

Anaphylactic and Anaphylactoid Reactions Occurring during Anesthesia in France in 1999–2000

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Background: Anaphylactic and anaphylactoid reactions occurring during anesthesia remain a major cause of concern for anesthesiologists. The authors report the results of a 2-yr survey of such reactions observed during anesthesia in France.

Methods: Between January 1, 1999, and December 31, 2000, 789 patients who experienced immune-mediated (anaphylaxis) or nonimmune-mediated (anaphylactoid) reactions were referred to one of the 40 participating centers. Anaphylaxis was diagnosed on the basis of clinical history, skin tests, and/or specific immunoglobulin E assay.

Results: Anaphylactic and anaphylactoid reactions were diagnosed in 518 cases (66%) and 271 cases (34%), respectively. The most common causes of anaphylaxis were neuromuscular blocking agents (NMBAs) (n = 306, 58.2%), latex (n = 88, 16.7%), and antibiotics (n = 79, 15.1%). Rocuronium (n = 132, 43.1%) and succinylcholine (n = 69, 22.6%) were the most frequently incriminated NMBAs. Cross-reactivity between NMBAs was observed in 75.1% of cases of anaphylaxis to an NMBA. No difference was observed between anaphylactoid and anaphylactic reactions when the incidences of atopy, asthma, or drug intolerance were compared. However, atopy, asthma, and food allergy were significantly more frequent in the case of latex allergy when compared with NMBA allergy. Clinical manifestations were more severe in anaphylaxis. The positive predictive value of tryptase for the diagnosis of anaphylaxis was 92.6%; the negative predictive value was 54.3%. The diagnostic value of specific NMBA immunoglobulin E assays was confirmed.

Conclusions: These results further corroborate the need for systematic screening in the case of anaphylactoid reaction during anesthesia and for the constitution of allergoanesthesia centers to provide expert advice to anesthesiologists and allergists.

ALTHOUGH our understanding of anaphylactoid reactions occurring during anesthesia has substantially increased over the past 30 yr, these remain a major cause for concern and a source of continuing debate among anesthesiologists.

This article is accompanied by an Editorial View. Please see: Moss J: Allergic to anesthetics. ANESTHESIOLOGY 2003; 99:521–3.

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Received from the Service d'Anesthésie-réanimation, CHU de Nancy, Hôpital Central, Nancy, France. Submitted for publication January 24, 2003. Accepted for publication May 9, 2003. Support was provided solely from institutional and/or departmental sources.

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Anesthesiology represents a pharmacologically unique practice of medicine, with patient exposure to a large number of drugs and substances over a relatively short period of time. Any drug administered during the perioperative period can produce potentially life-threatening immune-mediated anaphylaxis. However, the clinical presentation of unpredicted clinical reactions alleged to be allergic during anesthesia might in fact represent different immune and nonimmune system responses. *Anaphylaxis* is an acute allergic reaction resulting primarily from the rapid antigen-induced, usually immunoglobulin (Ig) E-dependent release of potent, pharmacologically active mediators from mast cells and basophils. The diagnosis of anaphylaxis can be easily confirmed by the use of skin or biologic tests. If the immune mechanism has not been confirmed by allergologic tests, the general term *anaphylactoid reaction* should be used. Unfortunately, in these cases, the mechanisms of the reactions are not usually elucidated.

The true incidence of anaphylactic reactions and their associated morbidity and mortality remain poorly defined. This is due to uncertainties over reporting accuracy and exhaustivity. Most reports on the incidence of anaphylaxis originate in Australia,^{1,2} France,^{3,4} the United Kingdom,^{5–7} and New Zealand.⁸ Anaphylactic reactions have also been reported in smaller series in the United States.⁹ Nevertheless, precise epidemiologic studies are required to confirm and quantify the incidence of such rare serious adverse reactions.¹⁰ In this article, we report the results of a 2-yr survey of anaphylactoid and anaphylactic reactions observed during anesthesia in France (1999–2000). This survey was conducted by the Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques, a network of 40 French allergoanesthesia outpatient clinics organized in 1985. Its aim is to promote the survey of allergic and nonimmune-mediated reactions, to describe their clinical characteristics, to identify possible risk factors, and to identify responsible drugs.

Materials and Methods

This was a retrospective study involving patients who had experienced an adverse reaction suspected of being allergic during anesthesia between January 1, 1999, and December 31, 2000. The institutional ethics committee of Lorraine approved the research. In all cases, the im-

mune mechanism of the reaction was assessed on the basis of a standardized diagnostic protocol performed in an allergoanesthesia outpatient clinic. All the centers were members of the Groupe d'Etudes des Réactions Anaphylactoides Peranesthésiques network.

The protocol included a questionnaire regarding age at the time of reaction, sex, number of previous anesthetic procedures, history of allergy (possible history of atopy or drug, food, or latex intolerance), date of the reaction, and drugs used before the reaction. Details were obtained regarding the degree of reaction, graded from 1 to 4, depending on increasing severity (grade 1 = presence of cutaneous signs; grade 2 = presence of measurable but not life-threatening symptoms, including cutaneous effects, arterial hypotension [defined as a decrease of more than 30% in blood pressure associated with unexplained tachycardia], cough or difficulty in mechanical ventilation; grade 3 = presence of life-threatening reactions, including cardiovascular collapse, tachycardia or bradycardia, arrhythmias, severe bronchospasm; grade 4 = circulatory inefficacy, cardiac and/or respiratory arrest).

