

The Incidence of Perioperative Hypersensitivity Reactions: A Single-Center, Prospective, Cohort Study

Felicia Berroa, MD, PhD,* Alberto Lafuente, MD, PhD,† Gracia Javaloyes, MD, PhD,* Paula Cabrera-Freitag, MD, PhD,* Juan M. de la Borbolla, MD,* Rafael Moncada, MD,† Maria J. Goikoetxea, MD, PhD,* Maria L. Sanz, MD, PhD,* Marta Ferrer, MD, PhD,* and Gabriel Gastaminza, MD, PhD*

BACKGROUND: The incidence of perioperative hypersensitivity reactions, which can be life-threatening, ranges from 1 in 20,000 to 1 in 1361. These reactions are usually classified as IgE or non-IgE mediated. The aim of this study was to determine the incidence of allergic reactions during general anesthesia in our hospital, to establish the incidence of the allergic reactions for each drug used, to assess the frequency of IgE-mediated reactions in even mild reactions, and to compare the degree of agreement between anesthesiologist suspicion and allergy diagnosis.

METHODS: We included patients diagnosed with a clinical hypersensitivity reaction during a procedure under general anesthesia over a 30-month period (February 2008 to August 2010). Plasma histamine and serum tryptase concentrations were determined in these patients. We performed skin tests to diagnose the causative agent. Data from the hospital electronic prescribing system were collected to determine the ratio of reactions for each drug.

RESULTS: During the study period, 16,946 anesthetic procedures were performed (53% involved males; mean age, 51.6 years). Forty-four perianesthetic reactions were recorded, and the ratio of reactions was 1 in 385 operations (95% confidence interval, 1/529–1/287). Twenty-five reactions (25/44; 57%) occurred during the induction of anesthesia. Twenty-one reactions (21/44; 48%) were mild, involving only skin, and 23 of 44 (52%) were anaphylactic reactions. Four of 10 patients who had only a rash experienced IgE-mediated reactions. Five surgeries (11%) were suspended because of the severity of the reactions. Fifteen reactions (15/30; 50%) were IgE mediated, and, in 2 of 30 (7%), a non-IgE agent was found (cold urticaria and nonsteroidal anti-inflammatory drug intolerance). The ratio of reactions for each drug was as follows: protamine, 1 in 468; cisatracurium, 1 in 1388; amoxicillin-clavulanate, 1 in 1968; atracurium, 1 in 2039; and dipyrone, 1 in 3159.

CONCLUSIONS: Perioperative reactions are more common than previously reported. Mild hypersensitivity perioperative reactions—involving only skin—should be considered in evaluating patients because a substantial number of these reactions are IgE mediated. (Anesth Analg 2015;XXX:00–00)

Perioperative hypersensitivity reactions secondary to the administration of anesthetics, or other drugs administered during anesthesia induction or surgical procedure, are highly variable, ranging from 1 in 20,000 to 1 in 1361 among different countries in Europe and Australia.^{1–3} In Spain, data from 2 prospective studies reported an incidence of 1 in 10,263 anesthetics⁴ and 1 in 1480 procedures.⁵ These types of reactions represent a diagnostic challenge because multiple drugs are administered at once, and some of them can produce unspecific histamine release.^{6,7}

In some patients, these reactions could be life-threatening. Onset is within minutes, and the reactions may occur at any given moment of the procedure. They are usually classified as IgE or non-IgE mediated. When it is not possible

to demonstrate the presence of IgE antibodies, the reaction may be explained by a nonspecific release of histamine by the activation of complement, either through antibodies other than IgE or through other causes such as the mechanic effect of intubation, vagal reactions, pharmacological effects, malignant hyperthermia,⁸ or delay in performing the allergy studies.⁹

The aim of this study was to determine the incidence of allergic reactions during general anesthesia in our hospital, to establish the incidence of the allergic reactions for each drug used, and to assess the frequency of IgE-mediated reactions in even mild reactions. We also wanted to compare the degree of agreement between suspicion by the anesthesiologist and the results of the allergy diagnosis.

METHODS

The study was performed over a previously set 30-month period (February 2008 to August 2010). A joint protocol was designed by the Departments of Allergy and Anesthesiology at the Clínica Universidad de Navarra Medical School Hospital, Pamplona, Spain.

