

# Anaphylaxis during Anesthesia in Norway

## A 6-Year Single-center Follow-up Study

Torkel Harboe, M.D.,\* Anne Berit Guttormsen, M.D., Ph.D.,† Aagot Irgens, M.Sc.,‡ Turid Dybendal, M.Sc., Ph.D.,§ Erik Florvaag, M.D., Ph.D.||

**Background:** Several studies have recognized neuromuscular blocking agents as the most common cause of anaphylaxis during general anesthesia, but the reported frequencies vary considerably between countries. In Norway, the issue has raised special concern because of reports from the Norwegian Medicines Agency that suggest a high prevalence. This article presents the results from a standardized allergy follow-up examination of 83 anaphylactic reactions related to general anesthesia performed at one allergy center in Bergen, Norway.

**Methods:** Eighty-three cases were examined during the 6-yr period of 1996–2001. The diagnostic protocol consisted of case history, serum tryptase measurements, specific immunoassays, and skin tests.

**Results:** Immunglobulin E-mediated anaphylaxis was established in 71.1% of the cases, and neuromuscular blocking agents were by far the most frequent allergen (93.2%). Suxamethonium was the most frequently involved substance, followed by rocuronium and vecuronium. The few reactions in which other allergens could be detected were mainly linked to latex (3.6%).

**Conclusions:** Neuromuscular blocking agents were the dominating antigens causing immunoglobulin E-mediated anaphylaxis in this study. The data could not be used for estimation of the incidence of allergy toward neuromuscular blocking agents in Norway. Larger patient samples, standardization of reporting, and diagnostic protocols should be pursued by network formation to produce data more suitable for epidemiologic research.

ANAPHYLAXIS during anesthesia is an acute and dramatic adverse event that has received increasing attention during the past decades. The true incidence of reactions is unknown, and frequency estimates vary considerably between studies from different countries.<sup>1-3</sup> The optimal diagnostic approach has been debated; for example, conflicting recommendations exist as to the optimal drug concentrations for intradermal testing with neuromuscular blocking agents (NMBAs). Closely linked

is the discussion on the potential of rocuronium bromide to elicit anaphylaxis. In France and Norway, there have been claims of an increased risk, which has not been reported from other countries. No standardized follow-up studies on anaphylaxis during general anesthesia have previously been reported from Norway.

The aims of this study were to describe a patient population that developed perianesthetic anaphylaxis in the years 1996–2001 and to evaluate the standardized protocol used for allergy follow-up examination at one allergy outpatient clinic in Western Norway.

## Materials and Methods

This study covers all patients (n = 83) referred to the Center for Occupational and Environmental Allergy, Department of Occupational Medicine, Haukeland University Hospital, in Bergen, Norway, after anaphylactic reactions related to general anesthesia. The patients were mainly referred from hospitals in the western part of Norway, but because of limited capacity for allergy follow-up in other regions, a few patients were sent to us from the eastern and northern parts of the country. The reactions occurred between January 1996 and December 2001, and the mean time interval to follow-up was 8.5 months. Institutional review board approval was not required for this study.

### Recording of Medical History

The case histories were completed by documentation offered by the referring physician (including anesthetic charts) and by interviewing the patients. Data on age, sex, general history, previous allergy, previous anesthesia, prescription medication, anesthetic drugs given before the adverse reaction, time interval between administration of substances and the reaction, recorded clinical manifestations, and acute management of the episode were collected. The reactions were classified according to the severity scale for quantification of intensity of anaphylactoid reactions by Ring and Messmer,<sup>4</sup> scaling the severity in four degrees (skin reactions, systemic non-life-threatening reactions, life-threatening reactions, and cardiopulmonary arrest).

### Skin-prick Testing

Skin-prick tests (SPTs) were performed in duplicate according to the guidelines of the European Academy of Allergy and Clinical Immunology.<sup>5,6</sup> A standardized SPT panel was used, consisting of 10 mg/ml histamine chlo-

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\* Resident, † Consultant, Department of Anesthesia and Intensive Care, ‡ Statistician, Department of Occupational Medicine, || Associate Professor, Laboratory of Clinical Biochemistry, Haukeland University Hospital. § Senior Pharmacist, Kongsvinger Hospital Pharmacy, Kongsvinger, Norway.