Data regarding allergy investigations were systematically recorded: type of skin tests performed (*i.e.*, skin-prick test and/or intradermal test), dilution of the tested drug leading to a positive reaction, cross-reactivity between neuromuscular blocking agents (NMBAs) in cases of adverse reaction to an NMBA, results of plasma histamine and serum tryptase monitoring during the adverse reaction and of IgE-specific assays testing responses to quaternary ammonium or latex when available.

Skin tests for all the drugs administered during anesthesia were performed according to standardized procedures as recommended by the French Society of Anesthesiology.¹¹ Prick and intradermal tests were accompanied by control tests performed with negative (saline) and positive controls (9% codeine phosphate) to determine whether 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 (Stallergenes, Antony, France). Skin tests were interpreted after 15 min. A prick test result 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.

Intradermal tests were performed after the results of prick tests had been obtained. They were performed either on the forearm or on the back by injection of 0.02–0.05 ml 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 result was positive and a 10^{-3} dilution when

the prick test result was negative. Injection dilutions were progressively increased to a 10^{-1} dilution as long as the results remained negative. For morphine, rocuronium, and cisatracurium, a maximal dilution of 10^{-2} , and for atracurium and mivacurium, a maximal dilution of 10^{-3} was used. Intradermal test results were considered positive when the diameter of the wheal was twice or more the diameter of the injection wheal. When the test result was positive, cross-reactivity to other NMBAs was investigated.

The presence of specific muscle relaxant IgE was investigated using radioimmunoassay based on coupling of a choline analog to sepharose (QAS-RIA, positive threshold 1.5%) or p-aminophenylphosphorylcholine to agarose (PAPPC-RIA, positive threshold 1%), as described elsewhere.^{12,13} The specificity of antibodies was confirmed by an inhibition step performed with the incriminated drug (inhibition required > 15%). The sensitivity and specificity of these assays have been estimated at 89–97% and 97%, respectively.^{12,13}

In vitro testing for latex-specific IgE was performed using RAST (Cap System; Pharmacia & Upjohn, Saint Quentin en Yvelines, France) according to the manufacturer's instructions. Values of allergen-specific IgE above 0.35 kU/l were considered to be positive. Plasma concentrations of histamine (RIA Histamine; Immunotech, Marseille, France) and serum concentrations of tryptase (UniCAP Tryptase, Pharmacia & Upjohn) were determined using commercially available radioimmunoassay kits. Values above 9 nM for histamine and 25 µg/l for tryptase were considered to be positive.

Anaphylaxis was diagnosed on the basis of skin test and/or IgE assay results consistent with the clinical history of the adverse reaction and the anesthetic protocol. Otherwise, the diagnosis of anaphylactoid reaction was retained.

To compare the incidence of anaphylaxis to available NMBAs, the number of vials of each agent sold in France in 1999 and 2000 was obtained from the pharmaceutical companies marketing these drugs (Glaxo Wellcome, Marly-le-Roi, France; Organon Teknika, Puteaux, France; Pharmacia & Upjohn, Saint Quentin en Yvelines, France). The number of vials effectively used in anesthesia was then estimated on the basis of data obtained from a market survey in France, which provided an estimate of the consumption of each NMBA and its respective use during anesthesia, in intensive care units and in emergency settings in a representative sample of 100 French hospitals (Le Panel Hospitalier, MAPI, Lyon, France; Edition Domaine Medical, 2000).

Statistical analysis was performed using the SAS 8.02 software (SAS Institute Inc., Cary, NC). Results are expressed as mean ± SEM. Comparisons were performed using Pearson chi-square test. A *P* value of 0.05 or less was considered statistically significant.

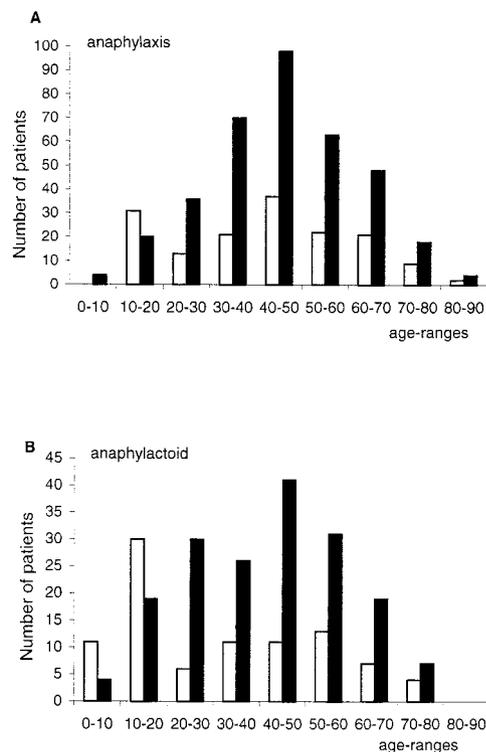


Fig. 1. Distribution of anaphylactic (A) and anaphylactoid (B) reactions according to sex and age ranges between January 1, 1999, and December 31, 2000, in France. Open bars = male (n = 156); filled bars = female (n = 362).