The study was approved by the local ethics committee. All patients diagnosed with a clinical hypersensitivity reaction were informed of the study protocol and gave their written consent to allow further testing.

From the Departments of *Allergy and †Anaesthesiology, Clínica Universidad de Navarra, Pamplona, Spain.

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Address correspondence to Gabriel Gastaminza, MD, PhD, Departamento de Alergología, Clínica Universidad de Navarra, 31008 Pamplona, Spain. Address e-mail to gastaminza@unav.es.

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Patients

All patients who experienced a perioperative hypersensitivity reaction during a procedure involving general anesthesia with intubation or regional anesthesia with sedation at any time during induction, maintenance, or in the postanesthesia care unit (PACU) were included. Local anesthetic procedures without sedation and procedures performed outside the operating room with sedation (i.e., endoscopies or bronchoscopies) were excluded.

To avoid potential bias in the selection of patients, the inclusion criteria were established and explained before the study. Two anesthesiologists ensured that each patient fulfilled these criteria, which comprised hypersensitivity reaction symptoms such as erythema, wheals, pruritus, angioedema, bronchospasm, increased airway pressure, desaturation <90%, wheezing, hypotension or hypertension, arrhythmia, ST changes, bradycardia/tachycardia, nasoconjunctival symptoms, hypothermia or hyperthermia, convulsion, abdominal symptoms, and cardiac arrest. Patients whose only manifestation was hypotension, bronchospasm, myocardial ischemia, or arrhythmias were included only if there was no other explanation for such symptoms. When the only symptom was generalized erythema, only those patients in whom skin rash lasted for >3 minutes were included.

For each hypersensitivity reaction, the anesthesiologist completed a questionnaire describing the patient's signs and symptoms, the timeframe of drug administration, and the time of the reaction onset. The severity of the reaction was established following the classification of Ring and Messmer as grade 1 (skin symptoms), grade 2 (measurable, but not life-threatening reaction affecting skin and other organs), grade 3 (shock life-threatening reaction), and grade 4 (cardiac and/or respiratory arrest).¹⁰ The classification used is described in Table 1. Grades 2 to 4 correspond to anaphylaxis.

Of note, 23 of 44 patients included in this study had also been part of a previously published study in which we analyzed the usefulness of serum tryptase and plasma histamine determinations in diagnosing perioperative allergic reactions.¹¹

Plasma Tryptase and Histamine

Tryptase was determined by enzyme immunoanalysis (ImmunoCAP FEIA, Thermo Fisher, Uppsala, Sweden) following the manufacturer's instructions. Samples were collected at the time of the reaction and 2 and 24 hours

afterward and were considered elevated when at least 1 of the first 2 determinations doubled basal levels. Plasma histamine was determined in heparinized blood samples extracted immediately after the reaction occurred (within the first 15 minutes) and 2 hours after the reaction took place. Histamine was measured by a fluorometric method following the technique described by Shore et al.¹² and modified by Siraganian¹³ using an AutoAnalyzer 3 (Bran Luebbe, SEAL Analytical Inc., Mequon, WI). Plasma histamine was considered elevated when levels were ≥ 28 ng/mL (sensitivity of 74.51% and a specificity of 80.7%).¹¹

Specific IgE

In some cases, to assess the causative agent, specific IgE was quantified using a fluorescence immunoassay (ImmunoCAP FEIA, Thermo Fisher), following the manufacturer's instructions. Values ≥ 0.35 kU_A/L were considered positive.

Allergy Study

All patients were assessed by an allergist on the day of the reaction. An early allergy study was performed within the first 4 days after the reaction occurred and reassessed 4 to 8 weeks later. Skin tests were performed sequentially, starting with skin prick tests (SPT) and, if negative, by intradermal tests (ID), with all the drugs administered before the reaction, plus latex and antiseptics used. Histamine (10 mg/mL) and saline solution were used as positive and negative controls, respectively. Test results were considered positive when papules >3 and >5 mm in diameter appeared in the SPT and the ID tests, respectively, although papules had to be accompanied by itching and erythema.¹⁴ The concentrations used were those recommended in published guidelines.^{5,15} For those drugs for which there were no reference dilutions, if a test was positive, we tested 10 controls to rule out unspecific results. In some patients, to achieve the diagnosis, it was necessary to perform a controlled exposure test.