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Address reprint requests to Dr. Harboe: Department of Anesthesia and Intensive Care, Haukeland University Hospital, N-5021 Bergen, Norway. Address electronic mail to: torkel.harboe@helse-bergen.no. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

ride (ALK Abelló, Hørsholm, Denmark), negative control (ALK Abelló), suxamethonium, rocuronium, vecuronium, pancuronium, atracurium, fentanyl, pentothal, propofol, and 100 histamine equivalent prick latex (ALK Abelló). All other solutions were freshly prepared, initially to 1:10 of vial concentrations and increasing to 1:1 for the last 35 patients after a revision of the protocol. From June 2001, chlorhexidine (1 mg/ml) was added. In individual cases, other involved substances were included, aiming at testing all relevant antigens. SPTs performed by a trained allergy nurse yielded a mean wheal diameter to 10 mg/ml histamine of 5.5 mm (83 duplicates), with a coefficient of variation between duplicates of 19.5%.

#### *Total and Specific IgE*

Total immunoglobulin E (IgE) and specific IgE toward latex, suxamethonium, and pentothal were analyzed in serum samples at the Laboratory of Clinical Biochemistry, Haukeland University Hospital, using the Pharmacia CAP FEIA system (Pharmacia Diagnostics AB, Uppsala, Sweden). Analysis was performed in serum samples collected both at the time of the reaction and at the follow-up examination. Screening for specific IgE directed toward quaternary ammonium ion epitopes was performed in cases where rocuronium had been administered before the reaction. This was done with both p-aminophenyl phosphoryl choline (PAPPC)-radioimmunoassay<sup>7</sup> and morphine-radioimmunoassay,<sup>8</sup> as described elsewhere.<sup>9</sup>

#### *Serum Tryptase*

Serum tryptase was measured using the Pharmacia UniCAP FEIA system (Pharmacia Diagnostics AB). We attempted to obtain serum samples at three time points: before, within 2 h after, and on the day after the reaction. The tryptase levels were considered increased if the 2-h serum concentration was above 24 µg/l (the upper reference area limit [97.5%] of the laboratory) or if the increase in the 2-h sample was at least three times that of the background concentration. Analyses were repeated at follow-up to determine whether any patients had chronically increased background concentrations, because this could indicate systemic mastocytosis.

#### *Histamine-release Testing*

Histamine-release tests (HRTs) were done in washed blood cells using a glass microfiber-based test.<sup>10</sup> Heparinized blood was washed once in Pipes buffer and preincubated for 15 min at 37°C, and then 25 µl was applied into microtiter wells. Twenty-five microliters of drug solution was added and incubated at 37°C for 1 h, and the wells were washed. Glass fiber-bound histamine was resolubilized, complexed with o-phthalaldehyd, and quantified fluorometrically. The amount of histamine released was assayed in duplicate 2.5-fold dilution series.

All relevant drugs used before and during the particular anesthesia were tested. A negative control was included.

#### *Diagnostic Criteria*

The diagnostic conclusions primarily aimed at defining severity, pathogenic mechanism, and cause of reaction. Severity was classified according to the severity scale for quantification of intensity of anaphylactoid reactions by Ring and Messmer.<sup>4</sup> Pathogenic mechanisms were defined in accordance with the new nomenclature of allergy proposed by the European Academy of Allergy and Clinical Immunology and the World Allergy Organization<sup>11,12</sup> into IgE-mediated and non-IgE-mediated reactions depending on the SPT, serum IgE, and HRT results. The degree of causality of a certain drug or antigen was principally defined in keeping with the World Health Organization terminology on adverse drug reactions.<sup>13</sup> However, because the sensitivity and specificity of the IgE-based methods varied for individual drugs and patients, we developed a modified categorization grading of causality of the IgE-mediated reactions (see appendix).