Results

Patients

Seven hundred eighty-nine patients who experienced a clinical adverse reaction suspected to be allergic, between January 1, 1999, and December 31, 2000, were included. At the end of the allergy workup, a diagnosis of documented anaphylaxis was established in 518 cases (66%), whereas the remaining 271 cases (34%) were considered as non-immune mediated. As a result, these were considered to be anaphylactoid reactions.

A significant female predominance was observed in both groups (anaphylaxis: female, n = 362 [70%]; male, n = 156 [30%]; anaphylactoid reactions: female, n = 178 [66%]; male, n = 93 [34%]) in comparison with the percentage of anesthetic procedures performed in men and women determined in the 1996 survey of anesthesia in France (female, 55%; male, 45%; $P < 0.0001$).¹⁴ This predominance was observed irrespective of the causal agent.

The distribution of anaphylactic and anaphylactoid reactions according to age and sex is shown in figure 1.

Causal Agents

Anaphylaxis. The drug responsible for the adverse reaction can only be precisely identified in case of anaphylaxis. The most common causes of anaphylactic reactions were NMBA (n = 306, 58.2%), followed by latex

Table 1. Agents Involved in Anaphylactic Reactions during Anesthesia (n = 518) between January 1, 1999, and December 31, 2000, in France

Causal Agent	Patients, No.
Neuromuscular blocking agent (n = 306, 58.2%)	
Rocuronium, 43.1%	132
Succinylcholine, 22.6%	69
Atracurium, 19.0%	58
Vecuronium, 8.5%	26
Pancuronium, 3.3%	10
Mivacurium, 2.6%	8
Cisatracurium, 0.6%	2
Gallamine, 0.3%	1
Latex (n = 88, 16.7%)	88
Antibiotics (n = 79, 15.1%)	
Penicillin, 41.8%	33
Cephalosporin, 39.2%	31
Vancomycin, 11.4%	9
Quinolone, 5.1%	4
Rifamycin, 1.3%	1
Aminosid, 1.3%	1
Hypnotics (n = 18, 3.4%)	
Propofol, 66.7%	12
Thiopentone, 16.7%	3
Midazolam, 16.6%	3
Opioids (n = 7, 1.3%)	
Nalbuphin	2
Fentanyl	2
Sulfentanyl	2
Remifentanyl	1
Colloids (n = 21, 4.0%)	
Gelatine, 95.0%	20
Hetastarch, 5.0%	1
Other agents (n = 7, 1.3%)	
Propacetamol	2
Chymopapain	1
Protamin	1
Ketoprofen	1
Methylene blue	1
Ethylene oxide	1

(n = 88, 16.7%) and antibiotics (n = 79, 15.1%) (table 1). Hypnotics and opioids were involved in 18 (3.4%) and 7 cases (1.3%), respectively; colloids in 21 cases (4.0%); and other substances in 7 cases (1.3%: propacetamol, n = 2; chymopapain, n = 1; lidocaine, n = 1; ketoprofen, n = 1; methylene blue, n = 1; ethylene oxide, n = 1). These results can be compared with our previous data obtained during our five previous surveys (table 2).^{3,4,15-17}

In eight cases, patients were found to be sensitized to two different agents: an NMBA and latex in two cases, an NMBA and propofol in three cases, an NMBA and a penicillin in one case, latex and a colloid in one case, latex and ethylene oxide in one case.

The respective contribution of each NMBA is shown in table 1. Rocuronium (n = 132, 43.1%) and succinylcholine (n = 69, 22.6%) were most frequently incriminated. Atracurium (n = 58, 19.0%) and vecuronium (n = 26, 8.5%) were also frequently involved, whereas reactions to pancuronium (n = 10, 3.3%), mivacurium (n = 8, 2.6%), cisatracurium (n = 2, 0.6%), and gallamine (n = 1,

Table 2. Substances Responsible for Anaphylaxis during Anesthesia in France

	1984–1989 (n = 821), %	1990–1991 (n = 813), %	1992–June 1994 (n = 1030), %	July 1994–1996 (n = 734), %	1997–1998 (n = 486), %	1999–2000 (n = 518), %
NMBAs	81.0	70.2	59.2	61.6	69.2	58.2
Latex	0.5	12.5	19.0	16.6	12.1	16.7
Hypnotics	11.0	5.6	8.0	5.1	3.7	3.4
Opioids	3.0	1.7	3.5	2.7	1.4	1.3
Colloids	0.5	4.6	5.0	3.1	2.7	4.0
Antibiotics	2.0	2.6	3.1	8.3	8.0	15.1
Others	2.0	2.8	2.2	2.6	2.9	1.3
Total	100	100	100	100	100	100

Results from six consecutive surveys.

n = number of substances responsible, NMBA = neuromuscular blocking agent.