Reactions were considered IgE mediated if either SPT or ID were positive in any of the 2 skin tests performed (early or late). When all tests were negative, the reactions were classified as non-IgE mediated.

Incidence of Reactions to Each Drug

For the patients admitted to our center, the computer system issues all prescriptions, and thus, it is possible to know how often and in what area a particular drug is administered to a patient. To determine the ratio of reactions to each of the drugs, data about drug administrations to each patient during every procedure in the operating room were collected from the electronic prescribing system for those drugs involved in the reactions of at least one patient during the study period (February 15, 2008, to August 15, 2010). When a drug (i.e., propofol) was administered to a patient more than once during the same anesthetic procedure, it was counted as one administration of the drug.

Statistical Analysis

All data were processed using the software package SPSS v.20.0 for Mac OS (Chicago, IL). Data were expressed as frequencies or percentages. Quantitative data were expressed as medians (interquartile range [IQR]). For comparison of

Table 1. Grade of Severity of Reactions According to Signs and Symptoms Presented

Grade	Definition	Signs
I	Only cutaneous signs	Erythema angioedema urticaria
II	Mild systemic reaction, not life-threatening	Cutaneous signs Cardiovascular: tachycardia, hypotension Respiratory disturbances: difficulty inflating, wheezing, cough
III	Life-threatening symptoms	Collapse, tachycardia or bradycardia, arrhythmias Severe bronchospasm
IV	Cardiac and/or respiratory arrest	

Table 2. Patients Included in the Study

No.	Age (y)	Sex	No. previous operations	Previous allergies	Timing of the reaction	Severity of the reaction ^a	Drug involved	Peak tryptase (μg/L)	Baseline tryptase (μg/L)	Peak histamine (ng/mL)
1	41	F	0	No	PACU	1	Dipyrone	4.25	3.90	32.37
2	54	M	19	No	Operation	2	Protamine	18.60	19.00	47.33
3	82	M	4	Yes	Induction	1	Cold urticaria	8.43		
4	30	F	3	No	PACU	1	Latex	23.80	8.16	
5	33	F	0	Doubtful	Induction	1	Cisatracurium	5.04	3.41	119.60
6	51	F	1	Doubtful	Induction	1	Povidone-iodine	3.30		32.21
7	15	M	9	No	PACU	1	Dipyrone + morphine	1.72	1.94	259.64
8	57	M	1	No	PACU	1	Intolerance to NSAIDs	6.46		19.29
9	55	M	2	No	Induction	3	Amoxicillin-clavulanate	8.99	3.43	46.72
10	23	M	3	Yes	Induction	3	Atracurium	23.60	1.66	69.98
11	64	M	4	Yes	Induction	3	Amoxicillin-clavulanate	34.70	5.45	74.35
12	25	M	1	Yes	Induction	1	Atracurium	8.30	6.52	30.19
13	15	M	2	No	Induction	1	Atracurium	4.89	4.87	36.11
14	79	F	6	No	Operation	2	Latex	69.50	11.60	45.79
15	56	M	1	Yes	Operation	2	Dipyrone	46.00	5.71	36.72
16	64	M	1	Yes	Operation	2	Amoxicillin-clavulanate	11.30	3.12	40.91
17	20	M	0	Yes	Induction	3	Atracurium	3.28	2.73	49.01
18	81	F	5	No	Induction	3	INC	3.67		91.72
19	77	F	3	Doubtful	PACU	1	INC	6.43		16.55
20	13	F	0	No	PACU	1	INC	2.98		17.31
21	48	F	0	No	Operation	1	INC	1.94	1.96	33.43
22	68	M	4	No	Induction	3	INC	5.13	3.15	119.85
23	59	F	1	No	Induction	3	INC	2.94	2.46	21.43
24	42	F	0	No	Operation	2	INC	31.10	5.68	8.77
25	60	F	0	No	Induction	3	INC	6.04		65.13
26	52	F	2	No	Operation	2	INC	3.99	4.04	36.05
27	70	F	1	Yes	Induction	3	INC	1.80	1.00	223.29
28	25	M	1	No	PACU	1	INC	2.55	2.99	28.42
29	32	M	1	No	Induction	1	INC	2.88	1.00	27.07
30	57	M	0	No	Induction	1	INC	3.83	2.95	10.65
31	47	M	0	No	Induction	3	INC	2.59	1.23	22.56
32	61	M	3	No	Induction	3	NAD	12.00	10.50	37.01
33	19	M	0	No	Induction	1	NAD	2.62	2.81	43.82
34	52	F	3	Yes	PACU	2	NAD	.90	3.00	110.59
35	52	F	6	Yes	PACU	1	NAD	2.05	3.05	38.51
36	16	F	1	No	Operation	3	NAD	5.06	4.90	27.79
37	12	M	1	No	Induction	1	NAD	3.12	1.71	85.39
38	57	F	2	No	Induction	2	NAD	6.58	7.07	45.24
39	19	F	0	No	PACU	1	NAD	7.21	6.19	51.16
40	29	M	1	No	Operation	2	NAD	3.08	4.79	23.25
41	45	M	0	No	Induction	1	NAD	2.74	2.33	25.76
42	46	M	10	No	Induction	3	NAD	3.51	4.39	33.21
43	33	F	2	No	Induction	3	NAD	6.10	3.94	49.46
44	48	F	1	No	Induction	1	NAD	3.07	2.89	39.14