#### *Statistical Analysis*

Descriptive statistics were performed by SPSS for Windows (SPSS Inc., Chicago, IL). Cohen's  $\kappa$  was used as the measure of agreement between different diagnostic methods. The two-sided confidence interval for a single proportion was calculated using a method of normal approximation with continuity correction.<sup>14</sup>

## **Results**

#### *Patients*

Eighty-three patients were examined for reactions related to general anesthesia during the period from January 1996 to December 2001. The female to male ratio was 3:1, and the mean age was 38.2 yr. A history of previous general anesthesia was reported by 67.5%, some form of allergic disease was reported by 61.4%, and previous adverse reactions to nonanesthetic drugs was reported by 25.3% of the patients. One patient had a history of one anaphylactic episode during general anesthesia before the reaction that led to the follow-up examination. No patients were found to have systemic mastocytosis. All drugs and other antigens reported administered before the reactions are summarized in table 1. In addition, we recognized that chlorhexidine is ubiquitously used for disinfection and that most patients probably also were exposed to latex in the operating room.

#### *Clinical Features*

Table 2 shows the spectrum of clinical signs reported from the reactions. The time intervals for the appearance

**Table 1. Drugs Administered before the reaction in 83 Cases**

Drug	Number of Cases	%
Suxamethonium	40	48.2
Rocuronium	33	39.8
Other NMBAs	20	24.1
Thiopental	63	75.9
Propofol	18	21.7
Midazolam	12	14.5
Ketamine	2	2.4
Fentanyl	66	79.5
Other opioids	7	8.4
Atropine	9	10.8
Local anesthetics	5	6.0
Antibiotics	2	2.4
Droperidol	1	1.2
Ephedrine	1	1.2
Phenylephrine	1	1.2
Hemaccel	1	1.2
Oxytocin	1	1.2

NMBA = neuromuscular blocking agent.

of clinical signs of anaphylaxis after induction of general anesthesia was within 5 min in 86.7%, between 5 and 10 min in four (4.8%), and between 20 min and 2.5 h in four cases (4.8%). On three occasions (3.6%), the precise timing of the reaction was not specified. All but five patients (6.0%) had clinical manifestations from two or more organ systems (cardiovascular, respiratory, or cutaneous signs). The most frequently reported clinical sign was bronchospasm in 65 (78.3%), whereas hypoxemia (oxygen saturation measured by pulse oximetry < 90%) was reported in 41 (49.4%) of the reactions. Systolic blood pressure decreased to 60 mmHg or below in 53 cases (63.9%), and in 15 of these (18.1%), it was not measurable. Five patients received cardiopulmonary resuscitation. Skin rash, angioedema, or both were reported in 52 of the events (62.7%). Severity grading allocated five reactions (6.0%) to grade IV, 52 (62.7%) to grade III, 25 (30.1%) to grade II, and 1 (1.2%) to grade I.<sup>4</sup>

#### Skin-prick Testing

Positive SPT results (mean weal diameter  $\geq$  3 mm larger than that of the negative control) were found in 43 cases and were obtained with suxamethonium, rocuronium, vecuronium, pancuronium, atracurium, and latex. The results of SPT with thiopental, propofol, and fenta-

**Table 2. Reported Clinical Signs of Anaphylaxis (n = 83)**

Clinical Signs	Number of Cases (%)	Sole Feature
Systolic blood pressure < 60 mmHg	53 (63.9)	1
Cardiac arrest	5 (6.0)	
Bronchospasm	65 (78.3)	3
Hypoxemia (saturation < 90%)	41 (49.4)	
Rash	45 (54.2)	1
Angioedema	14 (16.9)	

**Table 3. Causal Agents in 83 Cases of Perianesthetic Anaphylaxis**

Causal Agent	Number of Cases (%)	Probable Causality	Possible Causality
All NMBAs	55 (66.2)	45	10
Suxamethonium	30 (36.1)	28	2
Rocuronium	17 (20.5)	12	5
Vecuronium	6 (7.2)	4	2
Pancuronium	1 (1.2)	1	
Atracurium	1 (1.2)		1
Latex	3 (3.6)	3	
Hemaccel	1 (1.2)		1
Unknown	24 (28.9)		

NMBA = neuromuscular blocking agent.

nyl were negative in all patients. Severe dermographism making the skin-prick test difficult to interpret was seen in one patient; however, the presence of specific IgE toward rocuronium and vecuronium was indicated by a positive HRT result.