0.3%) were less common. These results should be examined in light of the actual clinical use of the different NMBAs, which could be estimated on the basis of the results of the NMBA market share survey in anesthesia and of their respective use in anesthesia over the same time period in France (table 3). When combined, succinylcholine and rocuronium represent more than 65% of the reactions but less than 16% of the market share in France.

Cross-reactivity to the muscle relaxants commercially available in France was tested in 293 of 306 patients who were allergic to an NMBA. Cross-sensitivity was observed in 220 cases (75.1%). The highest rate of cross-reactivity was observed with rocuronium (80.6%) and vecuronium (87.5%), whereas it was 76.8% for atracurium and 54.3% for succinylcholine.

Anaphylactoid Reactions. A precise identification of the drug responsible for the adverse reaction is more difficult to establish in the case of anaphylactoid reaction

Table 3. Market Share of NMBAs and Number of Anaphylactic Reactions Observed between January 1, 1999, and December 31, 2000, in France (n = 306)

	Market Share* in Anesthesia (Vials), %	Anaphylactic Shocks 1999–2000	
		No.	%
Succinylcholine, 100 mg/10 ml	6.7	69	22.6
Rocuronium, 50 mg/5 ml	8.8	132	43.1
Rocuronium, 100 mg/10 ml			
Vecuronium, 4 mg/1 ml	11.3	26	8.5
Vecuronium, 10 mg/1 ml			
Pancuronium, 4 mg/2 ml	9.5	10	3.3
Atracurium	54.1	58	19.0
Atracurium, 50 mg/5 ml			
Mivacurium, 10 mg/5 ml	5.5	8	2.6
Mivacurium, 20 mg/10 ml			
Cisatracurium, 20 mg/10 ml	4.1	2	0.6
Cisatracurium, 5 mg/2.5 ml			
Cisatracurium, 10 mg/5 ml			
Gallamine, 40 mg	—	1	0.3
Total		306	100

* Data obtained from "Le Panel Hospitalier"—MAPI 2000 and from Pharmaceutical Companies.

NMBA = neuromuscular blocking agent.

because the adverse reaction could result from additive side effects of different drugs injected simultaneously. However, when the anesthetic protocols used in the case of anaphylactoid *versus* anaphylactic reactions were compared, some differences could be observed.

When an NMBA was included in the anesthetic protocol, atracurium, which is usually considered as a potential histamine-releasing substance, was more frequently used in cases of anaphylactoid reaction than in cases of anaphylaxis (use of atracurium in the anesthetic protocol in anaphylactoid reactions: n = 121 [44.6%], anaphylaxis: n = 129 [24.8%]; $P < 0.0001$). On the contrary, succinylcholine (use of succinylcholine in the anesthetic protocol in anaphylactoid reactions: n = 8 [2.9%], anaphylaxis: n = 72 [13.7%]; $P < 0.0001$) and rocuronium (use of rocuronium in the anesthetic protocol in anaphylactoid reactions: n = 31 [11.4%], anaphylaxis: n = 150 [24.5%]; $P < 0.0001$) were more frequently used in the anesthetic protocol when anaphylactic reactions were involved.

When the hypnotic agent used was considered, with the exception of propofol, which was more frequently used in cases of anaphylactoid reactions (anaphylactoid reactions: n = 213 [78.6%], anaphylaxis: n = 354 [68.4%]; $P < 0.01$), no differences were observed.

Slight differences were also observed regarding opioids. Fentanyl use was less frequent in cases of anaphylactoid reactions (anaphylactoid reactions: n = 36 [13.3%], anaphylaxis: n = 106 [20.4%]; $P < 0.01$), whereas sufentanil was more frequently used (anaphylactoid reactions: n = 150 [55.4%], anaphylaxis: n = 234 [45.0%]; $P < 0.01$).

Finally, no differences were observed regarding the use of colloids and the administration of antibiotics between patients presenting with an anaphylactic or an anaphylactoid reaction.

Risk Factors

No differences were observed between anaphylactoid and anaphylactic reactions when the incidences of atopy, asthma, or drug intolerance were compared (table 4).

Significant differences were observed when anaphylac-

Table 4. Patients Characteristics According to the Mechanism of the Adverse Reaction

	Anaphylactic		Anaphylactoid	
	No.	%	No.	%
Atopy	42	15.5	66	12.7
Asthma	29	10.7	51	9.8
Drug intolerance	49	18.1	103	19.8

Anaphylactoid, n = 271; anaphylaxis, n = 518).

tic reactions were considered. When latex and NMBAs were compared, atopy, asthma, and food allergy seemed to be significantly more frequent in the case of latex allergy (table 5).

In 30 of 88 patients (34%) having experienced an anaphylactic reaction to latex, careful retrospective assessment of their medical history revealed the presence of symptoms suggestive of latex sensitization such as fruit allergy (n = 8) or intolerance to materials containing rubber latex (n = 22) before the reaction.

In addition, a history of previous adverse reaction during anesthesia was retrospectively noted in five patients diagnosed as having experienced an anaphylactoid reaction and in 10 patients diagnosed as having experienced an anaphylactic reaction. In the latter 10 patients, an NMBA was incriminated in seven cases, and propofol, latex, and gelatins were incriminated in the three remaining cases.