F = female; INC = incomplete study; M = male; NAD = full study with no triggering agent detected; NSAID = nonsteroidal anti-inflammatory drug; PACU = postanesthesia care unit.

^aSeverity of the reaction: According to the classification of Ring and Messmer.

variables, the Mann-Whitney *U* test was used (tryptase level comparisons) because normal distribution was not followed using the Shapiro-Wilk test (tryptase levels: grade 1, $P < 0.001$; grade 2, $P = 0.058$; grade 3, $P < 0.001$; IgE-mediated reactions, $P = 0.003$; and non-IgE-mediated reactions, $P = 0.040$). All differences were considered statistically significant when $P < 0.05$. The 95% confidence interval (CI) for ratios was calculated using the Clopper-Pearson method.^a

RESULTS

During the study period, 16,946 surgical procedures were performed with general anesthesia or local anesthesia with

sedation. The mean (range) of patient age was 51.6 (1–103) years, and 8931 (53%) patients were male.

Forty-four perianesthetic reactions were recorded during the study period; thus, the ratio of reactions in our study was 1 in 385 procedures (95% CI, 1/529–1/287). Twenty-two (22/44; 50%) patients were males. The median age (range) of patients was 45.79 (12–82) years. The mean of previous operations per patient was 2.5 (range, 0–19). Ten patients (10/44; 23%) had not previously undergone surgical procedures with general anesthesia. Ten patients (10/44; 23%) were atopic.

Twenty-five reactions (25/44; 57%) occurred during the induction of anesthesia, 9 of 44 (20%) in the course of the surgery procedure, and 10 of 44 (23%) in the PACU. Twenty-one reactions (21/44; 48%) were grade 1, and 23 of 44 (52%)

^a<http://epitools.ausvet.com.au/content.php?page=CIPProportion>. Accessed on April 13, 2015.

reactions that fulfilled anaphylaxis criteria (9/44 [20%] were grade 2; and 14/44 [32%] were grade 3). No patient experienced a grade 4 reaction, and no cardiorespiratory arrests or deaths were recorded. Five interventions (5/44; 11%) were postponed due to reaction severity. All these occurred during the induction phase.

The most common symptoms or signs involved the skin (rash, urticaria-angioedema, and pruritus), which presented in 37 patients (37/44; 84%), followed by those affecting the cardiovascular system (arrhythmias, changes in ST segment, tachycardia, or bradycardia) in 18 of 44 patients (41%). In 12 of 44 patients (27%), the respiratory system was affected (desaturation, increased airway pressure, wheezing), and one patient experienced convulsions (1/44; 2%). In 24 of 44 patients (54.5%), only one organ was involved (21/24, the skin only; 1/24, the respiratory system; and 2/24, the vascular system). Of the 21 patients with skin involvement as the only manifestation, 15 presented a rash for more than 3 minutes, which represents 34% of patients. In 16 of 44 patients (36%), 2 systems were involved (in 4/16 patients, both skin and the respiratory system were affected; in 8/16, both skin and the vascular system were affected; and in 4/16, both the respiratory and vascular systems were affected). In 4 of 44 patients (9%), 3 systems were affected (3/4 with involvement of the skin, vascular, and respiratory systems and 1/4 with involvement of the skin, vascular, and neurological systems).

