

Anaphylaxis during anaesthesia. Results of a two-year survey in France

M. C. Laxenaire^{1*}, P. M. Mertes² and Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques

¹Département d'Anesthésie-réanimation, CHU de Nancy, Hôpital Central, 29 Avenue de Lattre de Tassigny, F-54035 Nancy Cedex, France. ²Laboratoire d'Explorations Fonctionnelles Respiratoires et Allergologiques, CHU-Hopital Maison Blanche, F-51092 Reims, France

*Corresponding author

Between January 1, 1997 and December 31, 1998, 467 patients were referred to one of the allergeo-anaesthesia centres of the French GERAP (Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques) network and were diagnosed as having anaphylaxis during anaesthesia. Diagnosis was established on the basis of clinical history, skin tests and/or a specific IgE assay. The most frequent cause of anaphylaxis was a neuromuscular blocking agent (69.2%). Latex was less frequently incriminated (12.1%) than in previous reports. A significant difference was observed between the incidence of anaphylactic reactions observed with each neuromuscular blocking agent and the number of patients who received each drug during anaesthesia in France throughout the study period ($P < 0.0001$). Succinylcholine and rocuronium were most frequently incriminated. Clinical reactions to neuromuscular blocking drugs were more severe than to latex. The diagnostic value of specific IgE assays was confirmed. These results are consistent with changes in the epidemiology of anaphylaxis related to anaesthesia and are an incentive for the further development of allergeo-anaesthesia clinical networks.

Br J Anaesth 2001; **87**: 549–58

Keywords: allergy; neuromuscular block, allergy

Accepted for publication: June 6, 2001

Anaphylactic reactions to anaesthetic and associated agents used during the perioperative period have been reported with increasing frequency in most developed countries. The estimated incidence of anaphylaxis was between 1 in 10 000 and 1 in 20 000 in Australia in 1993,¹ and was 1 in 13 000 in France in 1996.² Although rare,² these reactions may lead to death, even when appropriately treated.^{2–3} Most published reports concerning the incidence of anaphylaxis originate in France,^{2–4} Australia,^{5–6} the UK^{7–8} and New Zealand.⁹ These reflect a long-term policy of systematic clinical and/or biological investigation of anaphylactoid reactions that are thought to be mediated by an immune mechanism.

The number of anaesthetic drugs is increasing, and active pharmacological surveillance of rare unexpected adverse effects of therapeutic agents is now regarded as essential.¹⁰ In addition, guidelines for the identification and/or management of high-risk groups have been proposed.^{11–12} Consequently, the confirmation and quantitative risk assessment of suspected rare serious adverse reactions require proper epidemiological studies.

Clinical symptoms and reaction severity do not allow one to distinguish between an immune-mediated anaphylactic reaction and an anaphylactoid reaction resulting from direct non-specific histamine release.^{2–13} Furthermore, no specific treatment has been shown to prevent the occurrence of anaphylactic reactions reliably.¹³ As a result, the only rational approach to a patient with perioperative symptoms consistent with either an anaphylactoid or an anaphylactic reaction is to assess precisely the type of reaction, to note the drugs responsible and eventual cross-reactivity with related drugs, and to avoid subsequent administration of incriminated drugs or agents. Diagnosis of type I allergy, mediated by specific IgE antibody, is usually confirmed by skin tests,^{9–14–15} supported whenever possible by specific IgE assays.¹⁶

In this paper we report the results of a 2-yr survey of the incidence of anaphylaxis during anaesthesia (1997–1998) conducted by the GERAP (Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques), a network of 38 French allergeo-anaesthesia outpatient clinics.

Patients and methods

This was a retrospective study involving patients who had experienced an adverse anaphylactic reaction during anaesthesia between January 1, 1997 and December 31, 1998. In each case the immune mechanism of the reaction was confirmed on the basis of a standardized diagnostic protocol performed in an allergeo-anaesthesia outpatient clinic. All the centres were members of the GERAP network, which was set up in 1985.

The protocol included a questionnaire about age at the time of reaction, sex, number of previous anaesthetic procedures, history of allergy (possible history of atopy, drug, food or latex intolerance), date of the reaction, and drugs used before the reaction. Details were obtained about the degree of reaction, which was 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 more than 30% in arterial 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; grade IV = circulatory inefficacy, cardiac and/or respiratory arrest].

Information about allergy investigations was recorded systematically: date of incident, type of skin tests performed (skin prick-test and/or intradermal testing), dilution of the tested drug leading to a positive reaction, cross-reactivity in cases of adverse reaction to a neuromuscular blocking agent, results of histamine and tryptase monitoring during the adverse reaction, and of IgE-specific assays testing responses to quaternary ammonium or latex when available.

Skin tests were performed according to standardized procedures recommended by the Commission Tripartite en Allergologie.¹⁷ Prick and intradermal tests were accompanied by control tests carried out with negative (0.4% phenol in saline) and positive (9% codeine phosphate) controls 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 in the cases of opioids, hypnotics, colloids and neuromuscular blocking agents, with the exception of atracurium, mivacurium and morphine, which were tested with 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, France). Skin tests were interpreted after 15 min. A prick test was considered positive when the diameter of the wheal was at least half of that produced by the codeine test and at least 3 mm greater than the negative control.

Intradermal tests with neuromuscular blocking agents were carried out after the results of prick tests had been obtained. However, in 12 centres, these were not performed

when prick test results were strongly positive. Intradermal tests were performed by injection of 0.02–0.05 ml of drugs diluted in 0.4% phenol physiological solution. 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 increased progressively to 10^{-1} for aminosteroid neuromuscular blocking agents, as long as the results remained negative. For atracurium and mivacurium, a maximal dilution of 10^{-3} was used when tests were performed on the forearm and 10^{-2} when performed on the back. Intradermal tests were considered positive when the diameter of the wheal was at least 8 mm, with a surrounding flare. When the test was positive, cross-reactivity to other neuromuscular blocking agents was investigated.