Anaphylaxis to an NMBA was observed in 37 patients (12.3%) with no history of anesthesia before the current adverse reaction, and, therefore, no previous exposure to any NMBA.

Clinical Features

Anaphylactic and anaphylactoid reactions cannot be distinguished on the basis of clinical symptoms alone. However, when a classification based on symptom severity was applied, clinical manifestations seemed to be more severe in patients with documented anaphylaxis than in patients presenting with an anaphylactoid reaction ($P < 0.001$; fig. 2). Most anaphylactic reactions were grade 2 (23%) or grade 3 (58.9%), whereas anaphylactoid reactions were mainly grade 1 (55.3%). Similarly, anaphylaxis due to NMBAs or antibiotics seemed to be more severe than anaphylactic reactions to latex ($P < 0.0001$) (fig. 3).

The various clinical features observed during anaphy-

Table 5. Patient Characteristics in Cases of Latex Compared with NMBA Anaphylaxis

	Latex (n = 84), %	NMBAs (n = 300), %	P Value
Atopy	21.4	9.7	<0.004
Asthma	21.4	5.0	<0.0001
Food allergy	23.8	4.0	<0.0001

NMBA = neuromuscular blocking agent.

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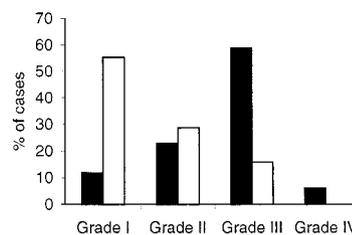


Fig. 2. Frequencies of clinical severity grades of anaphylactic (filled bars; n = 518) and anaphylactoid (open bars; n = 271) reactions during anesthesia in France between January 1, 1999, and December 31, 2000.

lactic and anaphylactoid reactions are summarized in table 6. Cutaneous symptoms were more frequent in anaphylactoid reactions (93.7% vs. 71.9%, $P < 0.0001$), whereas cardiovascular collapse (50.8% vs. 11.1%, $P < 0.0001$) and bronchospasm (39.8% vs. 19.2%, $P < 0.0001$) were more frequent in cases of anaphylaxis.

Clinical symptoms may occur as an isolated condition. When anaphylaxis was involved, cardiovascular collapse was the sole feature in 32 cases, hypotension in 2 cases, cardiac arrest in 10 cases, bronchospasm in 7 cases, and cutaneous symptoms in 50 cases. Angioedema never occurred alone. Cutaneous symptoms were the sole feature in 136 anaphylactoid reactions.

Diagnostic Tests

Tryptase and Histamine. Histamine and tryptase plasma concentrations were determined at the time of the adverse reaction in 24.1% (n = 190) and 32.8% (n = 259) of cases, respectively.

Histamine concentrations were significantly elevated (> 9 nm) in 31 anaphylactoid (49.2%) and 96 anaphylactic reactions (75.6%) and within the normal range in 32 (50.8%) and 31 cases (24.4%), respectively. Therefore, in our study, the sensitivity of this test for the diagnosis of anaphylaxis could be estimated at 75%, the specificity could be estimated at 51%, the positive predictive value could be estimated at 75%, and the negative predictive value could be estimated at 51%.

Similarly, tryptase concentrations were significantly elevated (> 25 $\mu\text{g/l}$) in 9 anaphylactoid (10.7%) and 112 anaphylactic reactions (64%) and within the normal

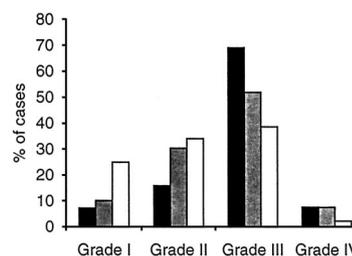


Fig. 3. Frequencies of clinical severity grades of anaphylactic reactions to neuromuscular blocking agents (NMBAs) (filled bars; n = 306), antibiotics (shaded bars; n = 79), and latex (open bars; n = 88) in France between January 1, 1999, and December 31, 2000.

Table 6. Clinical Features of Anaphylactic and Anaphylactoid Reactions during Anesthesia in France between January 1, 1999, and December 31, 2000

Clinical Symptoms	Anaphylaxis (n = 518)		Anaphylactoid Reactions (n = 271)	
	Patients No. (%)	Sole Feature	Patients, No. (%)	Sole Feature
Cardiovascular symptom	387 (74.7)		92 (33.9)	
Arterial hypotension	90 (17.3)	2	50 (18.4)	1
Cardiovascular collapse	264 (50.8)	32	30 (11.1)	2
Bradycardia	7 (1.3)	0	2 (0.7)	0
Cardiac arrest	31 (5.9)	10	—	0
Bronchospasm	207 (39.8)	7	52 (19.2)	2
Cutaneous symptoms	374 (71.9)	50	254 (93.7)	136
Angioedema	64 (12.3)	—	21 (7.7)	—

range in 75 (89.3%) and 63 cases (36.0%), respectively (fig. 4). Among the nine patients with an anaphylactoid reaction and presenting with elevated tryptase concentrations, five had tryptase values between 25 and 36 $\mu\text{g/l}$. Two patients had tryptase values of 70 $\mu\text{g/l}$, one had a tryptase value of 106 $\mu\text{g/l}$, and one had a tryptase value of 200 $\mu\text{g/l}$. Thus, in our series, when tryptase measurements were aimed at the diagnosis of anaphylaxis, sensitivity could be estimated at 64%, specificity could be estimated at 89.3%, positive predictive value could be estimated at 92.6%, and negative predictive value could be estimated at 54.3%.

