

Systematic follow-up increases incidence of anaphylaxis during adverse reactions in anesthetized patients

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Background: The incidence of hypersensitivity reactions during anesthesia is underestimated because clinical symptoms may vary and diagnosis is not obvious. Our aim was to investigate the consequences of a systematic follow-up of patients on the estimated incidence of allergic reactions during anesthesia.

Methods: We conducted a prospective study over a 2-year period (70,000 anesthetics). When patients were suspected with hypersensitivity reactions or with unexplained adverse reactions during anesthesia, blood was sampled to measure histamine and tryptase, and then skin tests were performed 4–6 weeks later.

Results: During the studied period, 39 patients were enrolled in the database. Eight were excluded because of lack of skin tests. Twenty-two patients had clinical features compatible with immediate hypersensitivity reaction, and nine had reactions rated as 'unexplained' by the attending physician. Following systematic investigation, we found 22 hypersensitivity reactions (15 patients with obvious and

seven with unexplained reactions) during anesthesia. This increases the estimated incidence of hypersensitivity reactions from 1:4667 to 1:3180 anesthetics. Tryptase concentrations were increased in only 50% of these patients. In our series, positive and negative predictive values of tryptase at T₀ for the diagnosis of anaphylaxis were 100% and 60%, respectively. Latex was the major causative agent, followed by neuromuscular blocking agents and antibiotics.

Conclusions: Systematic follow-up of patients with unexplained reactions during anesthesia increases the estimated incidence of IgE-mediated hypersensitivity reactions during anesthesia by 50%.

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IMMEDIATE hypersensitivity reactions occurring during anesthesia may be life-threatening, requiring rapid therapeutic intervention. Follow-up in order to identify the causative agent is mandatory. These reactions are mostly IgE mediated (1). Traditionally, when the reaction results from an allergen–antibody conflict, a release of histamine is observed, along with other mediators such as tryptase, an enzyme co-localized with histamine in mast cells.

Nevertheless, the clinical diagnosis of a hypersensitivity reaction during anesthesia can be difficult. For example, many symptoms may be misinterpreted as a result of an interaction between the clinical status of the patient and the drugs

administered during the procedure, dose-related side effect of the drugs, or a too light anesthesia, or may simply remained unexplained. Another difficulty for the positive diagnosis of hypersensitivity-IgE is the fact that cutaneous symptoms are absent in one-third of the cases and clinical symptoms, such as hypotension or bronchospasm, may occur as an isolated condition (2–4). However, the diagnosis of hypersensitivity reactions and their mechanism is of crucial importance to avoid any inappropriate reexposure of a patient to a substance toward which he is effectively sensitized. For these reasons, an extensive use of tryptase measurements in case of hypersensitivity reactions but also unexplained reactions occurring during anesthesia has been advocated (5, 6). Such a liberal use of tryptase measurements may lead to a better estimation of the rate of hypersensitivity-IgE

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reactions and may help to recognize patients requiring specialized allergological investigation such as skin tests to confirm the underlying mechanism and to identify the drug involved.

The objective of this prospective study was to better evaluate the incidence of hypersensitivity reactions during anesthesia. To this end, we systematically investigated all suspected hypersensitivity or unexplained reactions in anesthetized patients by performing serial circulating histamine and tryptase concentration measurements, followed by systematic allergological investigations including skin testing.

Material and methods

This 2-year prospective study was conducted at the University Hospital of Nantes from 1 May 2001 to 30 April 2003 after institutional ethics committee approval. During this period of time, nearly 70,000 surgical procedures were performed under anesthesia. A database was constructed including all patients who experienced a hypersensitivity reaction or an unexplained adverse reaction during anesthesia. Blood was systematically sampled to measure the concentrations of plasma histamine and serum tryptase within 1 h after the reaction and 24 h later. Skin tests were performed nearly 6 weeks later.