Fourteen patients (14/44; 32%) did not return for the follow-up consultation within the time limit of 4 to 8 weeks; thus, it was not possible to establish whether the reaction was IgE mediated (Table 2).

Of the 30 patients (30/44; 68%) who completed the study, a triggering agent was detected in 17 of them (17/30; 57%) (Table 2). In 15 patients (15/30; 50%), the mechanism was IgE mediated. One patient (1/30; 3%) exhibited intolerance to nonsteroidal anti-inflammatory drugs, and one patient (1/30; 3%) experienced cold urticaria due to the cold saline solution used. The remaining 13 of 30 reactions (43%) were classified as non-IgE-mediated reactions (Table 3).

In 4 of the 15 patients who had only a rash, an IgE-mediated mechanism was detected, and another patient was diagnosed with cold urticaria. Five of these patients did not complete the allergy study.

The causative drugs involved in IgE-mediated reactions (15/30) were neuromuscular-blocking drugs (NMBA) in 5 of 15 (33%) patients (4/5 atracurium, 1/5 cisatracurium), amoxicillin-clavulanate in 3 of 15 (20%) patients, latex in 2 of 15 (13.3%) patients, and dipyrone in 3 of 15 (20%) patients. In one diabetic patient, a reaction was caused by the anticoagulant protamine, and, in another patient, the culprit trigger was the antiseptic povidone-iodine. One of the patients sensitized to dipyrone also had positive skin tests with morphine (Table 2).

Among the 10 patients who had not previously undergone operations with general anesthesia, the drug responsible was detected in 3 patients (atracurium, cisatracurium, and dipyrone).

The main drugs assumed by the anesthesiologist to be causative were NMBA (16%), followed by opioids (14%), and analgesics (9%). The level of agreement between the anesthesiologists' suspicions and the final diagnosis of the

Table 3. Agreement Between the Causing Drug Suspected by Anesthetist and the Drug or Factor Finally Diagnosed as Doing the Cause

No. of patient	Drug suspected by anesthetist	Triggering drug or cause finally diagnosed	Agreement
1	Dipyrone	Dipyrone	X
2	Morphine	Protamine	
3	Midazolam	Cold urticaria	
4	None	Latex	
5	Fentanyl	Cisatracurium	
6	Atracurium	Povidone-iodine	
7	Morphine	Dipyrone + morphine	X
8	Diclofenac	Intolerance to NSAIDs	X
9	Amoxicillin-clavulanate	Amoxicillin-clavulanate	X
10	Atracurium, ketamine	Atracurium	X
11	Amoxicillin-clavulanate, atracurium	Amoxicillin-clavulanate	X
12	Cefazolin, atracurium	Atracurium	X
13	Cefazolin	Atracurium	
14	Atracurium	Latex	
15	Dipyrone	Dipyrone	X
16	Amoxicillin-clavulanate	Amoxicillin-clavulanate	X
17	Atracurium	Atracurium	X

NSAID = nonsteroidal anti-inflammatory drug.

patients was 59% (10/17). Table 3 shows the drug suspected by the anesthesiologist and the final cause diagnosed in each case in which a cause was found.

The ratio between the number of hypersensitivity reactions with each drug and the number of patients receiving this drug during an anesthetic procedure is shown in Table 4.

According to the time during which the reaction occurred, the drugs involved were as follows:

- Induction of anesthesia: NMBA (5), antibiotics (2), povidone-iodine (1), and cold urticaria (1)
- In the course of the operation: latex (1), analgesics (1), antibiotics (1), and anticoagulant (1)
- In the PACU: analgesics (3) and latex (1)

Nine patients (9/44; 20%) had increased tryptase levels, and in 6 of them, the drug responsible was detected; the 3 remaining patients did not complete the allergy study. Median tryptase levels were as follows: 3.3 µg/L in grade 1 (IQR, 2.7–6.4), 11.3 µg/L in grade 2 (IQR, 3.5–38.5), and 5.1 µg/L in grade 3 (IQR, 3.2–9.7) reactions. Statistically significant differences were found between tryptase levels in grade 1 and 2 reactions (Mann-Whitney *U* test, *P* = 0.035), but not between grade 1 and grade 3 and grade 2 and grade 3 reactions.

