CI: 78.05% to 99.9%).

. For remifentanil, due to the small serie, we couldn't conclude any predictive value.

3. Neuromuscular-blocking agents

The only NMBAs involved in our series was rocuronium in 22 patients. In the rest of cases, NMBAs were not used during the procedure when the reaction occurred. ST were negative in 100%. DCT were performed with rocuronium in 21 patients with a negative result in all cases. The NPV of the ST was 100% (CI 83.9% to 100%).

4. Sugammadex:

Sugammadex was involved in 3 patients and in all ST and DCT were negative. We tested the drug at concentration 0.1 mg/ml, the concentration recommended for other authors [11], but due to the negative results, we also perform skin tests at 1 mg/ml, all with negative result. Ten healthy controls exposure to sugammadex without any symptom had negative skin test at this concentration. Due to the small serie number of cases, we couldn't conclude any predictive value.

5. Other drugs:

Antibiotics were involved in 14 patients (10 cefazolin, 3 amoxicillin-clavulanate, 1 piperacillin-tazobactam). Hypersensitivity to antibiotics was confirmed in 7 patients, in 6 by ST and in 1 by DCT. 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 nonsteroidal anti-inflammatory drugs by positive ST. Metamizole was the causative drug in both cases.

6. Latex and antiseptics:

Latex allergy was confirmed by ST and by specific IgE (CAP-FEIA; Phadia®, Uppsala, Sweden) in one patient and was 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 n° 5. This patient, suffered an anaphylactic shock with CPA during the anesthetic procedure. ST to all general anesthetics involved were negative. However, DCT were only performed with fentanyl, midazolam, lidocaine, latex and chlorhexidine. No challenge test was performed with propofol or rocuronium, but the DCT with cisatracurium was negative.

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

The incidence of allergic reactions to general anesthetics during the DCT in our study was 4%, one with propofol, one case with fentanyl and another case with remifentanyl (both opioids in the same patient). All were mild and could be managed with iv antihistamines and corticosteroids, without the need for administration of epinefrine.

However, three non-allergic reactions were observed during the study consisting of hypoxia due to severe irritative bronchospasm secondary to manipulation of the airway. These patients presented as initial reaction, a bronchospasm in an isolated way. Allergy was ruled out using during the challenge test, fentanyl, sevoflurane and lidocaine.

Discussion

The incidence of PODR during anesthesia varies according to the different countries between 1/5,000 and 1/20,000 anesthetic procedures, with an associated mortality of 3-9% [19]. Is that are known to be mediated by IgE in up to 70% of cases [20].

The most frequently involved drugs in PODR may vary according to the different countries and population groups. Whereas in France [6, 20], Norway [21], Denmark

[22], Australia [23] and United Kingdom [24, 25]. NMBAs are the main cause of reactions (50-70% according the series reported), the antibiotics are the responsible for 50% of these conditions in the United States [26] and Spain [27].

In this work, the diagnosis of drug allergy was confirmed in 41% of patients. Of these, 75% had positive immediate ST, which suggested a mechanism mediated by IgE. The most frequently involved drugs were beta-lactams (59%), according with other series [27] and we did not observe any sensitization to NMBAs among our patients in contrast as others works reported in literature [28].

Most immediate PODR that occur in the operating room are mediated by IgE. So it is necessary, to establish the etiological allergological diagnosis to guarantee the safety of these patients in following surgical procedures.

Nevertheless, lack of standardization of the studies of allergy to general anesthetics and nonexistence of data establishing the sensitivity, specificity, PPV and NPV of skin tests for the majority of drugs used during anesthesia induction and maintenance, as well as lack of commercially available reagents to perform *in vitro tests*, difficult the etiological diagnosis. Currently, in most cases final diagnosis is just based on the medical history and the result of ST which is clearly inadequate.

At present, the challenge test is the only available procedure to confirm or rule out these reactions and to establish the etiological diagnosis in drug-induced PODR. In our study, 100% of the reactions due to anesthetics had negative ST and could only be diagnosed by DCT.