#### In Vitro Analysis

**Serum Tryptase.** A significant acute (2-h) increase of serum tryptase accompanied 40 (48.2%) of the anaphylactic reactions. In 25 cases (30.1%), no increase was detected, but for 15 of these, the time interval between reaction and blood sampling was not specified. From 18 (21.7%) of the events, 2-h serum samples were not obtained.

**Specific IgE.** Specific IgE toward suxamethonium was detected in 35 patients, and the agreement of SPT with suxamethonium was estimated to be 63.3% ( $\kappa = 0.32$ ). Specific IgE toward latex was positive in 4 cases, with an agreement with SPT of 97.3% ( $\kappa = 0.71$ ).

**Histamine-release Testing.** Histamine-release test results were positive in 23.5% of the 51 patients tested. In three cases, HRTs provided the only positive results suggesting an IgE-mediated mechanism. The agreement between HRT and SPT was 60.8% ( $\kappa = 0.15$ ).

#### Screening for Serum IgE toward Quaternary Ammonium Ions

Morphine- and PAPPC-radioimmunoassays performed in 31 of the 33 patients whose reactions were related to the administration of rocuronium were positive in 23 (74.2%) and 18 (58.1%), respectively. Compared with the diagnostic conclusions (based on the clinical information, SPT, HRT, and determination of specific IgE toward suxamethonium), the corresponding agreements were 84% ( $\kappa = 0.65$ ) and 81% ( $\kappa = 0.60$ ), respectively.

#### Diagnostic Conclusions

The diagnostic conclusions are presented in table 3. An IgE-mediated mechanism to a specified drug or antigen could be established in 59 cases (71.1%). NMBAs were the most frequently involved allergens, accounting

**Table 4. Diagnostic Conclusions and Serum Tryptase Related to the Severity of the Reactions (n = 83)**

Reaction Severity	Grade 1 (n = 1)	Grade 2 (n = 25)	Grade 3 (n = 52)	Grade 4 (n = 5)
Conclusion positive	0	13	42	4
Conclusion negative	1	12	10	1
Tryptase increased	0	5	32	3
Tryptase normal	0	15*	10*	0
Tryptase not obtained	1	5	10	2

\* Time relation between reaction and sampling unknown in 15 of 25 cases.

for 93.2% of the IgE-mediated reactions. The level of causality was probable in 48 and possible in 11 cases. None of the reactions were certain or unrelated. In 24 of the events (28.9%), an IgE-mediated mechanism was not identified. As shown in table 4, evidence for an IgE-mediated mechanism tended to occur more often in the severe (grade 3 and 4) reactions than in the mild (grade 1 and 2) reactions.

For the subpopulation of 33 patients whose reactions

were related to the administration of rocuronium, the diagnostic conclusions are summarized in table 5. Twenty reactions (60.6%) were IgE mediated. The causal agent was rocuronium in 17 cases (51.5%) (12 probable and 5 possible) and suxamethonium in 3 cases (9.1%), all probable. In 13 events (39.4%), the pathogenic mechanism was not identified, and consequently, the causal agent remained unknown and the level of causality remained unclassified. The test results indicated NMBA cross-sensitivity in 5 cases.