Thirty-two patients (32/44; 73%) had elevated plasma histamine levels (32.4 µg/L in grade 1 [IQR, 25.8–43.8], 40.9 µg/L in grade 2 [IQR, 29.6–46.6], and 49.2 µg/L in grade 3 reactions [IQR, 31.8–78.7]). Differences between IgE- and non-IgE-mediated reactions are described in Table 5.

DISCUSSION

As mentioned earlier,^{1,3,5,16} larger differences in the incidence of perioperative reactions among different studies have been established. In a study conducted in 20 hospitals in Catalonia (Spain), the incidence of allergic reactions in anesthesia was 1 in 10,263 procedures, with the frequency

Table 4. Number of Reactions and Ratios of the Drugs Involved in the Perianesthetic Reactions

Drug	Administrations (N)	Reactions (N)	Ratio	95% CI
Atracurium	8159	4	1/2039	1/7462–1/797
Amoxicillin–clavulanate	5904	3	1/1968	1/9524–1/674
Dipyrone	9477	3	1/3159	1/15,385–1/1081
Latex	Unknown	2		
Protamine	468	1	1/468	1/18,518–1/84
Cisatracurium	1388	1	1/1388	1/55,555–1/249
Diclofenac	2142	1	1/2142	1/83,333–1/385
Morphine	10,045	1	1/10,045	1/333,333–1/1802
Iodine	Unknown	1		

Data were collected from the electronic prescribing system.

There were no reactions to the next drugs. No of administrations of the drug during the study period is as follows: propofol, 14,328; etomidate, 692; pentothal, 40; ketamine, 442; succinylcholine, unknown; rocuronium, 907; vecuronium, 4; fentanyl, 12,597; remifentanyl, 3668; acetaminophen, 10,352; ketorolac, 2757; lidocaine, 10,576; mepivacaine, 512; bupivacaine, 369; midazolam, 4662; diazepam, 7175; atropine, unknown; ephedrine, 2028; phenylephrine, 424; adrenaline, 2180; cefazolin, 4083; clindamicina, 415; levofloxacin, 387; gentamicina, 816; vancomycin, 433; metronidazole, 1078; mitomycin, 59; ondansetron, 6667; ranitidine, 8264; methylethylgometrine, 124; oxytocin, 267; heparin sodium, 974; dexamethasone, 7121; insulin, 190; gelatin, 2300; hydroxyethyl Storch, 472; chlorhexidine, unknown.

CI = confidence interval.

Table 5. Differences Between IgE- and Non-IgE-Mediated Reactions

	IgE mediated	Non-IgE mediated
No. of previous surgeries, median (IQR)	2 (1–4)	1.5 (1–3)
History of atopy, n (%)	6/15 (40%)	2/15 (13%)
Tryptase level (µg/L), mean (IQR)	9 (4.2–24.0)	3.12 (2.7–6.3) ^a
Plasma histamine (ng/mL), mean (IQR)	46.2 (35–71)	39.1 (30.5–50.3)

IQR = interquartile range.

^aMann-Whitney U test: $P = 0.010$.

increasing to 1 in 1673 when only general anesthesia with NMBA was taken into account.⁴ In a French study, the incidence of reactions was 1 in 13,000, increasing to 1 in 6500 for general anesthetics with the use of NMBA.¹⁷ Although based in different methodological studies, the incidence of reactions observed in our hospital was more frequent (1/385 [95% CI, 1/529–1/287]).

Possible explanations for these differences are as follows: (1) differences in the types of anesthetics used in the study; (2) diverse anesthesia protocols and drugs used among countries; (3) differences on diagnostic and classification criteria; and (4) the retrospective nature of many studies published on the prevalence of perioperative reactions.¹⁸

In our opinion, because it is a prospective study and because we included all types of hypersensitivity reactions, not just anaphylaxis, our study found a higher incidence of hypersensitivity reactions than previous studies. We believe that mild reactions might have been underreported in many studies. According to our results, a significant number of mild reactions are IgE mediated. We postulate that if minor reactions were also studied, a significant number of severe anaphylaxis could be prevented in the future. IgE-mediated reactions in anesthesia are usually more severe than non-IgE-mediated reactions.¹⁹ In other studies,²⁰ systematic protocols applied to patients with reactions during anesthesia increased the incidence of reactions diagnosed as IgE mediated. These authors also maintained that in patients with a previous mild reaction, the lack of a proper diagnosis and allergy assessment may lead to more severe reexposure.