The limitations for the performance of challenge tests with anesthetics are similar to those for other drugs. But additionally they require coordination with the Anesthesiology Service due to the characteristics of these medicines. Some of the procedures must be done in the operating room and the drugs must be administered by

the anesthesiologist monitoring their therapeutic effects. Although this could be considered as a significant disadvantage, it confers great safety to the procedure. In the case that patient experiences a major adverse reaction, this will allow to act much more efficiently. Among our patients, only 10% suffered allergic reactions during the DCT (1 propofol and 2 opioids), all mild, and the rest these agents could be ruled out and ready to be administered later if needed.

On the other hand, we did have three moderate-severe reactions during the study which presented with bronchospasm and hypoxia arising from bronchial irritability secondary to manipulation of the airway. Knowledge of the real etiology of these conditions is very important. Otherwise they can be attributed to an allergic mechanism and the avoidance of certain drugs or the use of alternatives will not prevent the recurrence of problems in subsequent anesthetic procedures. Reaching a certain diagnosis will allow to take measures to avoid or palliate as far as possible these symptoms in new procedures.

Published studies to date provide data on tolerance of general anesthetics in patients followed up after the allergological study performed by ST and *in vitro* tests [28,29]. However, the diagnosis in this way requires a long-term follow-up, is complex and, in our opinion, suffers from some biases. Series are short, recommendations are based in most cases on the use of drugs different from those involved in the reaction and whose ST were negative, without reaching a true etiological diagnosis. As a result, there is the potential risk of new reactions, since the degree of cross-reactivity between drugs from the same group and the predictive value of the ST are unknown. Furthermore, in many of these cases, the procedures are performed years after the initial reaction, with the possibility that loss of immunological memory may alter the result. In some of the published series, recurrence of anaphylaxis was observed in subsequent surgical

procedures, despite the recommendations made after the allergological study following a first episode, though the cause of this recurrence could not be confirmed in all cases [13]. In a review of the literature, we only find a work by Asserhøj et al [12] with IV provocation test with propofol in patients with suspected perioperative allergic reaction and possible allergy food related.

With this study, we have confirmed the high NPV of the tests (96-100%) in the case of propofol, rocuronium and fentanyl. The NPV for sugammadex and remifentanyl was undetermined due to the small size of the sample. In a review of the literature, Tsur et al [31] reported only 10 cases of hypersensitivity to sugammadex proven by positive skin test, but in this review, no provocation tests with the drug were performed.

To our knowledge, this is the first study to describe DCT with general anesthetics and therefore the true NPV of ST, which gives a definitive diagnosis, and better safety in later surgical needs.

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

We propose a diagnostic protocol for PODR that allows to reach an etiological diagnosis as accurate as possible with the minimum risks for the patient.

Conflict of Interest Statement and financial sources: All authors disclose have not any financial relationships, which can originate a conflict of interest to publish the findings of our study.

References

1. Fraser BA, Smart JA. Anaphylaxis to cisatracurium following negative skin testing. *Anaesth Intensive Care*. 2005;33:816-9.
2. Mertes PM, Laxenaire MC, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. *Anesthesiology*. 2003;99:536-45
3. Leysen J, Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. *Clin Exp Allergy*. 2014;44:1069-75.
4. Brockow K. Dilemmas of allergy diagnosis in perioperative anaphylaxis. *Allergy*. 2014;69:1265-6.
5. Florvaag E, Johansson SG, Oman H, Venemalm L, Degerbeck F, Dybendal T et al. Prevalence of IgE antibodies to morphine. Relation to the high and low incidences of NMBA anaphylaxis in Norway and Sweden, respectively. *Acta Anaesthesiol Scand*. 2005;49:437-44.
6. Mertes PM, Malinovsky JM, Jouffroy L, Aberer W, Terreehorst I, Brockow K et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol*. 2011;21:442-53.
7. Leysen J, De Witte L, Bridts CH, Ebo D. Anaphylaxis during general anaesthesia: a 10-year survey 1 at the University Hospital of Antwerp. *Progam*. 2013;2:87-99.
8. Spoerl D, Nigolian H, Czarnetzki C, Harr T. Reclassifying Anaphylaxis to Neuromuscular Blocking Agents Based on the Presumed Patho-Mechanism: IgE-Mediated, Pharmacological Adverse Reaction or "Innate Hypersensitivity"? *J Mol Sci*. 2017;7:18.