Patients inclusion

Pre-anesthetic assessment and anesthetic procedures were at the discretion of the attending anesthesiologist. Reactions were rated by the anesthesiologist as a 'hypersensitivity reaction' or as an 'unexplained reaction.' Patients were rated as 'hypersensitivity reaction' if they presented with the classical signs described in the classification proposed by Ring and Messmer (7): cutaneous symptoms (i.e. urticaria and/or angioedema) isolated or in association with other clinical symptoms such as bronchospasm, hypotension or cardiovascular collapse. An immediate hypersensitivity reaction was also classically suspected in case of circulatory inefficacy in close relation with anesthetic drugs' injection (i.e. <5 min) and in the absence of any other explanation (peroperative myocardial infarction, drugs overdose). 'Unexplained reaction' mainly concerns severe hypotension that was not explained by excessive depth of anesthesia or other perioperative incidents. Details were obtained regarding the degree of reaction

graded from I to IV depending on increasing severity [grade I = presence of cutaneous signs; grade II = presence of measurable but not life-threatening symptoms, including cutaneous effects, arterial hypotension (defined as a decrease of >30% in blood pressure associated with unexplained tachycardia), cough or difficulty in mechanical ventilation; grade III = presence of life-threatening reactions: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, severe bronchospasm; and grade IV = circulatory inefficacy, cardiac and/or respiratory arrest] (7).

Mediator assays

Blood was sampled for plasma histamine and serum tryptase concentration determination. The first sampling time following the reaction (T_0) was at 30 min when the severity score was $\leq$ II, and between 30 and 60 min for those with a score $\geq$ III. In order to determine the baseline value of tryptase, a second blood sample was withdrawn 24 h after the reaction (T_{24h}).

Histamine was measured by radioimmunoassays (RIA, Immunotech, Beckman-Coulter, Marseille, France) (normal values <10.8 nmol/l, sensitivity <1 nmol/l, reproducibility 13%). Values above 11 nmol/l were considered to be positive (8). Tryptase was measured by RIA (UniCap tryptase, Pharmacia & Upjohn, Uppsala, Sweden, with normal values <12 μ g/l, sensitivity <0.2 μ g/l, reproducibility 7%) (9). Diagnostic values of two different thresholds 12 and 25 μ g/l were tested. We also calculated the ratio between tryptase concentrations at the time of the reaction and 24 h later (T_0/T_{24h}), which has been suggested to be a better marker than a single measure during anaphylaxis (9).

Skin tests

Skin tests for all the drugs administered during anesthesia were performed according to standardized procedures as recommended by the French Society of Anesthesiology (8). Prick and intradermal tests were accompanied by control tests carried out with negative (saline) and positive controls (9% codeine phosphate) to determine whether or not the skin was liable to release histamine and react to it.

Prick tests were performed on the anterior part of the forearm using a drop of undiluted drug, with the exception of atracurium, mivacurium and morphine, which were tested using a 1/10 dilution of the commercially available drug. Prick tests with

latex were performed using a standardized commercial fresh natural rubber latex extract (Staller-Genes, France). Skin tests were interpreted after 15 min. A prick test was considered positive when the diameter of the wheal was at least equal to half of that produced by the codeine test and at least 3 mm greater than the negative control.

Once the results of prick tests were obtained, intradermal tests were carried out, either on the forearm or on the back, by an injection of 0.02–0.05 ml of commercial drugs diluted in saline. Injections were performed every 15 min, according to a dilution scale, beginning with a 10^{-4} dilution when the prick test was positive, and a 10^{-3} dilution when the prick test was negative. Injection dilutions were progressively increased up to a 10^{-1} dilution, as long as the results remained negative. For morphine, rocuronium and cis-atracurium, a maximal dilution of 10^{-2} , and for atracurium and mivacurium, a maximal dilution of 10^{-3} was used. Intradermal tests were considered positive when the diameter of the wheal was twice or more than the diameter of the wheal at the injection site. When the test was positive, cross-reactivity to other neuromuscular blocking agents (NMBAs) was investigated.

Finally, hypersensitivity reaction was diagnosed on the basis of clinical history, mediator concentrations in blood and skin tests. When skin tests were negative, adverse reactions were considered as non-IgE-mediated hypersensitivity reactions (10).

The treatments used (fluid resuscitation, vasoconstrictors or bronchodilators and intensive care unit management) and follow-up until allergologic investigation were recorded and analyzed.

Statistics

Results are presented as median and range. Statistical analysis was performed using the Mann-Whitney *U* test with the Statview 4.5 software for McIntosh computer (Abacus Concept Inc., Berkeley, CA), with a significant value of *P* set at <0.05. Incidence of hypersensitivity and non-IgE-mediated hypersensitivity reactions, and sensitivity, specificity, positive and negative predictive values of histamine, tryptase, and tryptase ratio were then calculated.

Results

Thirty-nine patients were enrolled in the database over a 24-month period. Eight patients were

excluded from the study because of a lack of skin tests (impaired physical status or patient refusal). In 22 patients, a clinical diagnosis of hypersensitivity reaction was proposed, and in nine cases the adverse reaction was considered as unexplained by the attending physician (Table 1).