Of the 30 patients studied, we detected the drug triggering the reaction in 17 (57%), a figure similar to that reported

in other studies. However, a possible weakness of our work is that 14 of 44 (32%) patients did not return after the 4 to 8 weeks of the reaction to complete the study, and as a result, the allergy study was not completed. In view of these results, we suggest performing early allergy studies in the days following the reaction, when the patients are still admitted. This approach may prove beneficial, as shown by the results of a study recently published by our group.⁹

We have found no data in the literature correlating the number of allergic reactions per drug dose administered. In our study, the figure due to NMBA is lower than previously reported in other studies where NMBA are considered to be the cause of more than 40% of IgE-mediated reactions²¹ or even as many as 93% of such reactions.³

Antibiotics and analgesics were the second cause of IgE-mediated reactions during surgical procedures. Likewise, other studies reflect the decrease in the percentage of reactions due to NMBA and the increase in the frequency of reactions secondary to the administration of antibiotics.²¹

Although some studies have shown a low risk of adverse reactions following the administration of dipyrone,²² in our patients with allergy to analgesics, the drug involved was dipyrone, probably because it is used so widely in Spain. Only 2 of our patients were allergic to latex, which is again consistent with the published results, highlighting the decreasing frequency of latex as a cause for perioperative reactions.⁵

One of our patients was sensitized to povidone-iodine. This patient developed a skin rash during the induction of the anesthesia, which resolved after the administration of dexamethasone. Antiseptics such as chlorhexidine and povidone-iodine may act as hidden allergens in perioperative reactions, as has been reported previously,^{23–26} and thus, it is advisable to test these drugs in all patients.

Another patient developed a skin rash on the arm in which saline solution was infused. This rash spread subsequently and reappeared minutes later when saline was readministered. Skin test with all the drugs involved proved negative except for an ice-cube test. It is important to consider physical urticaria as a cause of perioperative hives or wheals, especially cold urticaria, given that some of the drugs to be administered during anesthesia are refrigerated until used, as is the case with heparins and NMBA.²⁷

In conclusion, the results of our work underscore the importance of studying all perioperative reactions, including mild reactions, to prevent future, more severe reactions. Even reactions as mild as generalized erythema can hide drug hypersensitivity that otherwise may be overlooked or attributed to unspecific reactions. ■■

DISCLOSURES

Name: Felicia Berroa, MD, PhD.

Contribution: This author helped conduct the study, analyze the data, write the manuscript, and patient recruitment, data collection, in vitro study.

Attestation: Felicia Berroa has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Alberto Lafuente, MD, PhD.

Contribution: This author helped design the study, conduct the study, analyze the data, write the manuscript, and patient recruitment, in vitro study.

Attestation: Alberto Lafuente has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Gracia Javaloyes, MD, PhD.

Contribution: This author helped patient recruitment and data collection.

Attestation: Gracia Javaloyes has seen the original study data and approved the final manuscript.

Name: Paula Cabrera-Freitag, MD, PhD.

Contribution: This author helped write the manuscript and patient recruitment.

Attestation: Paula Cabrera-Freitag has seen the original study data and approved the final manuscript.

Name: Juan M. de la Borbolla, MD.

Contribution: This author helped patient recruitment.

Attestation: Juan M. de la Borbolla has seen the original study data and approved the final manuscript.

Name: Rafael Moncada, MD.

Contribution: This author helped patient recruitment.

Attestation: Rafael Moncada has seen the original study data and approved the final manuscript.

Name: Maria J. Goikoetxea, MD, PhD.

Contribution: This author helped analyze the data, write the manuscript, and patient recruitment, data collection, in vitro study.

Attestation: Maria J. Goikoetxea has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Maria L. Sanz, MD, PhD.

Contribution: This author helped write the manuscript and in vitro study.

Attestation: Maria L. Sanz has seen the original study data and approved the final manuscript.

Name: Marta Ferrer, MD, PhD.

Contribution: This author helped write the manuscript.

Attestation: Marta Ferrer has seen the original study data and approved the final manuscript.

Name: Gabriel Gastaminza, MD, PhD.

Contribution: This author helped design the study, conduct the study, analyze the data, write the manuscript, and patient recruitment, data collection, in vitro study.

Attestation: Gabriel Gastaminza has seen the original study data, reviewed the analysis of the data, and approved the final manuscript, and is responsible for archiving the study files.

This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

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