Specific IgE Assays. Specific IgE assay was performed in 224 of 306 patients who experienced NMBA anaphylaxis. Results were positive in 176 cases (78.6%). In five patients, IgE assay results were positive with negative skin test results.

Specific latex IgE assay was performed in 65 patients who experienced an anaphylactic reaction to latex confirmed by prick test result positivity. It was positive in 58 cases (89.2%).

Discussion

This study is the sixth survey conducted in France by the Groupe d'Etudes des Réactions Anaphylactoïdes Per-anesthésiques^{3,17} since 1989 and represents one of the largest surveys ever conducted regarding the epidemiology of anaphylactic/anaphylactoid reactions occurring

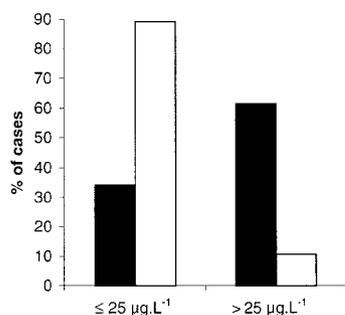


Fig. 4. Frequency of tryptase values according to a diagnostic threshold of 25 mg/l after anaphylactic (filled bars) and anaphylactoid (open bars) reactions.

during anesthesia. In view of the constant evolution in anesthesiologic practice as well as the relative complexities of allergy investigation, our results underline the need for an active policy of at-risk patient identification. Furthermore, they emphasize the need for specialized allergeoanesthesia centers to provide expert advice to anesthetists and allergists. In this series, the diagnosis of anaphylaxis was established on the basis of clinical history and systematic skin testing combined with a wide use of specific IgE assays for NMBAs and latex. Immune-mediated anaphylactic reactions seem to be relatively frequent because 66% of the reactions investigated were diagnosed as anaphylaxis. However, in a third of our cases, the precise mechanisms of reactions remain unclear. Consequently, further efforts must be made to determine the possible mechanisms. This could be of major importance for the design of new drugs and can be illustrated by results recently published regarding rapacuronium, where higher affinity for M2 *versus* M3 muscarinic receptors might account for the high incidence of bronchospasm observed in clinical practice.¹⁸ Such information represents a strong incentive for the evaluation of the potential to selectively inhibit M2 muscarinic receptors of newly designed NMBAs.

The incidence of anaphylactoid and anaphylactic reactions remains difficult to estimate. In France, it has been reported that up to 30–40% of patients presenting with anaphylactoid reactions during anesthesia did not benefit from further allergic workup.¹⁹ Moreover, some patients might have been investigated in centers other than those involved in this study. It should be also kept in mind that because of our study design, severe reactions resulting in death or major clinical sequelae impeding patient follow-up remained unaccounted for.

Because the drugs responsible for adverse reactions can only be precisely identified in cases of anaphylaxis, most of the discussion regarding the various substances incriminated will focus on anaphylaxis. The overall distribution of the various causal agents incriminated in anaphylaxis was similar to previously reported distributions (table 2).^{4,17,20} Among the drugs and other agents involved in anaphylaxis, muscle relaxants are still most

frequently involved.^{4,7,17,21} Anaphylactic reactions have been reported for all NMBAs, even recently commercialized substances. In most reports, succinylcholine seems to be more frequently involved,^{3,16,22} with some differences reflecting variations in anesthesiology practices from one country to another.^{17,23} However, as shown in our previous survey,¹⁷ in this study, rocuronium seems to be the most frequently involved agent, whereas the number of cases involving succinylcholine remains relatively stable.¹⁷ The controversy regarding adverse reactions to rocuronium remains a matter of debate. Some reports suggest an increased frequency of anaphylaxis to rocuronium,^{17,24} whereas others consider that the incidence of reactions involving rocuronium reflect market use.^{25,26} In our study, diagnosis was mainly based on history and skin test results, which have been extensively used for the diagnosis of anaphylaxis during anesthesia.^{7,27-29} However, in the absence of a diagnostic gold standard, skin test sensitivity and specificity remain difficult to establish. It has been suggested that rocuronium prepared at a solution of 10 mg/ml requires dilution to 10^{-2} to avoid false-positive intradermal test results.³⁰ This corresponds to the maximal dilution now recommended in France¹¹ and was the maximal tested concentration used by centers participating in this study. As a result, the differences observed in the relative frequencies of sensitization against the various commercially available NMBAs cannot be explained by an increased number of false-positive results due to an excessive maximal testing concentration. We suggest classification of the various NMBAs as high (succinylcholine, rocuronium), medium (pancuronium, vecuronium, mivacurium), and low (atracurium, cisatracurium) risk of sensitization.