#### *In-hospital Frequency of Reactions*

When calculating frequency of reactions in our material, we must limit the material to the subset of 19 reactions that were referred internally at Haukeland University Hospital, because we have no data to estimate the size of the exposed population behind the total 83 reactions. During the 6-yr period (1996–2001), 113,000 general anesthetics were performed at the Haukeland University Hospital according to the annual reports of the

**Table 5. Diagnostic Results for the 33 Cases of Anaphylaxis in Which Rocuronium Was Administered at Induction of General Anesthesia before the Reactions**

Patient No.	SPT	HRT	IgE-Sux	Morphine-RIA	PAPPC-RIA	Causal Agent	Level of Causality
1	<b>Roc, Sux</b>	<b>Roc</b>	<b>Pos</b>	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Probable</b>
2	Neg	Neg	<b>Pos</b>	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Possible</b>
3	<b>Roc</b>	ND	Neg	<b>Pos</b>	Neg	<b>Rocuronium</b>	<b>Probable</b>
4	Neg	Neg	Neg	Neg	Neg	Unknown	Unclassified
5	<b>Roc, Vec, Pan</b>	ND	Neg	ND	ND	<b>Rocuronium</b>	<b>Probable</b>
6	Neg	Neg	Neg	Neg	Neg	Unknown	Unclassified
7	Neg	Neg	Neg	Neg	Neg	Unknown	Unclassified
8	<b>Roc</b>	*	<b>Pos</b>	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Probable</b>
9	Neg	<b>Roc</b>	Neg	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Probable</b>
10	<b>Sux</b>	Neg	<b>Pos</b>	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Possible</b>
11	<b>Sux</b>	Sux	Neg	<b>Pos</b>	<b>Pos</b>	<b>Suxamethonium</b>	<b>Probable</b>
12	Neg	Neg	Neg	<b>Pos</b>	Neg	Unknown	Unclassified
13	<b>Roc, Sux</b>	Neg	Neg	<b>Pos</b>	Neg	<b>Rocuronium</b>	<b>Probable</b>
14	Neg	Neg	<b>Pos</b>	ND	ND	<b>Rocuronium</b>	<b>Possible</b>
15	Neg	*	Neg	<b>Pos</b>	Neg	Unknown	Unclassified
16	Neg	Neg	Neg	<b>Pos</b>	Neg	Unknown	Unclassified
17	Neg	*	<b>Pos</b>	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Possible</b>
18	Neg	<b>Roc</b>	Neg	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Probable</b>
19	Neg	Neg	Neg	Neg	Neg	Unknown	Unclassified
20	Neg	*	Neg	<b>Pos</b>	Pos	Unknown	Unclassified
21	Neg	*	Neg	Neg	<b>Pos</b>	Unknown	Unclassified
22	<b>Atr</b>	<b>Roc, Fen</b>	<b>Pos</b>	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Probable</b>
23	<b>Roc, Nor</b>	<b>Roc, Nor</b>	<b>Pos</b>	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Probable</b>
24	Neg	Neg	Neg	Neg	Neg	Unknown	Unclassified
25	<b>Sux</b>	Neg	Neg	<b>Pos</b>	<b>Pos</b>	<b>Suxamethonium</b>	<b>Probable</b>
26	<b>Roc</b>	*	Neg	<b>Pos</b>	Neg	<b>Rocuronium</b>	<b>Probable</b>
27	<b>Sux†</b>	Neg	Neg	<b>Pos</b>	<b>Pos</b>	<b>Suxamethonium</b>	<b>Probable</b>
28	<b>Roc</b>	ND	<b>Pos</b>	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Probable</b>
29	<b>Roc</b>	ND	<b>Pos</b>	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Probable</b>
30	Neg	Neg	Neg	<b>Pos</b>	Pos	Unknown	Unclassified
31	Neg	Neg	<b>Pos</b>	<b>Pos</b>	<b>Pos</b>	<b>Rocuronium</b>	<b>Possible</b>
32	Neg	Neg	Neg	Neg	Neg	Unknown	Unclassified
33	Neg	Neg	Neg	Neg	Neg	Unknown	Unclassified

Boldface entries indicate positive test results and positive diagnostic conclusions.

\* Inconclusive. † Positive intracutaneous test for suxamethonium.