The presence of specific IgE against muscle relaxants was investigated using radioimmunoassay (RIA) based on coupling of a choline analogue to Sepharose (QAS RIA, positive threshold 1.5%) or *p*-aminophenylphosphorylcholine to agarose (PAPPC RIA, positive threshold 1%), as described elsewhere.^{18 19} The specificity of antibodies against the suspected neuromuscular blocking agent was confirmed by an inhibition step performed with the drug (inhibition required >15%).

In vitro testing for latex-specific IgE was carried out using RAST (Cap System; Pharmacia, France) according to the manufacturer's instructions. Values of allergen-specific IgE above 0.35 kU l^{-1} were considered positive. Plasma concentrations of histamine (RIA Histamine; Immunotech) and tryptase (UniCAP Tryptase, Pharmacia & Upjohn, France) were determined with commercially available RIA kits. Values above 9 nmol l^{-1} for histamine and $12 \text{ } \mu\text{g l}^{-1}$ 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 anaesthetic protocol. To reduce further the risk of false positives when intradermal skin test positivity for aminosteroid neuromuscular blocking agents was observed only at 1/10 dilution, the presence of specific IgE on RIA assay was required to confirm sensitization to the neuromuscular blocking agent administered at the time of the reaction.

To compare the incidences of anaphylaxis to available neuromuscular blocking agents, the number of vials of each agent sold in France in 1997 and 1998 was obtained from the pharmaceutical companies that marketed these drugs (Glaxo Wellcome, Organon Teknika, Pharmacia & Upjohn, Rhône Poulenc Rorer). The number of vials effectively used in anaesthesia was then estimated on the basis of data obtained from a market survey in France, which provided an estimate of the consumption of each neuromuscular blocking agent and its respective use during anaesthesia in intensive care units and in emergency settings in a representative sample of 100 French hospitals (data obtained from *Le Panel Hospitalier*, MAPI, Lyon, Edition

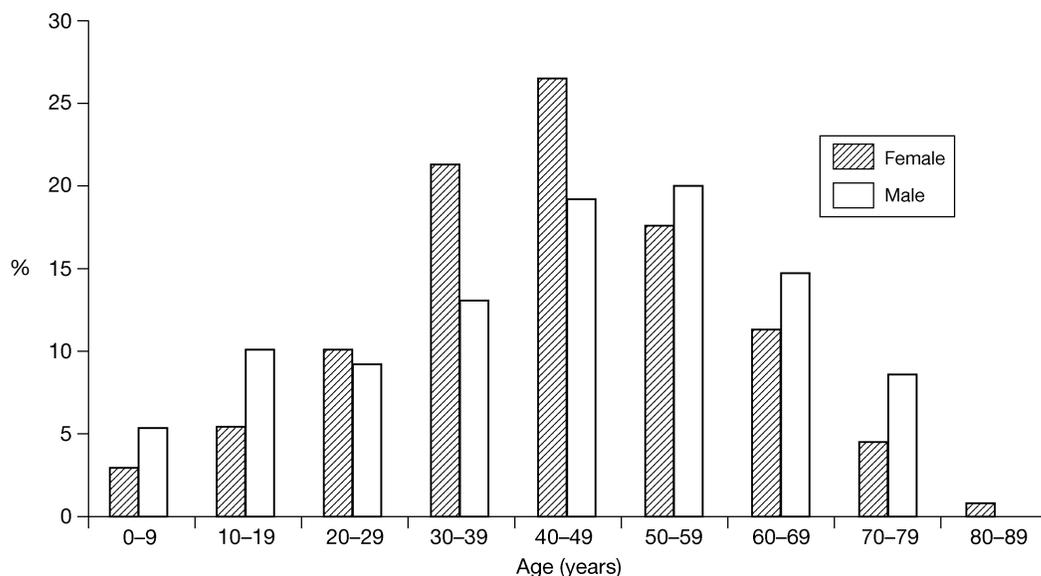


Fig 1 Distribution of anaphylactic reactions in France between January 1997 and December 1998 according to sex and age range (males $n=130$, females $n=342$).

Domaine Medical, 1998). To estimate the number of patients effectively exposed to each compound, a correction factor was applied. This factor took the average number of vials of a specific neuromuscular blocking agent used during a standard anaesthetic procedure into account. It depended on the commercially available presentation of the neuromuscular blocking agent, and was established in accordance with Glaxo Wellcome and Organon Teknika for the products they sold.

Statistical analysis

StatView IV software (Abacus Concepts, Berkeley, CA, USA) was used. Results are expressed as mean (SEM). Comparisons were performed using the χ^2 test or analysis of variance when appropriate. $P \leq 0.05$ was considered statistically significant.

Results

Subjects

Four hundred and seventy-seven patients who presented with an anaphylactic reaction during the study period were registered. A significant female predominance was observed [female, $n=347$ (72.7%); male, $n=130$ (27.3), $P < 0.0001$] in comparison with the percentage of anaesthetic procedures performed in men and women determined in the 1996 survey of anaesthesia in France (female, 55%; male, 45%).²⁰ This predominance was observed irrespective of the causal agent. The age distribution was as follows: 1–10 yr, $n=17$ (3.56%); 10–20 yr, $n=32$ (6.71%); 20–30 yr, $n=47$ (9.85%); 30–40 yr, $n=91$ (19.08%); 40–50 yr, $n=117$

(24.53%); 50–60 yr, $n=87$ (18.24%); 60–70 yr, $n=58$ (12.16%); 70–80 yr, $n=26$ (5.45%); 80–90 yr, $n=2$ (0.42%). The distribution according to age and sex is shown in Fig. 1. Peak incidence was in the fourth decade in the female group and in the fifth decade in the male group.