Latex sensitization remains the second most common cause of anaphylaxis during anesthesia in the general population. It was involved in 16.9% of cases. Despite increasing awareness of the risk of latex sensitization in children with spina bifida³¹ or healthcare workers,³² combined with the efficacy of surgery in a latex-safe environment,^{33,34} this level has remained relatively stable over time (16.6% in 1996, 12.1% in 1998 in France).^{4,17}

Allergic reactions to antibiotics continue to increase with time. Currently, they account for 15% of the anaphylactic reactions diagnosed in our centers. They only accounted for 8.3% in 1996.⁴ Penicillins were most frequently involved in France, whereas cephalosporins were most commonly incriminated in Australia.^{17,22}

Anaphylactic reactions to colloids were slightly increased when compared with our previous survey (4.04% *vs.* 2.7%).¹⁷ As could be expected, gelatin was the most frequently involved volume-expanding fluid.³⁵ This probably reflects the increased use of gelatins as volume-expanding fluids in France over this study period.

Allergic reactions to local anesthetics remain uncom-

mon despite their frequent use.²³ Our results are in agreement with the literature, which suggests that most of adverse reactions to local anesthetics are related to inadvertent intravascular injection leading to excessive blood concentrations of the local anesthetic or systemic absorption of epinephrine that was combined with the local anesthetic.³⁶

The potential severity of anaphylaxis during anesthesia underscores the interest of developing a rational approach to reduce its incidence by identifying potential risk factors before surgery. Our results confirm the female predominance for both anaphylactic (2.4 female/1 male) and anaphylactoid reactions (1.9 female/1 male). This difference persists even when the sex ratio (1.1 female/1 male) of anesthetized patients established by the French survey of anesthesia is taken into account.¹⁴ Although less marked than that reported in other studies, where it ranges from 8 females for 1 male³⁷ to 3.5 females for 1 male,⁸ these results are very similar to those previously reported in France.⁴ However, this does not imply any need for systematic allergy investigation in female patients before anesthesia. A slight male predominance was observed in the 10- to 20-yr-old age group, but this is related to the higher proportion of male subjects anesthetized during this age period in France.

Atopy and presence of drug or food intolerance were assessed by history. No difference was observed between anaphylactic and anaphylactoid reactions regarding these potential risk factors. However, when anaphylactic reactions are involved, the presence of atopy or food intolerance was significantly higher in cases of latex allergy compared with allergy to NMBAs. Therefore, atopy, which has long been considered as a risk factor for sensitization to muscle relaxants, does not seem to be a significant risk factor for muscle relaxant sensitivity.^{38,39} On the other hand, our results regarding latex allergy are in agreement with previous reports that emphasize the increased risk of sensitization to latex in the case of atopy^{17,40} or in the case of allergy to several fruits (avocado, kiwi, banana, fig, chestnut, hazelnut, sweet pepper, melon, pineapple, papaya, and others) due to cross-sensitization with latex.⁴¹ Moreover, in 30 latex allergy cases (34%), careful assessment of medical history performed after the reaction revealed the presence of symptoms suggestive of latex sensitization before the anaphylactic reaction. These include pruritus, urticaria, contact angioedema, conjunctivitis, rhinitis, and asthma in subjects wearing gloves containing natural latex or confined to an area in which the air is polluted by latex particles. This strongly reinforced the need for an active policy to identify at-risk patients at the preanesthetic visit according to well-defined guidelines such as those recently proposed in France.^{11,40}

The difference between anaphylactoid and true anaphylactic reactions cannot be made on clinical grounds

alone. As expected, clinical symptoms reported in patients with true anaphylactic reactions and in patients with non-IgE-mediated anaphylactoid reactions were similar. However, when a classification based on symptom severity was applied,⁴² clinical manifestations were more severe in patients with documented anaphylaxis. Nevertheless, one should keep in mind that because of our study design, the mortality rate related to anaphylactic or anaphylactoid reactions could not be investigated in this report.

In most cases, anaphylactic reactions were severe (88.1% of cases, grade 2 or more) and often life-threatening (65.1%, grades 3 and 4). This contrasts with anaphylactoid reactions of a nonimmune type, which were of grade 1 55.3% of the time. Nevertheless, some cases corresponding to true IgE-mediated anaphylactic reactions were classified as grade 1 or 2. As a result, any suspected anaphylactoid reaction occurring during anesthesia should be thoroughly investigated to establish a precise diagnosis and appropriate recommendations. Similarly, for unexplained reasons, anaphylaxis against NMBAs or antibiotics seems to be more severe than anaphylactic reactions to latex ($P < 0.005$; fig. 3).