9. Dewachter P, Chollet-Martin S, Mouton-Faivre C, de Chaisemartin L, Nicaise-Roland P. Comparison of Basophil Activation Test and Skin Testing Performances in NMBA Allergy. *J Allergy Clin Immunol Pract*. 2018;6:1681-9.
10. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA et al. International Consensus on drug allergy. *Allergy*. 2014;69:420-37.
11. Laguna JJ, Archilla J, Doña I, Corominas M, Gastaminza G, Mayorga C. Practical guidelines for perioperative hypersensitivity reactions. *J Investig Allergol Clin Immunol*. 2018;28:216-32.
12. Asserhøj LL, Mosbech H, Krøigaard M, Garvey LH. No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut†. *Br J Anaesth*. 2016;116:77-82.
13. Trautmann A, Seidl C, Stoevesandt J, Seitz CS. General anaesthesia-induced anaphylaxis: impact of allergy testing on subsequent anaesthesia. *Clin Exp Allergy*. 2016;46:125-32.
14. Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol*. 2004;114:371-6.
15. Ring, J.; Messmer, K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet*. 1977;1, 466–9.
16. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al; ENDA/EAACI Drug Allergy Interest Group. Skin test concentrations for systemically administered drugs - an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*. 2013;68:702-12.
17. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy*. 2003;58:854–63.

18. Blaabjerg MS, Andersen KE, Bindslev-Jensen C, Mortz CG. Decrease in the rate of sensitization and clinical allergy to natural rubber latex. *Contact Dermatitis*. 2015;73:21-8.
19. Tacqard C, Collange O, Gomis P. Anaesthetic hypersensitivity reactions in France between 2011 and 2012: the 10th GEAP epidemiologic survey. *Acta Anaesthesiol Scand*. 2017;61:290-9.
20. Laxenaire M-C, Mertes PM. Anaphylaxis during anaesthesia. Results of a two-year survey in France. *Br J Anaesth*. 2001;87:549-58.
21. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. *Anesthesiology*. 2005;102:897-903.
22. Garvey LH, Roed-Petersen J, Menné T, Husum B. Danish Anaesthesia Allergy Centre - preliminary results. *Acta Anaesthesiol Scand*. 2001;45:1204-9.
23. Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. *Ann Fr Anesth Reanim*. 1993;12:97-10.
24. Meng J, Rotiroti G, Burdett E, Lukawska JJ. Anaphylaxis during general anaesthesia: experience from a drug allergy centre in the UK. *Acta Anaesthesiol Scand*. 2017;61:281-9.
25. Harper NJN, Cook TM, Garcez T, Lucas DN, Thomas M, Kemp H et al. Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6). *Br J Anaesth*. 2018;121:172-88.
26. Gurrieri C, Weingarten TN, Martin DP, Babovic N, Narr BJ, Sprung J, Volcheck GW. Allergic reactions during anesthesia at a large United States referral center. *Anesth Analg*. 2011;113:1202-12.

27. Lobera T, Audicana MT, Pozo MD, Blasco A, Fernández E, Cañada P, et al. Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. *J Investig Allergol Clin Immunol*. 2008;18:350-6.
28. Mertes PM, Volcheck GW, Garvey LH, Takazawa T, Platt PR, Guttormsen AB, et al. Epidemiology of perioperative anaphylaxis. *Presse Med*. 2016;45:758-67.
29. Guyer AC, Saff RR, Conroy M, Blumenthal KG, Camargo CA, Long AA, et al. Comprehensive allergy evaluation is useful in the subsequent care of patients with drug hypersensitivity reactions during anesthesia. *J Allergy Clin Immunol Pract*. 2015;3:94-100.
30. Audicana MT, Lobera T, González I, Tomás L, Reyes S, Muñoz D. Allergic Reactions in Anesthesia: Do Diagnostic Studies Ensure the Safety of Reoperation? *J Investig Allergol Clin Immunol*. 2015;25:441-3.
31. Tsur A, Kalansky A. Hypersensitivity associated with sugammadex administration: a systematic review. *Anaesthesia*. 2014;69:1251-7.

Table 1. Concentrations used for skin tests and challenge tests with general anesthetics.

Drug	Skin tests	DCT (i.v.)
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
Remifentanyl	-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

IDT: intradermal test; DCT: Drug challenge test; i.v.: intravenous route.

Figure 1. Diagnostic algorithm.