The median (range) age of the patients was not different between those with IgE-mediated hypersensitivity reactions [43 (8–80)] and other reactions [45 (19–78)]. Twenty-nine reactions (94% of reactions) occurred during general anesthesia, whereas only two occurred during regional anesthesia.

Among the 22 patients with a clinical hypersensitivity reaction, 15 were diagnosed as IgE-mediated hypersensitivity reactions on the basis of positive skin tests. In these patients, histamine levels were increased in 12 and tryptase levels in seven patients (cut-off values of 12 and 25 µg/l). In the five remaining patients with negative skin tests, histamine levels were increased but tryptase concentrations were within the normal range. These reactions were considered as non-IgE-mediated hypersensitivity reactions (Tables 1 and 2).

For the nine patients with reactions initially considered as 'unexplained,' systematic skin tests were found to be positive in seven, and a diagnosis of IgE-mediated hypersensitivity reactions was proposed. In these patients, histamine was increased in four cases and tryptase in two. In the four remaining patients, skin tests and tryptase measurements were negative and the diagnosis of IgE-mediated hypersensitivity reaction was excluded (Tables 1 and 2).

Histamine and tryptase concentrations in blood at T_0 , and tryptase ratio T_0/T_{24h} are summarized in Table 2. When a cut-off value of 25 µg/l was used, 41% of patients with anaphylaxis had increased tryptase concentrations whereas none of the patients with a diagnosis of non-IgE-mediated hypersensitivity reactions or 'unexplained reactions' had increased tryptase concentrations. The respective diagnostic values depending on the threshold of increased histamine and tryptase concentrations and ratio T_0/T_{24h} are shown in Table 3.

Among the 70,000 anesthetics performed during the study period, skin tests revealed 22 (71%) IgE-mediated hypersensitivity reactions. This leads to an estimated overall incidence of IgE-mediated hypersensitivity reactions of 1:3180 anesthetics. As can be seen in Table 1, latex was the main causative agent (12 patients, 55%), followed by NMBAs (six patients, 27%), gelatins (three patients, 14%) and antibiotics (one patient, 5%). Retrospective

Table 1

Database of patients with hypersensitivity reactions during anesthesia.

Patients	Gender	Age	Surgery	Classification of reaction by attending physician	Histamine (ng/ml)	Tryptase T ₀ (μg/l)	Tryptase T _{24h} (μg/l)	Grade of severity	Causative agents
<i>Positive skin tests</i>									
1	Male	46	Colectomy	Unexplained reaction	17.1	21	2.6	III	Latex
2	Male	73	Coronary artery bypass	Hypersensitivity reaction	1	183	2.5	IV	cis-atracurium
3	Male	58	Coronary artery bypass	Unexplained reaction	34.5	258	13.3	IV	Atracurium
4	Female	23	Cesarean section	Hypersensitivity reaction	<1	26	10.8	III	Latex
5	Female	38	Cesarean section	Hypersensitivity reaction	1	14.5	—	II	Latex
6	Male	70	Craniotomy	Unexplained reaction	6.6	9.4	4.9	II	Rocuronium
7	Male	53	Partial pharyngectomy	Hypersensitivity reaction	1150	48	6.6	III	Gelatin
8	Male	43	Spinal fusion	Hypersensitivity reaction	2000	41	6.8	III	Latex
9	Female	17	Spinal fusion	Hypersensitivity reaction	307	11.3	7.1	III	Gelatin
10	Male	80	Osteosynthesis material extraction	Hypersensitivity reaction	38	18.4	2.8	III	Gelatin
11	Female	35	Hip arthroplasty	Unexplained reaction	219	9.5	3.3	II	Latex
12	Female	53	Breast prosthesis implantation	Hypersensitivity reaction	150	46	6.6	III	Latex
13	Female	27	Breast prosthesis implantation	Hypersensitivity reaction	—	62.9	5.6	III	Latex
14	Female		Breast prosthesis implantation	Hypersensitivity reaction	37.9	23.2	5.5	III	Latex
15	Female	53	Breast prosthesis implantation	Hypersensitivity reaction	40.3	9.7	2.6	III	Latex
16	Female	42	Breast prosthesis implantation	Hypersensitivity reaction	650	582	0.1	III	Succinylcholine
17	Female	18	Emergency laparotomy	Hypersensitivity reaction	995	16	7.6	III	Succinylcholine
18	Male	35	Emergency femoral fracture fixation	Hypersensitivity reaction	2140	6179	197.4	IV	Succinylcholine
19	Female	36	Emergency tibial fracture fixation	Unexplained reaction	1350	7.4	—	III	Amoxicillin + clavulanic acid
20	Male	29	Orchidectomy	Hypersensitivity reaction	36	9.9	2.0	I	Latex
21	Female	54	Cystostomy	Hypersensitivity reaction	1.4	6.9	—	II	Latex
22	Male	8	Ectopy fixation	Unexplained reaction	146	4	0.6	III	Latex
<i>Negative skin tests</i>									
23	Male	30	Cholecystectomy	Unexplained reaction	45	7.9	2.9	II	—
24	Female	45	Thyroidectomy	Hypersensitivity reaction	143	3.1	—	II	—
25	Male	39	Thyroidectomy	Hypersensitivity reaction	1	4.9	0.8	III	—
26	Female	78	Leg amputation	Unexplained reaction	3.1	3.8	1.3	I	—
27	Male	53	Partial pharyngectomy	Hypersensitivity reaction	56.5	4	—	III	—
28	Male	27	Osteosynthesis material extraction	Hypersensitivity reaction	18	23	1	I	—
29	Female	19	Breast prosthesis implantation	Hypersensitivity reaction	2.2	6.2	1.1	II	—
30	Female	48	Ureterectomy	Hypersensitivity reaction	8.7	5.4	3.9	III	—
31	Male	69	Nephrectomy	Unexplained reaction	15.4	3.4	1.8	II	—