Causal agents

The most common cause of adverse reactions was neuromuscular blocking drugs ($n=336$, 69.2%), followed by latex ($n=59$, 12.1%) and antibiotics ($n=39$, 8%) (Table 1). Hypnotics and opioids were involved in 18 (3.7%) and seven (1.4%) cases respectively, colloids in 13 cases (2.7%) and other substances in 14 cases (2.9%; propacetamol, $n=4$; aprotinin, $n=2$; chymopapain, $n=2$; protamine, $n=1$; bupivacaine, $n=1$; ketoprofen, $n=1$; hyaluronidase, $n=1$; methylene blue, $n=1$; ethylene oxide, $n=1$).

In nine cases, patients were found to be sensitized to two different agents: a neuromuscular blocking agent and latex in three cases, a neuromuscular blocking agent and propofol in two cases, a neuromuscular blocking agent and methylene blue in one case, latex and a colloid in one case, latex and ethylene oxide in one case, and propofol and a colloid in one case.

History of atopy, allergy, asthma or a previous adverse reaction during anaesthesia

Atopy was present in 121 cases (25.4%), and asthma in 41 cases (8.6%). A history of drug intolerance was reported in 76 cases (15.9%) and food allergy was present in 14 cases (2.9%). When latex and neuromuscular blocking agents were compared, atopy appeared to be significantly more frequent in the case of latex allergy (39 vs 24.8%, $P < 0.01$).

Table 1 Agents involved in anaphylactic reactions during anaesthesia in France between January 1997 and December 1998

Causal agent	Number of patients
Neuromuscular blocking agents (<i>n</i> =336, 69.2%)	
Succinylcholine	78
Vecuronium	59
Rocuronium	98
Pancuronium	20
Atracurium	71
Cisatracurium	1
Mivacurium	9
Latex (<i>n</i> =59, 12.1%)	
Antibiotics (<i>n</i> =39, 8.0%)	
Penicillin	22
Cephalosporin	11
Vancomycin	2
Rifamycin	1
Quinolone	3
Hypnotics (<i>n</i> =18, 3.7%)	
Thiopental	5
Propofol	10
Midazolam	3
Opioids (<i>n</i> =7, 1.4%)	
Morphine	1
Fentanyl	4
Sufentanil	2
Colloids (<i>n</i> =13, 2.7%)	
Gelatin	11
Hetastarch	2
Other agents (<i>n</i> =14, 2.9%)	
Propacetamol	4
Aprotinin	2
Chymopapain	2
Bupivacaine	1
Protamine	1
Ketoprofen	1
Hyaluronidase	1
Methylene blue	1
Ethylene oxide	1

In five patients, careful assessment of the medical history revealed the onset of an adverse reaction during a previous anaesthetic. In three cases, no allergic investigations had been performed after the initial incident. In the two remaining cases, diagnosis of sensitization to a neuromuscular blocking agent had been made after the initial incident.

Clinical features

Most adverse reactions were grade II (22.9%) or grade III (62.6%); only 10.1% were grade I and 4.4% grade IV. Cutaneous symptoms were present in 69.6% of cases (*n*=332), angio-oedema in 11.7% (*n*=56), bronchospasm in 44.2% (*n*=211), arterial hypotension in 17.8% (*n*=85), cardiovascular collapse in 53.7% (*n*=256), bradycardia in 2.1% (*n*=10) and cardiac arrest in 4% (*n*=19) (Table 2). Cardiovascular collapse was the sole feature in 40 cases, hypotension in 10 cases, bronchospasm in 15 cases and cutaneous symptoms in 37 cases. Angio-oedema never occurred in isolation.

Table 2 Clinical features of anaphylaxis during anaesthesia in 477 patients in France between January 1997 and December 1998

Clinical symptoms	Number of cases (%)	Sole feature (number of patients)
Cardiovascular symptoms		
Arterial hypotension	85 (17.8%)	10
Cardiovascular collapse	256 (53.7%)	40
Bradycardia	10 (2.1%)	
Cardiac arrest	19 (4.0%)	
Bronchospasm	211 (44.2%)	15
Cutaneous symptoms	332 (69.6%)	37
Angio-oedema	56 (11.7%)	

Bronchospasm was associated with a grade II reaction in 45 cases (21.3%), a grade III reaction in 159 cases (75.4%) and a grade IV reaction in seven cases (3.3%).

Severe complications, such as transient renal failure (*n*=2), coma (*n*=4), persistent vegetative state (*n*=1), hemiplegia (*n*=1) and neurological sequelae in the newborn of a pregnant patient *n*=1, were observed.

No differences in symptom severity were observed with respect to sex, history of atopy, asthma or food and drug intolerance. In eight cases, long-term treatment with β -blockers was noted. Seven of these cases were of grade III severity and one was of grade IV with cardiac arrest.

A significant association between the onset of bronchospasm and a history of atopy or asthma was observed ($P<0.005$).

Specific considerations for neuromuscular blocking agents and latex allergy

Neuromuscular blocking agents

The respective contribution of each neuromuscular blocking drug is shown in Table 1. Three hundred and thirty-six cases of anaphylaxis involved a neuromuscular blocking agent. Although succinylcholine (*n*=78) remains a major causal agent, rocuronium (*n*=98) was the drug incriminated most frequently over the 2 yr (1997–1998) study period. Atracurium (*n*=71) and vecuronium (*n*=59) were also involved frequently, whereas reactions to pancuronium (*n*=20), mivacurium (*n*=9) and cisatracurium (*n*=1) were less common. When considering these results, the actual clinical use of these drugs in France should be taken into account. This can be estimated on the basis of the results of the survey of the market share of neuromuscular blocking agents. The percentages of vials of each drug used in operating rooms and in intensive care units were also considered (Table 3). A correction factor based on the average number of vials used during anaesthesia in one patient, defined with and accepted by the principal manufacturers of neuromuscular blocking agents (Glaxo Wellcome and Organon Teknika) was also used to estimate the number of anaesthetized patients exposed to each

Table 3 Patient exposure to the various neuromuscular blocking agents and number of reactions observed between January 1997 and December 1998 in France ($n=336$). *Data obtained from Le Panel Hospitalier, MAPI (Lyon: Edition Domaine Medical, 1998) and from pharmaceutical companies. †Established in collaboration with pharmaceutical companies using a correction factor taking into account the average number of vials used for one patient during an anaesthetic