Atr = atracurium; Fen = fentanyl; HRT = histamine-release test (negative results not shown); IgE = immunoglobulin E; ND = not done; Neg = negative; Pan = pancuronium; PAPPC = P-aminophenyl phosphoryl choline; Pos = positive; RIA = radioimmunoassay; Roc = rocuronium; SPT = skin-prick test (negative results not shown); Sux = suxamethonium; Vec = vecuronium.

Department of Anesthesia and Intensive Care. Approximately half of these did not include NMBAs. During the same period, 19 anaphylactic reactions were referred, of which 11 (57.9%) were shown to be IgE mediated (7 probable, 4 possible). Therefore, an approximate frequency of one NMBA-induced IgE-mediated anaphylaxis per 5,200 general anesthetics encompassing NMBAs could be estimated (95% confidence interval, 1:14,285–1:3,125).

## Discussion

The 6-yr results from this single center study in Norway showed that 71.1% of the examined anaphylactic reactions were IgE mediated, and this is in accord with the findings in large population studies from other countries.<sup>1,15,16</sup> Our results, however, show a higher proportion of NMBA allergy (93.2%) relative to other drug allergies among the IgE-mediated reactions. This difference could be explained by referral bias, differences in allergy testing methods, or actual geographical differences in sensitization toward the relevant antigens, and these factors are discussed below.

### *Referral Bias*

The possibility of referral bias is a fundamental problem in studies on rare adverse events collected by volunteer reporting. There may be tendencies to refer suspected reactions toward certain agents (in this case NMBAs), and opposite tendencies not to refer suspected reactions toward other agents (antibiotics or latex). This is an uncontrollable factor that must be considered when our results are interpreted. Still, it may be difficult to show in what way the referral bias may specifically change from one study and country to another.

### *Test Methods and Diagnostic Challenges*

Skin-prick testing performed with all involved substances was the main diagnostic tool in the study, together with the clinical picture and tryptase measurements. We may have underestimated the number of IgE-mediated anaphylactic reactions by using in part a one-tenth vial concentration for SPTs, because the SPT sensitivity to a degree is concentration dependent. However, there are studies to support that no significant sensitivity was lost by using SPTs and not intradermal tests.<sup>17–19</sup> Disagreement exists on the specificity of intradermal tests with NMBAs and on the choice of test concentrations defining hypersensitivity.<sup>2,19</sup> A recent study also questioned the specificity for SPTs with NMBAs.<sup>20</sup> This contrast with the general view on SPTs, and a study on nonallergic individuals, suggested high specificity for SPTs when using the same method as we did.<sup>21</sup> With the uncertainties related to skin test results in mind, we do not have information to infer that our

choice of testing methods explains the relatively high proportion of NMBA allergy found.

Other diagnostic challenges are illustrated by the varying agreement between SPT, specific IgE, and HRT. Agreement was poor between SPT and HRT, good between SPT and IgE toward latex, but only fair between SPT and IgE toward suxamethonium. In the 33 cases exposed to rocuronium, morphine-radioimmunoassay was the diagnostic method with the highest fraction of positive results. Other authors have found morphine-radioimmunoassay more sensitive than specific NMBA-radioimmunoassays.<sup>8</sup> In our study, it also showed good agreement with the diagnostic conclusions based on the combination of SPT, HRT, and IgE toward suxamethonium.

The uncertainty related to test sensitivity and specificity had to be taken into account in the diagnostic conclusions. We therefore adopted a system of graded causality. Accidental rechallenge information on suxamethonium was reported for one patient only. The first occasion was during a cesarean delivery in general anesthesia on top of an inadequately functioning epidural anesthesia. In this situation, profound hypotension and moderate hypoxemia could have explanations other than anaphylaxis. Therefore, causality was designated probable in this case. In situations where causality was reduced to possible, the evidence for an IgE-mediated reaction was either indirect (with IgE detected toward an NMBA other than the one used), or the clinical picture could have alternative explanations (e.g., profound hypotension at the end of bypass surgery related to polygeline infusion). The causality was not stated as unrelated to any of the cases because the time relation between the reaction and administered agents was always plausible, and the possibility of false-negative allergy assessments could not be excluded. The cases with negative tests were therefore considered unclassified or of unknown pathogenesis. To avoid speculative conclusions on causative agents and also to be in keeping with the European Academy of Allergy and Clinical Immunology and World Allergy Organization nomenclature, we did not use the term *anaphylactoid*.<sup>11,12</sup> We also recognize that in the whole population of 83, there must be some cases that were not hypersensitivity reactions but rather perianesthetic episodes of hypotension and bronchial obstruction of other causes that cannot be clarified by allergy evaluations.