Anaphylaxis may occur at any time during anesthesia and may progress slowly or rapidly. Alertness is essential because reactions may be well established before they are noticed. Therefore, information regarding the various clinical features encountered is essential. Cutaneous symptoms were more frequent in anaphylactoid reactions (93.7% vs. 71.9%, $P < 0.0001$), whereas cardiovascular collapse (50.8% vs. 11.1%, $P < 0.0001$) and bronchospasm (39.8% vs. 19.2%, $P < 0.0001$) were more frequent in case of anaphylaxis. Thus, the absence of any cutaneous symptoms does not preclude the diagnosis of anaphylaxis. In addition, clinical features may occur as an isolated condition (table 6). These results concur with previously published data.^{4,20,23} As a result, an anaphylactic reaction restricted to a single clinical symptom (e.g., bronchospasm, tachycardia with hypotension) can easily be misdiagnosed because many other pathologic conditions may present identical clinical manifestations.^{23,43} In mild cases restricted to a single symptom, spontaneous recovery may be observed even in the absence of any specific treatment. It should be kept in mind, however, that, under such circumstances, the lack of a proper diagnosis and appropriate allergy assessment could lead to fatal reexposure.⁴⁴

Every patient who experiences an adverse reaction suspected to be allergic should benefit from immediate and delayed investigations to discriminate between an anaphylactic and an anaphylactoid reaction, to identify the responsible drug in cases of anaphylaxis, and to detect possible cross-reactivity when an NMBA is incriminated.^{11,29} The diagnostic strategy for a suspected anaphylactic reaction is based on laboratory test results, on samples taken during and shortly after the reaction, and

on the results of tests performed days to weeks later. Early tests are essentially designed to determine whether an immunologic mechanism is involved.

Elevated concentrations of plasma histamine do not establish the cause of the reaction but are suggestive that histamine is involved. However, this does not allow one to distinguish between anaphylactoid and anaphylactic reactions. In addition, the rise is usually transient,⁴⁵ and in most cases, sampling must be performed at a time when resuscitation is a priority. These considerations concur with the low specificity (51%) of histamine measurements for the diagnosis of anaphylaxis in our patients.

Anaphylaxis involves the activation of basophils and mast cells, whereas non-immune-mediated anaphylactoid reactions are considered to activate only basophils. Mast cells activated during an IgE-mediated hypersensitivity reaction release proteases such as tryptase, pre-stored histamine, and newly generated vasoactive mediators. Considering that in human basophils, tryptase content is 300- to 700-fold less than that of mast cells, increased tryptase concentration in serum is a marker for systemic mast cell activation. Therefore, increased concentrations of tryptase greater than 25 $\mu\text{g/l}$ are considered as a highly sensitive indicator of anaphylactic reactions during anesthesia,²² although elevated tryptase concentrations can be observed in other situations.⁴⁶

Tryptase concentrations peak between 30 and 60 min; thus, its concentration should be determined approximately an hour after the start of the reaction. The biologic half-life of tryptase is estimated at 2 h; therefore, increased concentrations can sometimes still be detected for 1–6 h or more after the onset of anaphylaxis. Increased tryptase concentrations in postmortem sera suggest systemic anaphylaxis as a cause of death. However, a negative test result does not completely rule out anaphylaxis, particularly if sampling is performed at the beginning of the reaction, or in cases of mild reactions.^{20,22} This is confirmed by the excellent specificity of tryptase measurement in the diagnosis of anaphylaxis (89.3%) observed in our series, combined with a relatively low sensitivity. The diagnosis of anaphylaxis should not rely on a single test, and patients in whom mast cell tryptase concentrations are not increased still require skin testing.

Radioimmunoassay for the detection of drug-reactive IgE antibody may provide important information for identification of the causative agent of anaphylaxis.²³ In this study, specific IgE assay results were positive in 78.6% of cases of anaphylaxis to an NMBA and in 88.4% of cases of latex allergy. These results support the widespread use of specific IgE assay to NMBAs and latex in suspected cases of adverse reactions to anesthetics. Although classically performed several weeks after the reaction, they can be performed on blood drawn at the time of the reaction. As a result, the presence of specific

IgE against the suspected drug at the time of the reaction can be substantiated.⁴⁷ These tests can also help to confirm the diagnosis by identifying the responsible drug in patients in whom skin tests either could not be performed or yielded negative results.

In conclusion, anaphylactoid reactions remain a significant adverse event during anesthesia, and anaphylaxis is probably underdiagnosed. However, in a large number of cases, the precise mechanisms of reactions remain unclear, and further efforts must be made for their identification. As for all rare events, specific epidemiologic surveys are advised. Because no premedication can effectively prevent an allergic reaction, it is the anesthesiologist's responsibility to ensure that any suspected anaphylactic reaction is thoroughly investigated using immediate and postoperative testing. In addition, systematic inquiries aimed at identifying patients belonging to an at-risk group must be performed before any anesthesia. In view of the constantly evolving anesthesiology practices and the relative complexity of allergy investigation, the constitution of specialized allergoanesthesia centers should be promoted.

The authors thank Geneviève Lapeyre, M.D. (Medical Director, Pharmacia & Upjohn, Saint Quentin en Yvelines, France), Patrick Boen, M.D. (Medical Director, Organon Teknika, Puteaux, France), and Patrick Sandrat, M.D. (Product Manager, Glaxo Wellcome, Marly-le-Roi, France) for providing us the information required to establish the market share of each neuromuscular blocking agent.

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