	Market share in anaesthesia (vials, %)*	Patients exposed (%)†	Anaphylactic reactions 1997–1998		Ratio % reactions/% patients exposed
			Number	(%)	
Succinylcholine 100 mg/10 ml 6.5	7.6	78	23.2	3.05	
Rocuronium 50 mg/5 ml, 100 mg/10 ml 8.6	10	98	29.2	2.92	
Vecuronium 4 mg/1ml, 10 mg/1 ml	17.5	11.5	59	17.6	1.53
Pancuronium 4 mg/2 ml	7	3.3	20	5.9	1.78
Atracurium 25 mg/2.5 ml, 50 mg/5 ml	51.2	60.0	71	21.1	0.35
Mivacurium 10 mg/5 ml, 20 mg/10 ml	7	5.4	9	2.7	0.5
Cisatracurium 20 mg/10 ml, 5 mg/2.5 ml, 10 mg/5 ml	1.4	1.7	1	0.3	0.17
Gallamine 40 mg	0.8	0.5	–	–	–
	100%	100	336	100%	

compound. A significant difference was observed when percentage of anaphylactic reactions to each drug was compared with the estimated percentage of patients who received these drugs over the same time period ($P<0.0001$). Succinylcholine and rocuronium appeared to be involved most frequently, followed by vecuronium and pancuronium, and atracurium was involved least frequently.

A significant female predominance was observed in reactions to neuromuscular blocking drugs [female, $n=248$ (73.81%); male, $n=88$ (26.19%); $P<0.0001$]. The distribution according to age range and sex is shown in Fig. 2A. No difference was observed in relation to sex or age when the different neuromuscular blocking drugs were considered.

A difference in the severity of the reactions was observed when neuromuscular blocking drugs and latex were compared ($P<0.0001$) (Fig. 3). Reactions to neuromuscular blocking drugs were of grade I in 7.0%, grade II in 21.0%, grade III in 67.1% and grade IV in 4.9% of patients. They appeared to be more severe than reactions to latex, which were of grade I in 25.9%, grade II in 27.8%, grade III in 44.4% and grade IV in 1.9%.

A history of one or more previous anaesthetics was obtained in 326 out of 336 cases. Detailed anaesthetic notes were available only rarely or not at all. Anaphylaxis was observed in 48 patients (14.7%) who had no history of anaesthesia or previous exposure to neuromuscular blocking agents.

Early plasma histamine and tryptase determinations were performed in 90 and 97 cases respectively. They were considered to be positive in 81 and 94 cases respectively. When both tests were performed in a patient, they were both negative in only two cases. This corresponded to a positive intradermal reaction to atracurium at a dilution of 10^{-3} .

The numbers of positive intradermal test results according to the dilution threshold and the different agents involved are summarized in Table 4. Skin tests were performed in 331 out of 336 patients. They were negative in four cases. In each of these four cases, the severity grade of the reaction was III or IV, and specific IgE against a neuromuscular blocking agent was detected. Moreover, tryptase determination was positive in three of them.

Cross-reactivity to the muscle relaxants commercially available in France was tested in 317 cases. Cross-sensitivity was observed in 262 cases (82.6%). The highest rate of cross-reactivity was observed with rocuronium (89.4%) and vecuronium (92.7%); it was 72.6% for succinylcholine.

Specific IgE assay was performed in 234 patients. Results for the various agents studied are summarized in Table 5. They were positive in 202 cases (86.3%). Negative results for both IgE and skin tests were never observed. In the four cases of life-threatening reaction and negative skin tests, the IgE assay was positive, with a high percentage of specific IgE binding in the presence of the offending molecule.

Latex

Fifty-nine cases of latex anaphylaxis were reported during the study period. A significant female predominance was observed [female, $n=43$ (72.9%); male, $n=16$ (27.1%); $P<0.001$]. The distribution according to age range is shown in Fig. 2B. This distribution was significantly different from those observed with neuromuscular blocking agents ($P<0.0001$), for which the incidence was higher in the younger age ranges.

Reactions to latex were less severe than those observed with neuromuscular blocking drugs ($P<0.0001$) (Fig. 3). On

four occasions, these reactions occurred during gynaecological procedures, after injection of oxytocin, and in one case after removal of a tourniquet.

A history of previous anaesthesia was found in 51 of the 59 cases of latex allergy (86.4%). No detailed information was available about the number of previous anaesthetics or the patients' occupational status. A history evocative of latex sensitization, such as fruit allergy or intolerance to materials containing rubber latex, was noted retrospectively in 14 cases (23.7%). Atopy was present in 23 cases (39%) and asthma in seven (11.9%).

Skin prick tests were performed in 58 out of 59 cases and were positive in 57 patients (98.3%). In the patient with a

negative skin test and the patient not investigated using the prick-test, IgE latex-specific assay was positive. Specific latex IgE assay was performed in 41 of these patients. It was positive in 38 cases (92.7%).

Discussion

This study represents one of the largest surveys ever published of the incidence of anaphylaxis during anaesthesia over a 2-yr period. Diagnosis was established on the basis of systematic skin testing of the various suspected agents combined with widespread use of specific IgE assays. Nevertheless, this survey underestimates the real picture,