The severity of reactions was rated according to the Ring and Messmer score (7).

Table 2

Median (range) of histamine and tryptase concentrations in blood at T_0 , and tryptase ratio T_0/T_{24h} according to suspected hypersensitivity reactions or unexplained reactions during anesthesia.

	Histamine concentrations (nmol/l)	Tryptase concentrations (μ g/l)	Ratio T_0/T_{24h}
<i>Positive skin tests</i>			
Suspected hypersensitivity reactions ($n = 15$)	150 (1–2140)	23.2 (7.0–6179)	6.57 (0.1–197)
Unexplained reactions ($n = 7$)	34.5 (1–1350)	9.5 (4–258)	2.95 (0.6–13.31)
Overall data base ($n = 22$)	93.15 (1–2140)	19.7 (4.0–6179)	5.52 (0.1–197)
<i>Negative skin tests</i>			
Suspected hypersensitivity reactions ($n = 5$)	8.7 (1.7–143)	5.4 (1.9–6.2)	2.45 (0.48–3.86)
Unexplained reactions ($n = 4$)	8.6 (1.7–45)	2.4 (1.0–7.9)	1.79 (1.0–2.93)
Overall data base ($n = 9$)	6.9 (1.7–143)	3.4 (1.0–7.9)	1.42 (0.48–3.86)

All statistical comparisons were not significant.

Table 3

Sensitivity (Sens) and specificity (Spec), and positive predictive value (PPV) and negative predictive value (NPV) of tryptase concentrations measured in blood after reaction (T_0) and of the ratio between T_0 and T_{24h} .

	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Histamine $H_0 > 12$	71	80	88	57
Tryptase $T_0 > 12$	64	100	100	53
Tryptase $T_0 > 25$	41	100	100	41
Tryptase $T_0/T_{24h} > 3$	63	83	92	42

analysis of data showed that four out of 12 patients (30%) with latex allergy presented symptoms suggestive of pre-anesthetic sensitization. Clinical signs occurred before induction in one case (antibiotic prophylaxis), immediately after induction in six cases (in five cases related to NMBAs), during maintenance of anesthesia in 22 cases and in the post-anesthetic care unit in two patients (latex allergy).

Hemodynamic and respiratory changes, and use of vasoconstrictors were not different for IgE-mediated or non-IgE-mediated reactions. Despite similar symptoms, reactions with NMBAs required more longer treatment than those with latex; 100% and 30% of the patients were admitted in ICU, respectively ($P < 0.004$).

Discussion

Systematic follow-up of unexplained reaction during anesthesia allowed us to detect more IgE-mediated hypersensitivity reactions than if we had investigated suspected hypersensitivity reactions alone. Based on these results, the estimated overall incidence of IgE-mediated hypersensitivity

reactions was increased by 50%, from 1:4667 (2) to 1:3180 anesthetics. As expected, increased tryptase value is a strong argument to support the diagnosis of IgE-mediated hypersensitivity reactions. However, despite an excellent positive predictive value, the relatively low sensitivity of tryptase measurement cannot support its use as a sole screening tool to determine the need for a specific allergological investigation.