### *Antigens Other Than NMBAs*

In studies from France, latex caused 12–19% of anaphylactic reactions,<sup>3,15,16</sup> whereas the current study only identified three cases (3.6%) ascribed to IgE-mediated latex allergy. Latex allergy has long been an occupational health risk for healthcare personnel. To reduce the risk of sensitization and allergic reactions in hospital staff and patients, most hospitals have systematically reduced the unnecessary and undeclared use of natural rubber latex in medical products and equipment. Different degrees of

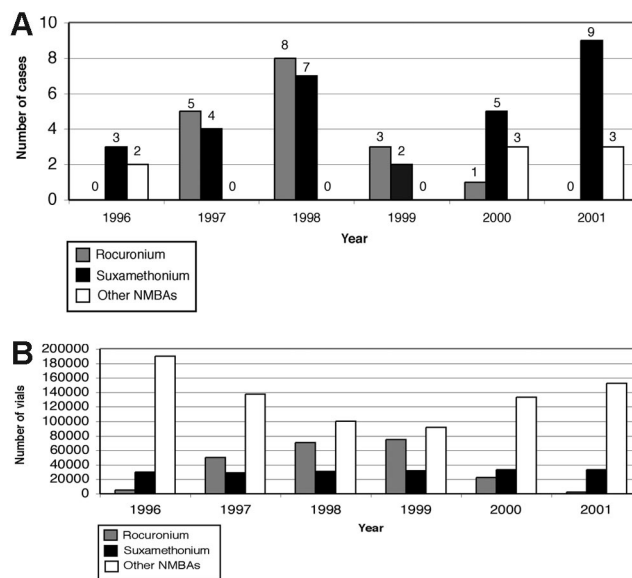
exposure in operating rooms may explain different percentages of latex reactions. Still, referral bias (as discussed above) may also explain the discrepant findings, and so could varying degrees of sensitization to latex in France and Norway.

In this study, most patients were not routinely tested for allergy toward chlorhexidine unless indicated by the case history. In Denmark, chlorhexidine was recently shown to be a more frequent cause of anaphylaxis during general anesthesia than NMBAs.<sup>22</sup> The chlorhexidine-reactive patients in the Danish study experienced symptoms 20–40 min after induction of anesthesia,<sup>23</sup> whereas more than 90% of the patients in our study reacted within 5–10 min. The late onset of chlorhexidine anaphylaxis is partly related to the fact that the major use normally starts some time after induction and that, applied on skin or mucosal surfaces, the absorption is delayed compared with intravenously administered antigens. The short reaction times argue in addition against chlorhexidine being a seriously underdiagnosed causative agent in this study.

Fentanyl, thiopental, and propofol did not give positive SPTs in any of the patients, even though one or more of these drugs were routinely used in all anesthesia. The finding that allergy toward opioids and anesthetic agents such as thiopental and propofol are much rarer than reactions to NMBAs is in keeping with previous reports.<sup>1,16,22</sup> General anesthesia without the administration of NMBAs is common. During the study period, we saw only 1 of 83 patients react during anesthesia without the use of NMBAs. This adds additional strength to the argument that NMBAs are the major causative agents in the current study population.