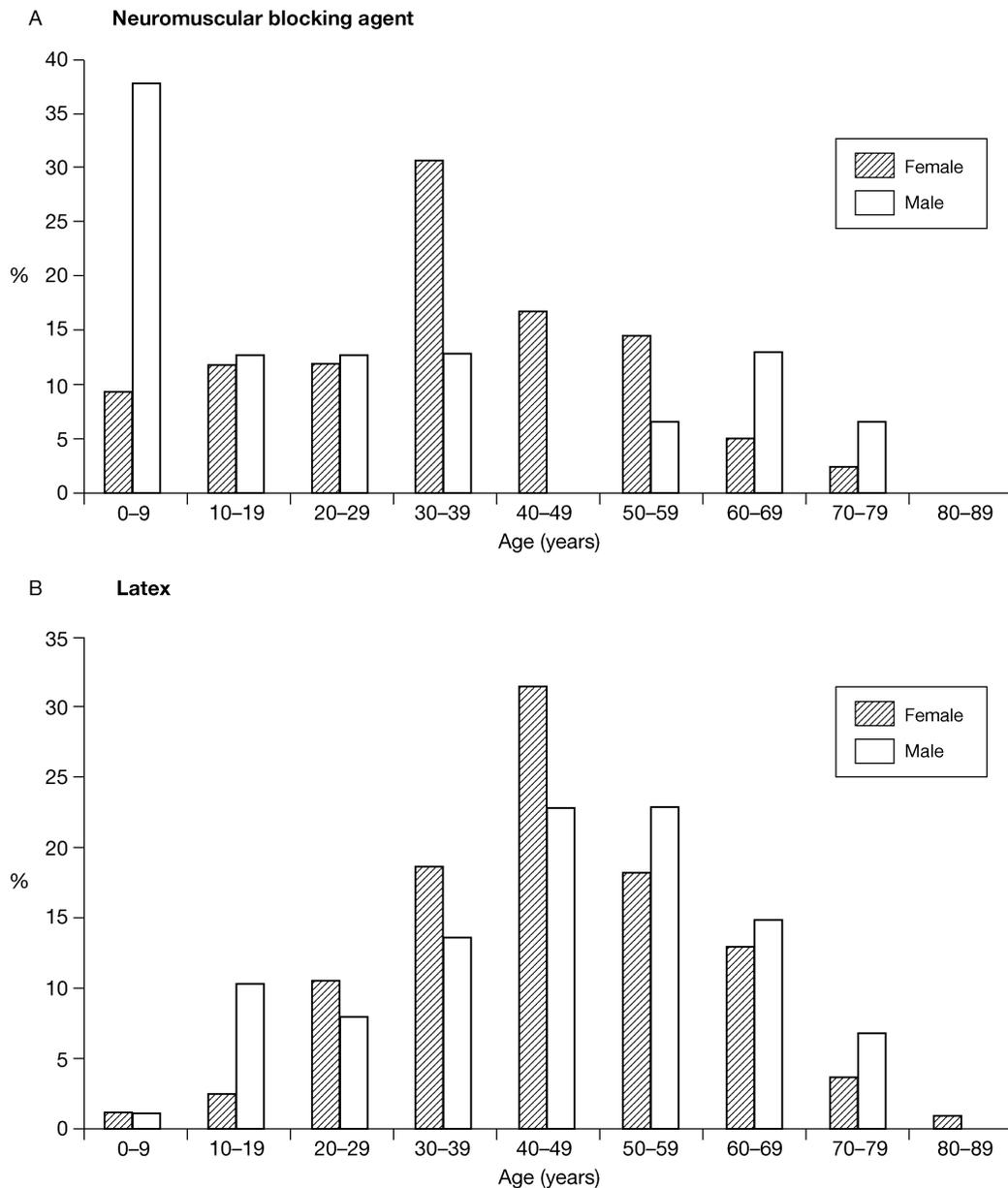


Fig 2 Distribution according to age range of anaphylactic reactions to (A) neuromuscular blocking agents (males $n=88$, females $n=248$) and (B) latex (males $n=16$, females $n=43$), in France between January 1997 and December 1998.

because it has been demonstrated that in France 30–40% of patients presenting with anaphylactoid reactions during anaesthesia did not have further allergic work-up.²¹ Moreover, some patients who had experienced an adverse reaction during an anaesthetic might have been investigated in centres other than those involved in this study.

Our results confirm the large female predominance (2.7 female/1 male) of anaphylactic reactions, although it is less marked than that reported in other studies, where it ranges from 8 females/1 male²² to 3.5 females/1 male.⁹ It should be noted that this difference persists even when the sex ratio of anaesthetized patients established by the French survey of anaesthesia (1.1 female/1 male) is taken into account.²⁰

Atopy and the presence of drug or food intolerance were assessed by history. Immunological assessment by skin testing or immunoassay was not performed systematically. The presence of atopy was reported in 25.4% of our patients. This rate is similar to that observed in our previous survey² and that observed in normal subjects.²³ However, as

reported previously,^{2 24} the presence of atopy was significantly more frequent in cases of latex allergy than in allergy to neuromuscular blocking agents (39 vs 24.8%, $P < 0.01$). A history of drug allergy was present in 15.9% of our patients, a rate that approaches that reported in normal subjects (15%).²⁵ In most cases, clinical reactions were severe (90% of cases were at least grade II) and often life-threatening (67% were grade III or IV). These results confirm the severity of immune-mediated adverse reactions. This contrasts with reports of anaphylactoid reactions of a non-immune type, 49% of which were of grade I.² In addition, it should be noted that, because of the design of the present study, severe reactions resulting in death or major clinical sequelae impeding patient follow-up remained unaccounted for. Clinical observations in which tryptase was determined post-mortem²⁶ or specific muscle relaxant IgE was detected in blood samples taken during a fatal anaesthetic anaphylactic event³ have been reported.

The most common features in this study were cardiovascular manifestations, present in 71.47%, followed by cutaneous symptoms (69.6%) and bronchospasm (44.2%). Cardiovascular symptoms were the sole feature in 10.5% of cases and in 10 cases were limited to hypotension. Similarly, bronchospasm was the only sign in 15 cases. These results concur with previous data^{2 16 27} and may explain why the reaction can be attributed to causes other than anaphylaxis. As in previously reports, asthmatic patients with anaphylaxis often presented with bronchospasm.^{16 27} Reaction severity was more pronounced in cases of sensitization to neuromuscular blocking agents than in cases of latex sensitization.²

The overall distribution of the various causal agents was similar to those reported previously.^{2 27} Anaphylactic reactions to local anaesthetics appear to be uncommon.¹⁶ Adverse reactions to colloids were less frequent than in some previous studies²⁷. This probably reflects the decreased use of gelatins as volume expanders in France. Latex sensitization was involved in 12.1% of cases. These results differ significantly from previous reports from a time when latex allergy was poorly recognized.⁹ The relative decrease in the number of cases diagnosed is encouraging;

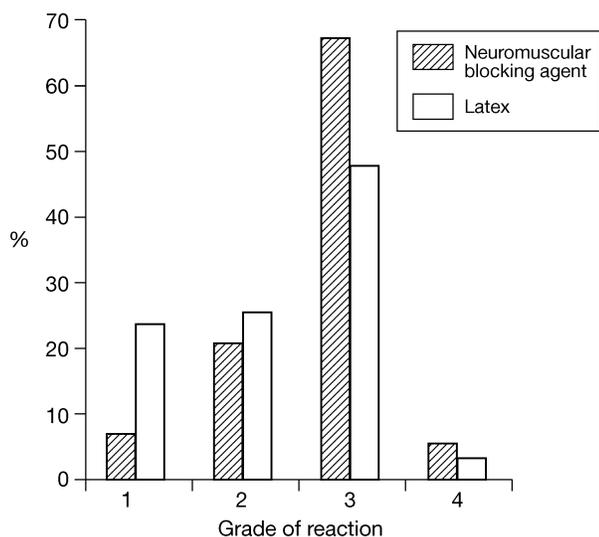


Fig 3 Frequencies of clinical severity grades of anaphylactic reactions to neuromuscular blocking agents ($n=336$) and latex ($n=59$) in France between January 1997 and December 1998.

Table 4 Intradermal skin test results according to the neuromuscular blocking agent involved in the anaphylactic reaction ($n=331$)

Neuromuscular blocking agent	Skin test positivity threshold (number of cases)					
	Dilution					
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
Succinylcholine	1	24	20	11	2	2
Rocuronium	6	33	28	9	1	
Vecuronium	13	17	17	3	2	
Mivacurium		3	4	2		
Pancuronium	6	9	3			
Atracurium		16	37	9	1	
Cisatracurium				1		

Table 5 Results of IgE-specific assay according to the neuromuscular blocking agent involved in the anaphylactic reaction ($n=234$)

IgE	Positive	Negative
Succinylcholine	54	5
Rocuronium	68	5
Vecuronium	31	4
Pancuronium	10	1
Mivacurium	5	3
Atracurium	34	14
	202	32

in our last published survey latex allergy was involved in 16.6% of cases.² Increasing awareness of the risk of latex sensitization in spina bifida children²⁸ or health-care workers,²⁹ combined with the efficacy of surgical procedures in a latex-free environment,³⁰ could be responsible for the decrease in the incidence of latex anaphylaxis we observed.

Although succinylcholine ($n=78$) remains a major causal agent, there are differences in this report, compared with our last survey, in the involvement of other neuromuscular blocking agents.² Rocuronium ($n=98$) appears to be the agent involved most frequently. As can be seen in Table 3, when account is taken of differences in the anaesthesia market share and the number of patients exposed, there are significant differences among the drugs that have been incriminated. These observations rely on the estimation of the number of patients exposed and should therefore be considered with circumspection. In addition, anaesthetists might have paid more attention to the effects of the drugs that have become available more recently, especially in cases of mild reactions. However, the increasing awareness of adverse reactions to rocuronium and the incidence of anaphylaxis (82 cases) is noteworthy.^{2 27 31-38}

In our study, positive diagnosis was mainly based on clinical history and skin test results, often corroborated by specific IgE assay. Although skin tests have been used extensively for more than two decades, there has been controversy recently concerning their use in the diagnosis of sensitization to rocuronium.³⁹ According to Levy and colleagues,³⁹ rocuronium prepared as a solution of 10 mg ml⁻¹ requires dilution to 10⁻² to avoid false-positive intradermal test results. This differs from the 10⁻¹ dilution recommended by the Commission Tripartite en Allergologie, which was the highest test concentration used by our participating centres.¹⁷ However, in the report of Levy and colleagues, intradermal testing was performed on the anterior face of the forearm rather than on the patient's back. The latter approach is favoured in France because the skin of the forearm is more likely to release histamine non-specifically.¹⁵ Moreover, an unexpected mean weal diameter of almost 6 mm with a negative control injection of saline was reported by Levy and colleagues. According to the Commission Tripartite en Allergologie

recommendations, such a result would have invalidated the test. Among the 98 cases of sensitization to rocuronium we observed, intradermal testing was considered positive at a dilution of 10⁻¹ in only six cases. These observations corresponded to three grade II and three grade III reactions, and in all of these cases the specific IgE assay against rocuronium was positive.

Nevertheless, the differences observed in the relative frequencies of sensitization to the various commercially available neuromuscular blocking agents remain to be explained. Indeed, one of the mechanisms of anaphylaxis to these drugs involves the presence of quaternary ammonium ions,⁴⁰ but other factors, such as the distance between the quaternary ammonium ions and the flexibility of the entire molecule, may also be important.⁴¹ The differences observed in cross-sensitization between different agents in this study have also been noted in previous reports; cross-sensitization appears to be more frequent with aminosteroid neuromuscular blocking agents than with benzyloisoquinoline-derived neuromuscular blocking agents.^{42 43}

The need for early as well as delayed laboratory investigations to confirm the occurrence of anaphylaxis should be stressed. In this series, early histamine and tryptase determinations were performed in 90 and 97 cases of anaphylaxis due to a neuromuscular blocking agent, and were found to be positive in 81 and 94 cases respectively. Moreover, when both tests were performed in the same patient, they were both negative in only two patients. This is consistent with previous reports concerning the value of these tests in the diagnosis of anaphylaxis to anaesthetic drugs.^{44 45}

Similarly, determination of specific muscle relaxant IgE, when performed, was positive in 86.3% of cases. These results were obtained with RIAs based on coupling an analogue of choline to Sepharose (QAS-RIA)¹⁸ or *p*-aminophenylphosphorylcholine to agarose (PAPPC-RIA).¹⁹ These RIA methods offer greater sensitivity (QAS-RIA, 87.5%; PAPPC-RIA, 97%) and specificity (QAS-RIA, 100%; PAPPC-RIA, 97%) than classic commercially available RIA kits, such as the RAST-succinylcholine test (sensitivity 66%).¹⁸ In addition, when performed, specific latex IgE assays were positive in 92.7% of cases, confirming the quality of this RIA. These results support the widespread use of the specific IgE assay in suspected cases of adverse reactions to anaesthetics. Moreover, serum samples can be drawn at the time of the adverse reaction and stored for testing later. This can facilitate further investigation of fatal anaphylactic reactions.³

In conclusion, our study confirms the predominance of sensitization to neuromuscular blocking agents and latex in anaphylactic reactions during anaesthesia. The differences observed over time concerning the relative contributions of the various neuromuscular blocking agents strengthen the need for post-marketing risk detection for new drugs. In addition, our results underline the need for wider use of

specific IgE assays combined with skin testing in the diagnosis of sensitization to neuromuscular blocking agents and latex, even in cases of minor adverse reactions. As suggested by the reduced incidence of anaphylaxis to latex, which is a probable consequence of generalized identification and preventative measures, an active policy to identify at-risk patients through the establishment of allergeo-anaesthesia centres should be promoted.

Acknowledgements

We thank Geneviève Lapeyre of Pharmacia & Upjohn, Mrs Christine Nussas, Bart Bots and Patrick Boen of Organon Teknika, Isabelle Thénard of Glaxo Wellcome and Jean-François Brin of Rhône-Poulenc Rorer for the information required to establish the market share of each neuromuscular blocking agent and the correction factor used for each drug.

Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Amiens: B. Benabes, C. Quequet. Angers: C. Cottineau, M. Drouet. Besançon: M. Neidhardt, P. Girardin, M. Vigan. Bordeaux-Pellegrin Tripode: S. Guez. Pessac: M. Tunon de Lara. Brest: J. C. Rakatoseheno. Caen: D. Laroche, M. C. Vergnault. Dijon: E. Collet, N. Louvier. Dreux: J. B. Duffin. Grenoble: C. Jacquot, P. Zambelli, D. Coperan. Lille: A. Facon. Limoges: I. Orsel. Lorient: F. Le Pabic. Lyon: Y. Benoît, J. Motin, L. Guilloux. Marseille: J. Birnbaum, D. Vervloet. Montpellier: M. C. Bonnet, T. Ryckwaert. Nancy: M. C. Laxenaire, C. Mouton, D. A. Moneret-Vautrin, S. Widmer, J. L. Guéant, I. Gastin. Nantes: F. Wessel. Nice: G. Occelli, J. Amédéo. Nîmes: M. Joncourt. Paris-Pitié: A. M. Korinek. Paris-Necker: D. Brunet-Langot, J. Labbez. Paris-Broussais: B. Fontaine. Paris-Tenon: F. Leynadier. Poitiers: K. Breuil. Reims: A. Gallet, F. Lavaud. Rennes: M. M. Lucas, Y. Delaval. Saint-Etienne: C. Dzvinga. Strasbourg: J. Valfrey. Suresnes: M. T. Guinépain. Tarbes: J. Gayraud. Toulouse-Purpan: D. Giamarchi, M. Miguères, H. Perelroizen. Toulouse-Rangueil: A. Didier. Tours: P. Carré.

References

- Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. *Ann Fr Anesth Réanim* 1993; **12**: 97–104
- Laxenaire MC. Epidémiologie des réactions anaphylactoïdes peranesthésiques. Quatrième enquête multicentrique (juillet 1994–décembre 1996). *Ann Fr Anesth Réanim* 1999; **18**: 796–809
- Fisher MM, Baldo BA. The diagnosis of fatal anaphylactic reactions during anaesthesia: employment of immunoassays for mast cell tryptase and drug-reactive IgE antibodies. *Anaesth Intens Care* 1993; **21**: 353–7
- Laxenaire MC, Moneret-Vautrin DA, Boileau S, Moeller R. Adverse reactions to intravenous agents in anaesthesia in France. *Klin Wochenschr* 1982; **60**: 1006–9
- Fisher MM. Intradermal testing after severe histamine reactions to intravenous drugs used in anaesthesia. *Anaesth Intens Care* 1976; **4**: 97–104
- Fisher MM. Anaphylactoid reactions during anaesthesia. In: Prys-Roberts C, ed. *International Practice of Anaesthesia*. Oxford: Butterworth-Heinemann, 1996; 1–13
- Clarke RS. Epidemiology of adverse reactions in anaesthesia in the United Kingdom. *Klin Wochenschr* 1982; **60**: 1003–5
- Clarke RS, Watkins J. Drugs responsible for anaphylactoid reactions in anaesthesia in the United Kingdom. *Ann Fr Anesth Réanim* 1993; **12**: 105–8
- Galletly DC, Treuren BC. Anaphylactoid reactions during anaesthesia. Seven years' experience of intradermal testing. *Anaesthesia* 1985; **40**: 329–33
- Sjoqvist F. Drug safety in relation to efficacy: the view of a clinical pharmacologist. *Pharmacol Toxicol* 2000; **86**: 30–2
- Task Force on Latex Sensitivity. *Natural Rubber Latex Allergy: Considerations for Anesthesiologists*. Park Ridge: American Society of Anesthesiologists, 1999
- Prévention du risque allergique peranesthésique. *Recommandations Pour la Pratique Clinique*. Paris: Société Française d'Anesthésie et de Réanimation, 2001.
- Mertes PM, Laxenaire M. Anaphylaxis during general anaesthesia. Prevention and management. *CNS Drugs* 2000; **14**: 115–33
- Fisher M. Intradermal testing after anaphylactoid reaction to anaesthetic drugs: practical aspects of performance and interpretation. *Anaesth Intensive Care* 1984; **12**: 115–20
- Moneret-Vautrin D, Laxenaire M. Skin tests in diagnosis of allergy to muscle relaxants and other anaesthetic drugs. *Monogr Allergy* 1992; **30**: 145–55
- Fisher M, Baldo BA. Anaphylaxis during anaesthesia: current aspects of diagnosis and prevention. *Eur J Anaesthesiol* 1994; **11**: 263–84
- Laurent J. Commission tripartite de consensus en allergologie. *Rev Fr Allergol* 1997; **37**: 776–7
- Guéant JL, Mata E, Monin B, et al. Evaluation of a new reactive solid phase for radioimmunoassay of serum specific IgE against muscle relaxant drugs. *Allergy* 1991; **46**: 452–8
- Guilloux L, Ricard-Blum S, Ville G, Motin J. A new radioimmunoassay using a commercially available solid support for the detection of IgE antibodies against muscle relaxants. *J Allergy Clin Immunol* 1992; **90**: 153–9
- Clergue F, Auroy Y, Pequignot F, et al. French survey of anaesthesia in 1996. *Anesthesiology* 1999; **91**: 1509–20
- Laroche D, Bricard H, Laxenaire MC. Allergeo-anaesthesia consultation: not enough patients are tested after an anaphylactoid anaesthetic incident. *Ann Fr Anesth Réanim* 1998; **17**: 89–90
- Youngman PR, Taylor KM, Wilson JD. Anaphylactoid reactions to neuromuscular blocking agents: a commonly undiagnosed condition? *Lancet* 1983; **2**: 597–9
- Beaudoin E, Pupil P, Jacson F, Laxenaire M, Moneret-Vautrin D. Allergie professionnelle au latex. Enquête prospective sur 907 sujets du milieu hospitalier. *Rev Fr Allergol* 1990; **30**: 157–61
- Tan BB, Lear JT, Watts J, Jones P, English JS. Perioperative collapse: prevalence of latex allergy in patients sensitive to anaesthetic agents. *Contact Dermatitis* 1997; **36**: 47–50
- Haddi E, Charpin D, Tafforeau M, et al. Atopy and systemic reactions to drugs. *Allergy* 1990; **45**: 236–9
- Edston E, van Hage-Hamsten M. Beta-tryptase measurements post-mortem in anaphylactic deaths and in controls. *Forensic Sci Int* 1998; **93**: 135–42
- Whittington T, Fisher MM. Anaphylactic and anaphylactoid reactions. *Baillieres Clin Anaesthesiol* 1998; **12**: 301–23
- Nieto A, Mazon A, Estornell F, Reig C, Garcia-Ibarra F. The search for latex sensitization in spina bifida: diagnostic approach. *Clin Exp Allergy* 2000; **30**: 264–9
- DuBuske L, Babahkin A, Cieslewicz G, Nolte H, Sheffer AL. Clinical assessment of latex allergy among hospital health care providers. *Int Arch Allergy Immunol* 1999; **118**: 253–4
- Holzman RS. Clinical management of latex-allergic children. *Anesth Analg* 1997; **85**: 529–33
- Donnelly T. Anaphylaxis to rocuronium. *Br J Anaesth* 2000; **84**: 696
- Allen SJ, Gallagher A, Paxton LD. Anaphylaxis to rocuronium. *Anaesthesia* 2000; **55**: 1223–4
- Matthey P, Wang P, Finegan BA, Donnelly M. Rocuronium

- anaphylaxis and multiple neuromuscular blocking drug sensitivities. *Can J Anaesth* 2000; **47**: 890–3
- 34** Heier T, Guttormsen AB. Anaphylactic reactions during induction of anaesthesia using rocuronium for muscle relaxation: a report including 3 cases. *Acta Anaesthesiol Scand* 2000; **44**: 775–81
- 35** Neal SM, Manthri PR, Gadiyar V, Wildsmith JA. Histaminoid reactions associated with rocuronium. *Br J Anaesth* 2000; **84**: 108–11
- 36** Barthelet Y, Ryckwaert Y, Plasse C, Bonnet-Boyer MC, d'Athis F. Severe anaphylactic reactions after administration of rocuronium. *Ann Fr Anesth Réanim* 1999; **18**: 896–900
- 37** Duvaldestin P, Wigdorowicz C, Gabriel I. Anaphylactic shock to neuromuscular blocking agent: a familial history. *Anesthesiology* 1999; **90**: 1211–2
- 38** Yee R, Fernandez JA. Anaphylactic reaction to rocuronium bromide. *Anaesth Intensive Care* 1996; **24**: 601–4
- 39** Levy JH, Gottge M, Szlam F, Zaffer R, McCall C. Weal and flare responses to intradermal rocuronium and cisatracurium in humans. *Br J Anaesth* 2000; **85**: 844–9
- 40** Baldo BA, Fisher MM. Substituted ammonium ions as allergenic determinants in drug allergy. *Nature* 1983; **306**: 262–4
- 41** Birnbaum J, Vervloet D. Mechanisms of anaphylactic reactions to muscle relaxants: role of allergenic determinants. Allergy to muscle relaxants. *Monogr Allergy* 1992; **30**: 15–23
- 42** Leynadier F, Dry J. Anaphylaxis to muscle-relaxant drugs: study of cross-reactivity by skin tests. *Int Arch Allergy Appl Immunol* 1991; **94**: 349–53
- 43** Laxenaire MC, Gastin I, Moneret-Vautrin DA, Widmer S, Gueant JL. Cross-reactivity of rocuronium with other neuromuscular blocking agents. *Eur J Anaesthesiol Suppl* 1995; **11**: 55–64
- 44** Laroche D, Vergnaud MC, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs. Comparison of plasma histamine and tryptase. *Anesthesiology* 1991; **75**: 945–9
- 45** Watkins J, Wild G. Improved diagnosis of anaphylactoid reactions by measurement of serum tryptase and urinary methylhistamine. *Ann Fr Anesth Réanim* 1993; **12**: 169–72