Tryptase is a trypsin-like protease co-released with histamine when mast cells are activated during anaphylaxis. There are two structural forms of tryptase identified by specific antibodies. α -tryptase is a useful marker of a pathologically increased number of mast cells, as observed in mastocytosis (11). β -tryptase is post-transcriptionally modified, stored, concentrated in mast cell granules and released during mast cell activation and particularly during anaphylaxis (12–14). Unlike histamine, which has a half-life of very few minutes, the β -tryptase level peaks 1 or more hours after an anaphylactic event and remains elevated in serum for several hours. Unfortunately, as the only RIA commercially available measures both tryptase isoforms, to date it is not possible to distinguish the respective contribution of basal α -tryptase secretion and β -tryptase release in response to a likely mast cell activation. Therefore, controversy still persists concerning the optimal diagnostic threshold, or the interest of repeated sampling to compare peak with basal values in individuals. In this series, we compared the diagnostic performance of 12 μ g/l tryptase threshold (maximal normal value established in healthy subjects), of 25 μ g/l threshold, as recommended by the French Society of Anesthesiology (8), and the ratio between tryptase values at the time of the reaction and 24 h later. Our results demonstrate that neither a modification of

the actual diagnostic threshold nor the determination of tryptase basal values the day following the adverse reaction will increase the diagnostic value in a clinically relevant manner. However, one could not exclude that serial blood sampling following a suspected reaction could have enhanced the diagnostic performance of this test. With both normal tryptase level and negative skin tests, one can be fairly certain to reject the diagnosis of IgE-mediated hypersensitivity reactions, but not on a normal tryptase value alone. In addition, an increased tryptase concentration remains a strong argument for the diagnosis of IgE-mediated hypersensitivity reactions when skin tests could not be performed (5, 6).

By a systematic investigation of unexplained adverse reactions occurring during anesthesia, we found a higher estimated incidence of IgE-mediated hypersensitivity reactions than previously published in epidemiological studies in France or elsewhere (2, 15–22). However, these previous reports were only retrospective, based on physicians' spontaneous declarations, leading to a possible underestimation of the true incidence of anaphylaxis. Hypersensitivity reactions have been reported to occur every 1:3500 in Great Britain (20), 1:6000 in Norway (23, 24), 1:7000 in Spain (15), 5000–13,000 in New Zealand (18, 22), 1:5000 to 1:20,000 in Australia (17, 18, 21) and from 1:4600 to 1:13,000 anesthetics in France (2, 19). This wide variability may be attributed to differences in environmental conditions (25), genetics, anesthetic practices within countries and the protocols used for allergy investigation. Although we found a higher incidence of hypersensitivity reactions than reported previously, we observed a similar ratio between IgE- and non-IgE-mediated reactions of 7:3 (4).

Hypersensitivity reactions during anesthesia were mostly related to latex (55%) and NMBA (27%), followed by gelatins and antibiotics. In our series, the incidence of latex allergy was higher than expected (4), and a retrospective review of data revealed the presence of symptoms of latex sensitization before anesthesia in four patients. Similar results have previously been reported by the French expert study group of perianesthetic anaphylactic reactions (3, 4). This emphasizes the need to develop a sensitive questionnaire to detect latex allergy, available at pre-operative screening of such at-risk patients.

One of the limitations of this study is the relatively limited number of patients who experienced

adverse reactions during anesthesia in a single center. In addition, the criteria used to define unexplained adverse reactions are largely subjective. A large proportion of these reactions were classified as 'unexplained' because of the lack of concomitant cutaneous signs in the presence of hemodynamic or respiratory signs that were not attributed to (pharmacological or postural) side effects of anesthetic and surgical procedures. However, the lack of cutaneous symptoms particularly in severe IgE-mediated hypersensitivity reactions has been reported in the literature (3, 4).

Another important point to consider is that in the absence of any gold standard criteria for the diagnosis of IgE-mediated reactions, skin tests were used as the reference for the diagnosis of allergic reactions. Thus, one cannot exclude the possibility of false-positive results when the diagnosis of the reaction relies on a single allergological test.

In conclusion, our results support the liberal use of immediate biological investigation and skin test in case of hypersensitivity reactions but also in case of adverse events considered as unexplained by anesthesiologists. In addition, our results emphasize the need for a better pre-operative screening of latex sensitization in anesthetized patients.

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