### Rocuronium

Rocuronium rapidly reached an NMBA market share of approximately 50% within a few years after it was introduced in Norway. It soon challenged suxamethonium as the NMBA most frequently related to anaphylactic reactions (fig. 1). Twenty-nine cases of anaphylaxis were reported to the Norwegian Medicines Agency after approximately 150,000 patients had been exposed to rocuronium between October 1997 and April 30, 2000. The Agency therefore issued a letter to Norwegian anesthesiologists advising the use of rocuronium on special indication only. In contrast, Sweden and Denmark together reported 3 cases after approximately 430,000 patient exposures.<sup>24</sup> The large difference in reporting frequency has not been explained, but several factors may contribute to bias. Increased awareness and reporting of untoward effects may follow when new drugs are introduced to the market. Estimating the incidence of adverse reactions when the numbers of exposed patients are derived from sales data and the number of reactors is generated by spontaneous reporting may further favor bias.<sup>25</sup> Even if the number of registered ana-



**Fig. 1.** (A) Frequency of neuromuscular blocking agent (NMBA) allergy in 83 cases of anaphylaxis during anesthesia, examined at Haukeland University Hospital, 1996–2001. (B) NMBA market shares in Norway, 1996–2001, number of vials. Data provided by Norwegian Institute of Public Health.

phylactic reactions were correct, the statistical power would be low.<sup>1,24</sup> In addition, the diagnostic tools have their limitations as discussed above. Estimates of the national incidence of rocuronium-related anaphylaxis cannot be obtained from our data, and we cannot add substance to the debate on whether the reaction frequency reflects the market share of the drug relative to other NMBAs. Reporting bias might contribute to the different frequencies of reactions to rocuronium and other NMBAs in Scandinavia. However, the allergenic properties of the NMBAs have been related to the quaternary ammonium ion, which is also found in numeral drugs and other environmental chemical compounds.<sup>26</sup> There may be differences in sensitization based on differences in environmental exposure. In Norway and Sweden, different degrees of immunologic sensitization toward quaternary ammonium ion-containing drugs have recently been documented.<sup>27</sup>

In conclusion, this 6-yr single-center follow-up study demonstrates that NMBAs, foremost suxamethonium, are the most important inducers of IgE-mediated anaphylaxis during anesthesia in Norway. The study design only allows estimating the frequency of reactions for the Haukeland University Hospital to be one IgE-mediated anaphylaxis in 5,200 general anesthetics in which NMBAs were administered. Better knowledge on the epidemiology of perianesthetic anaphylaxis would demand more complete data from larger and well-defined populations. Constituting a national or even a Nordic network with standardized and well-founded procedures for reporting and allergy evaluations would be one essential step in this direction.

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## Appendix: Causality Assessment of Suspected IgE-Mediated Allergic Reactions Related to Anesthesia

### *Certain Causality*

- A clinical event with a typical picture of an immediate type allergic reaction (and/or with transiently increased serum tryptase) that occurs at a plausible time relation to an administered substance
- The event cannot be explained by concurrent disease
- The same reaction occurs on (accidental) rechallenge
- Specific IgE toward the substance is detected

### *Probable Causality*

- A clinical event with a typical picture of an immediate-type allergic reaction (and/or with transiently increased serum tryptase) that occurs at a plausible time relation to an administered substance
- The clinical event is unlikely to be attributed to concurrent disease
- Rechallenge is not performed
- Specific IgE toward the substance is detected

### *Possible Causality*

- A clinical event with a picture that could be explained by an immediate-type allergic reaction (and/or with transiently increased serum tryptase) that occurs with a reasonable time relation to an administered substance
- The event could also be explained by concurrent disease or other drugs or chemicals
- Rechallenge is not performed
- Specific IgE toward the substance is detected by an analysis with an uncertain or low specificity

### *Unlikely Causality*

- A clinical event with or without transiently increased serum tryptase but with a temporal relation to administration of the drug, which makes a causal relation improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations, *or*
- A clinical event with or without transiently increased serum tryptase that occurs at a plausible time relation to an administered substance but where a complete IgE allergy assessment is negative (the event can still be a non-IgE-mediated reaction)

### *Unclassified Causality*

- A clinical event with or without transiently increased serum tryptase reported as an immediate-type reaction, about which more data are essential for a proper assessment

### *Unclassifiable Causality*

- A report suggesting an immediate-type reaction that cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified