

Original article

Anaphylaxis during anesthesia: results of a 12-year survey at a French pediatric center

Background: Following adverse reactions to anesthesia, tests are carried out to determine the mechanism of the reaction and to identify the agent responsible. No specific data are available in France concerning such skin tests in children.

Methods: Between 1989 and 2001, we assessed hypersensitivity reactions to general anesthesia in 68 children. Thirty underwent more than one operation, for congenital malformations. Immunoglobulin (Ig)E-mediated anaphylaxis was diagnosed on skin tests combined with the clinical history.

Results: Grade I, II and III reactions were observed in 20, 27 and 21 children, respectively. IgE-mediated anaphylaxis was diagnosed in 51 children: 31 (60.8%) for neuromuscular blocking agents (NMBA), 14 (27%) for latex, seven (14%) for colloids, five (9%) for opioids and six (12%) for hypnotics. Vecuronium was the NMBA causing the largest number of reactions. Cross reactivity to NMBA available in France was observed in 23 of 30 children (76%), particularly for vecuronium and atracurium or pancuronium. The estimated frequency of IgE mediated anaphylactic reactions was one in 2100 operations. Based on our results, 25 children subsequently received a different anesthetic with no adverse reaction.

Conclusions: As in adults, NMBA, then latex were responsible for most anaphylactic reactions during anesthesia. Our results confirm that skin tests with anesthetic agents are feasible and safe in children and improve the safety of subsequent anesthetic procedures.

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Key words: anaphylaxis; anesthesia; children; skin testing.

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Accepted for publication 7 August 2004

The development of surgical and medical techniques has increased the frequency of general anesthesia for therapeutic and diagnostic purposes. In France, the rate of anesthetic procedures increased from 6.6 to 13.5 per 100 inhabitants between 1980 and 1996 (1). These trends are particularly clear in children: the annual rate of anesthetic procedures increased by 92% between 1980 and 1996 in children under the age of 5 years (1).

The adverse clinical reactions that occur during general anesthesia are collectively known as reactions of hypersensitivity (2, 3). The estimated incidence of these reactions during anesthesia is 1/1250 in Australia and 1/3500 in France and Great Britain (4). In France, the estimated incidence of immunoglobulin (Ig)E-mediated anaphylactic reactions is 1/13 000 anesthetic procedures (5). No data specific to children are available.

In France, on the French Society of Anesthesia and Reanimation's instigation (FSAR), patients that display hypersensitivity reactions to anesthesia are subjected to well developed procedures (6), and performed allergenic tests to determine whether these reactions are IgE-mediated anaphylaxis and to determine which drug or

agent was responsible so that it is not used during subsequent operations in the same patient.

The aims of this work were: to estimate the frequency of IgE-mediated anaphylactic reactions in a French pediatric population over a 12-year period; to determine which drugs are involved and to precise the value of skin testing in the management of subsequent anesthetic procedures.

Material and methods

Population

Between 1989 and 2001, 68 children (42 boys and 26 girls) were referred to the Pediatric Pneumology and Allergology Department of Necker-Enfants Malades Hospital (Paris, France) following the occurrence of anaphylaxis during general anesthesia: 35 of these children were referred by pediatric surgical departments at Necker Hospital and 33 were referred by other hospitals.

The severity of the hypersensitivity reactions was classified according to the Ring and Messmer scale: grade I: generalized cutaneous and mucosal signs; grade II: moderate multi-system

organ involvement, with cutaneous and mucosal signs, unusual hypotension and tachycardia, bronchial hyperreactivity; grade III: life-threatening multi-system organ failure requiring specific treatment, cutaneous signs may be absent; grade IV: circulatory and/or respiratory failure.

Skin tests

Skin tests were performed according to standardized procedures (6–8). Prick tests were performed on the anterior part of the forearm with each suspected undiluted anesthetic drug (8). Prick tests with latex were performed using two different standardized commercial fresh natural rubber latex extracts (Allerbio and Stallergenes, France).

If prick tests were negative, intradermal tests were carried out either on the forearm or on the top of the shoulder. This involved the injection of 0.04 ml of a solution of the drug in saline. Injections were performed every 20 min, according to a dilution scale (10^{-4} , 10^{-3} , 10^{-2} and 10^{-1}) beginning with the 10^{-4} dilution. For atracurium and mivacurium, a maximal dilution of 10^{-3} was used. For suxamethonium, rocuronium and cis-atracurium, the last dilution used was 10^{-2} . The intradermal test was considered positive if the mean diameter of the wheal obtained was at least 8 mm, and double that of the injection wheal. We stopped the intradermal tests when a positive result was obtained for one of the lower dilutions (6).

To determine whether cross-sensitization to members of the neuromuscular blocking agents (NMBA) family occurred, all the NMBA used in pediatric anesthesia at the time of the study were tested.

Diagnostic tests

Specific IgE for the quaternary ammonium ion of NMBA were sought using a radioimmunoassay based on p-aminophenyl phosphoryl-choline bound to agarose (PAPPC-RIA, positive threshold 1%) (9). No inhibition test has been done to detect the specificity of the antibodies detected by the PAPPC-RIA.

Latex-specific IgE were detected by radioallergosorbent test (Pharmacia CAP system, Pharmacia, France); values of above 0.35 KU/l were considered positive.

Protocol

Each child referred to our department was examined by both an allergist and an anesthetist. The patient's anesthesia records or a letter from the department in which the patient had been anesthetized was requested.

In all cases, all safety precautions necessary were taken when carrying out tests and a venous line was inserted before the test began. All drugs that could potentially modify skin reactions were discontinued at least 2 weeks before the tests.

The dilutions required for the skin tests were prepared immediately before use, on the morning of the test, once the child had arrived. The various anesthetics used for premed (when known) and the general anesthetics were successively tested by prick tests and then intradermal injections, as described above. Prick tests with latex were also carried out. Specific IgE were then determined.

At the end of the allergy work-up, IgE-mediated anaphylaxis was diagnosed on the basis of the skin test results concordant with the patient's clinical history of adverse reactions and the anesthetic protocol, and on the literature recommendations (6). In the absence of a positive skin test, a non-IgE-mediated reaction was diagnosed (6). Specific IgE tests were not systematically available.

Statistics

Results are presented as mean $\pm$ SD. The Chi² test was used to compare: (i) the distributions of the various anesthetic drugs as a function of age (Fig. 2) and severity of the adverse reaction (Fig. 1), (ii) the distributions of atopy and drug hypersensitivity in children who presented IgE-mediated anaphylaxis and those who presented non-IgE-mediated reactions.

Statistical tests were carried out with STATVIEW 4.0 (Abacus Concepts, Berkeley, CA). *P*-values below 0.05 were considered significant.

Results

The products used in the 68 general anesthetic procedures and details concerning all the tests carried out are summarized in Table 1. Antibiotics were used in 12 cases; if suspected to be the cause of the reaction, either oral antibiotics were reintroduced after skin tests negative, but no allergic reactions were detected (10), either the drug have been used again by the children between the accident and the skin tests, or the antibiotic used before or during the anesthesia have been kept after the accident. NMBA were used as muscle relaxants 52 times, in 49 children. Three children received two members of the NMBA family each. Latex was used 60 times; in the other eight cases, latex was not used because the child was already known to be sensitive to latex. IgE-mediated anaphylaxis was diagnosed in 51 cases (75%), in 31 boys and 20 girls. Expressed as their respective populations, we observed

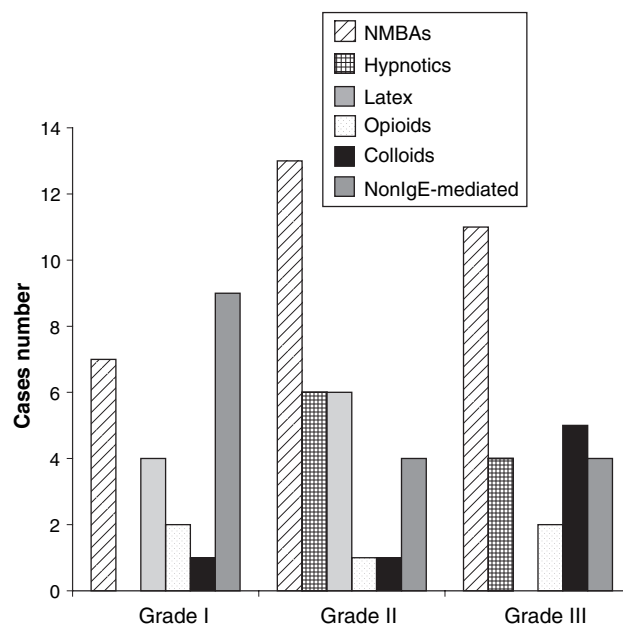


Figure 1. Frequency of non-IgE-mediated reactions and frequency of various anesthetic agents with positive skin tests according to the severity of the hypersensitivity reaction during anesthesia (*n* = number of cases).

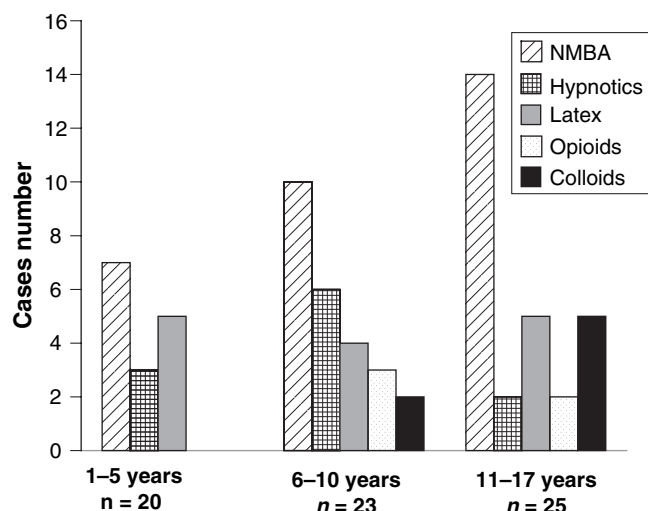


Figure 2. Number of positive skin tests according to age (n = number of children).

Table 1. Results of skin tests for the drugs used during anesthesia

Drugs used during anesthesia (n)	Positive skin tests (n)	Double sensitization
NMBA 52 (n = 49)	31/49 (63%)	
Pancuronium (5)	2	
Vecuronium (31)	24	9 (3 Latex/4 colloids/2 opioids)
Atracurium (8)	3	1 (Midazolam)
Mivacurium (3)	2	
Cis-atracurium (2)	0	
Suxamethonium (3)	0	
Latex (n = 60)	14 (23%)	5 (3 Vecuronium/1 colloid/1 propofol)
Hypnotics (n = 67)	6/67 (9%)	
Propofol (38)	2	1 (latex)
Thiopentone (14)	1	1 (Vecuronium)
Ketamine (3)	1	
Midazolam (8)	2	1 (Atracurium)
Dipotassium clorazepate (4)	0	
Opioids (n = 50)	5/50 (10%)	
Afentanyl (23)	2	1 (Vecuronium)
Sufenta (10)	2	1 (Vecuronium + colloid)*
Fentanyl (17)	1	
Colloids (n = 10)	7/10 (70%)	
Gelatin (4)	3	3 (2 Vecuronium/1 latex)
Hetastarch (6)	4	2 (Vecuronium)

NMBA, neuromuscular blocking agents.

*Triple sensitization.

IgE-mediated anapylaxis in 31 of 42 (73.8%) boys and 20 of 26 (76.9%) girls.

Incidence of anaphylactic reactions

Thirty-five of the 68 children studied were referred by the pediatric surgery departments of Necker-Enfants

Malades Hospital. During the 12-year study period, these departments carried out about 64 800 general anesthesia procedures. The anesthetic was shown to be responsible for the IgE-mediated anaphylactic reaction in 25 of the 35 cases, corresponding to an estimated frequency of one in 2100 anesthetic procedures.

Population

The mean age of the 68 children was 8 years and 10 months $\pm$ 4 years and 2 months (range = 14 months to 17 years). The mean age of the boys was 7 years and 8 months and that of the girls was 10 years and 2 months ($P = 0.01$).

Clinical features

Thirty-eight of the children had undergone only one intervention (in most cases abdominal surgery, fracture reduction or tonsillectomy) and 30 had already undergone several interventions (2 to 31). A 9-year-old child with an imperforate anus and only one kidney had undergone 31 operations.

Thirty-one of the children (46%) had a history of atopic manifestations (asthma, atopic dermatitis, rhinitis, food allergies). Nine other children (13%) presented hypersensitivity to a single drug (antibiotics, aspirin). Of the 51 patients presenting an IgE-mediated anaphylactic reaction, 23 were atopic (45%), seven presented hypersensitivity to a drug (13.7%) and 21 were not atopic (41%). Nine of the 17 patients in whom the adverse reaction was not IgE-mediated were atopic (53%), one have an hypersensitivity to a drug (5%) and seven were not atopic (41%). The distributions of atopy and drug hypersensitivity were not significantly different in these two groups of patients.

Twenty of the 68 children studied, were referred for grade I reactions, 27 for grade II reactions and 21 for grade III reactions. None of the children had a grade IV reaction. Plasma substitutes were given to 10 children; five of the 10 incidents observed were grade III and four of these five accidents were because of hetastarch. The distribution of the various anesthetic drugs and of the non-IgE-mediated reactions is shown according to the severity of the adverse reaction (Fig. 1). No significant relationship was found between the type of drug, nor the character IgE-mediated or non-IgE-mediated of the reaction and the severity of the reaction.

No significant relationship was found between the occurrence of an anaphylactic reaction during anesthesia and the number of previous anesthetic procedures.

The mean delay between the incident and the allergy tests was 6.2 $\pm$ 6.3 months (range = 6 weeks to 3 years): 6-8 weeks in 20 children, between 2 and 6 months in 25 children, between 7 and 12 months in 15 children, more than 1 year in seven children. This delay could not be determined in one case.

Causal agents

The NMBA were responsible for 60.8% of cases of IgE-mediated anaphylaxis (31 of 51), latex for 27% (14 of 51), colloids for 14% (7 of 51), opioids for 9% (5 of 51) and hypnotic agents for 12% (6 of 51). Adverse reactions to NMBA appeared to become more frequent with age, although no significant association was found (Fig. 2). This trend cannot be explained by the larger number of older children who had undergone multiple interventions. The responsibility of the NMBA was proved in 11 of 26 (42%) girls and 20 of 42 (47%) boys.

The responsibility of an anesthetic drug for the hypersensitivity reaction was based on positive skin tests consistent with the clinical history: for two patients, a prick test was positive (the first with vecuronium, the intradermal test was also positive for the 10^{-1} concentration, the second with a gelatin, intradermal tests were not carried out), and the intradermal tests were positive in the other cases.

Concerning the whole NMBA skin tests, a positive test was obtained for the last dilution authorized, except in seven cases with vecuronium (one prick test, one for the 10^{-3} dilution and five for the 10^{-2} dilution).

In 11 cases, skin tests were positive for two or three agents from different families (Table 1).

Cross-reactivity to muscle relaxants

We tested cross-reactivity to NMBA commercially available in France in 30 of the 31 patients who had presented an IgE anaphylactic reaction to a NMBA. Cross-reactivity was observed in 23 of 30 cases (76%; Fig. 3). The highest rates of cross-reactivity were observed between vecuronium and atracurium, and between vecuronium and pancuronium.

In the 18 patients with negative skin tests to a NMBA, we carried out skin tests for all available NMBA to check for cross-sensitization. In six cases, we observed positive skin tests for a NMBA that had not been used for the

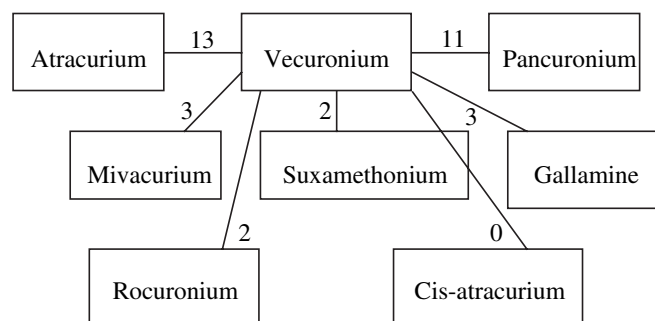


Figure 3. Cross-sensitization between neuromuscular blocking agents (30 children) (the numbers indicate the number of cross reactions observed).

general anesthetic (these six cases are not included in Fig. 3).

Diagnostic tests

We sought specific IgE for quaternary ammonium groups in 20 children (Table 2); the skin tests and the IgE tests gave concordant results in 50% of cases. With one exception, latex-specific IgE were found when sought, consistent with the results obtained in the skin test for latex.

Fate of the children studied

Thirty-five of the 68 children in this study were referred by one of the pediatric surgery departments of our hospital. Twenty of these 35 children underwent surgery again, once or twice, within a few months of the allergy tests. No incidents or accidents occurred during these operations, which took into account the results of the allergy tests. All positive skin tests were taken into account, even if the corresponding specific IgE were negative. The child with negative skin tests who tested positive for NMBA-specific IgE did not undergo surgery again: however, this profile would have led us to recommend that NMBA were not used.

Five of the children that came from other hospitals also underwent surgery again, with no adverse reaction; 11 did not undergo surgery again and 17 were lost to follow-up.

Discussion

The main findings of this 12-year study were: (i) the estimated frequency of IgE-mediated anaphylactic incidents during general anesthesia is high (one of 2100 anesthetic procedures); (ii) NMBA and latex were responsible for most of these incidents; (iii) allergy tests with anesthetic agents are feasible and safe in children and improve the safety of subsequent anesthetic procedures.

The decision to carry out allergy tests is justified whenever an hypersensitivity reaction occurs during general anesthesia, to avoid similar problems during subsequent operations. This is especially important for children with malformations that often require one or several successive interventions.

The incidence of proven allergic reactions in France was one in 13 000 anesthetic procedures in 1996 (5). The

Table 2. Results of diagnostic tests and skin tests for NMBA (n = number of children)

	Positive specific IgE	Negative specific IgE
Positive skin test	$n = 3$	$n = 9$
Negative skin test	$n = 1$	$n = 7$

NMBA, neuromuscular blocking agents; IgE, immunoglobulin E.

frequency was considerably higher in our series (one of 2100), probably because of the nature of our study population, which consisted of a large number of children with congenital malformations requiring repeated operations. Because of recruitment bias, the percentage (46%) of atopic children was higher than that reported in other published studies (11, 12) and in the background population (13). Atopy is not considered to be a risk factor for sensitization to anesthetic drugs, particularly NMBA (11) and our results are consistent with this. However, atopy may favor the nonspecific release of histamine during the administration of agents known to trigger the release of histamine (14, 15). This may account for the high percentage (9%) of anaphylactic reactions observed with hypnotics. Despite use of recommended dilutions, it is also possible that some false positive results were obtained. In the general French population, the frequency of anaphylaxis because of hypnotics was 3.7 and 3.4% for 1997–1998 and 1999–2000, respectively (16, 17).

Our percentage (76.9%) of girls presenting an IgE-mediated anaphylaxis is only a little more superior to those of boys (73.8%), different from the sex distribution observed in French adults studies. Moreover, we did not observe differences in sex-distribution for IgE-mediated anaphylaxis because of NMBA; in previous studies, the sex ratio was 2.7–8.1 (17).

The NMBA are the agents most frequently implicated. Our results are similar to those for the French general population, with NMBA identified as the causal agent in 58.4% of cases in 1999–2000 (17). However, despite we followed strictly the recommendations for testing, we could not be absolutely sure we did not observe false positive tests: we did not have a children control group and most of the tests were positive for the last dilution authorized.

Fourteen cases of latex IgE-anaphylaxis were reported during the study period. This frequency (27%) is higher than that reported in a recent study on the French general population (16.1% for 1999–2000) (17). Primary prevention measures are a priority in children with spina bifida or who require numerous operations (18–23). Indeed, the large number of surgical interventions required in spina bifida patients is correlated with sensitization to latex (24, 25). In our study, 30 of 68 children underwent more than one operation. In eight cases, latex was not used because the child was already known to be sensitive to latex. The regular use of skin tests associated or not with specific IgE tests should be encouraged in multi-operated children, to detect a new sensitization to latex rapidly (26).

The skin tests were carried out according to standard procedures (6). The recommended dilutions of atracurium and mivacurium for the prick tests are unclear because these tests for these two NMBA are always negative when the pure extract is used. We therefore did not feel that it was necessary to dilute the general anesthetic for prick tests in children. Intradermal injections

are commonly used in pediatrics for Mantoux test. The reactivity and fineness of the skin did not affect the results; we always carried out a control injection in parallel.

We used physiological serum to dilute drugs instead of the recommended phenol physiological serum (6), so we could not exclude some impact on the results. However, we took care to have the saline solution as negative control.

Use a dilution scale increases the value of intradermal skin testing. In France, this scale is well established by the FSAR recommendations (6). However, Levy et al. (27) suggested that skin testing for hypersensitivity to rocuronium and cis-atracurium should be performed with concentrations $<10^{-4}$ and 10^{-5} respectively to avoid false-positive skin tests. They argued that the high incidence of positive cutaneous responses to rocuronium reported in France occurred in patients who were skin-tested with a 10^{-1} solution, and may represent false positive tests. We did not observe sensitization to cis-atracurium and the rocuronium has not been used in our pediatric population. However, in 24 cases, the NMBA tests were positive to the last authorized dilution and some false positive tests could not be excluded.

Given the incidental nature of allergic reactions during anesthesia, it is possible that a long delay between the incident and the allergy tests could reduce or mask a hidden sensitivity. In the seven children tested more than 1 year after the event, all tests were negative in five cases. Based on the model of skin sensitization to penicillins, it is possible that sensitization is lost without clinical allergy being lost (28). However, with NMBA, specific IgE persist and skin tests are reproducible for up to 30 years after the first accident (29, 30).

In 11 cases, we observed simultaneous sensitization to several anesthetic agents and/or latex. In our study, the timing of the adverse reaction with respect to the clinical chronology of drug injections did not indicate clearly which drug was responsible, and biological tests were rarely available. Conversely, even if anesthetic practices can be useful for diagnostic purposes and if skin sensitization does not necessarily mean clinical allergy, we feel that it is safest to consider that all the anesthetic agents giving positive skin tests should be avoided during subsequent operations.

The skin tests for NMBA and NMBA-specific IgE levels were consistent in only 50% of cases. In their series of 29 patients, Baldo and Fisher (31) obtained concordant results in 62% of cases. During the 12-year period, the immunoassays tests used have been improved and only a few of the drugs used during anesthesia have been explored by immunotests. This is undoubtedly a weak point in our study. In practice, even if NMBA-specific IgE are positive and skin tests negative ($n = 1$ child), we recommend that NMBA are not used again. Regardless of the specific IgE results, NMBA are contraindicated if the skin tests were positive.

Another weakness is the nonmeasure of plasma concentrations of tryptase and histamine; indeed skin testing is much more specific in patients in whom the cause of anaphylaxis has been confirmed by high mast cell tryptase concentrations (32).

When testing cross-sensitization to other NMBA, it is possible to obtain a positive result for a curare that has never been used, but this does not necessarily mean that that NMBA would cause an adverse reaction if used. However, we advise against the use of NMBA that gave positive results, even if the test for the NMBA used in the general anesthetic was negative. Despite the high specificity, positive predictive value and sensitivity of skin tests for NMBA (8), an anesthesia protocol that does not include NMBA is usually recommended. If the use of a NMBA is unavoidable, a less allergenic drug is chosen (e.g. with a rigid chain). Most studies have reported no further incidents during subsequent interventions with a NMBA that gave a negative skin test result (11). Avoiding NMBA is also recommended if the initial incident was severe (33).

Furthermore, the frequency of sensitization to quaternary ammonium ions in the absence of previous anesthesia is unknown in children, but reported as 9.3%

in the adult population, aged 20–40 years; with no risk factor identified (12).

Conclusion

The high frequency of IgE-anaphylactic reactions and the feasibility of skin tests in children justify systematic allergy testing whenever an hypersensitivity reaction occurs during general anesthesia. The information obtained during these tests increases the safety of subsequent anesthetic procedures. The presence of both an anesthetist and an allergist during consultations increases the pertinence of the results.

The use of latex could also be systematically avoided when operating on children requiring multiple interventions.

More frequent use of more reliable biological tests, and the regular monitoring of cohorts of children should increase the accuracy of allergy tests. In the meantime, the young age and the fragility of our patients, poly-operated, incline us to be extremely careful when interpreting allergy test results for children, meaning accepting false positive tests.

References

1. Clergue F, Auroy Y, Péquignot F, Jouglé E, Lienhart A, Laxenaire MC. French survey of anaesthesia in 1996. *Anesthesiology* 1999;**91**:1509–1520.
2. Johansson SGO, Hourihane JO'B, Bousquet J, Brujnzeel-Koomen C, Dreborg S, Haahtela T et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.
3. Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;**113**:832–836.
4. Watkins J. Editorial II: skin testing and the anaesthetist. *Br J Anaesth* 2000;**85**:814–817.
5. Laxenaire MC. Epidémiologie des réactions anaphylactoïdes peranesthésiques. Quatrième enquête multicentrique (juillet 1994–décembre 1996). *Ann Fr Anesth Reanim* 1999;**18**:796–809.
6. Prévention du risque allergique peranesthésique. Recommandations pour la pratique clinique. <http://www.sfar.org>. 2001. *Ann Fr Anesth Reanim* 2001;**20**:56–76.
7. Leynadier F, Sansarrica M, Didier JM, Dry J. Prick tests in the diagnostic of anaphylaxis to general anesthetics. *Br J Anaesth* 1987;**59**:683–689.
8. Watkins J. Investigation of allergic and hypersensitivity reactions to anaesthetic agents. *Br J Anaesth* 1987;**59**:104–111.
9. Guilloux L, Ricard-Blum S, Ville G, Motin J. A new radioimmunoassay using a commercially available solid support of the detection of IgE antibodies against muscle relaxants. *J Allergy Clin Immunol* 1992;**90**:153–159.
10. Ponvert C, Le Clainche L, Blic(de) J, Le Bourgeois M, Scheinmann P, Paupe J. Allergy to beta-lactam antibiotics in children. *Pediatrics* 1999;**104**:e45.
11. Birnbaum J, Porri F, Pradal D, Charpin D, Vervloet D. Allergy during anesthesia. *Clin Exp Allergy* 1994;**24**:916–921.
12. Porri F, Lemiére C, Birnbaum J, Guilloux L, Didelot R, Charpin D et al. Prevalence of muscle relaxant sensitivity in a general population: implications for a preoperative screening. *Clin Exp Allergy* 1999;**29**:72–75.
13. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;**351**:1225–1232.
14. Akagi K, Townley RG. Spontaneous histamine release and histamine content in normal subjects and subjects with asthma. *J Allergy Clin Immunol* 1989;**83**:742–749.
15. Laxenaire MC, Mata E, Guéant JL, Moneret-Vautrin DA, Haberer JP. Basophil histamine release in atopic patients after *in vitro* provocation with thiopental, diprivan and chlormethiazole. *Acta Anaesthesiol Scand* 1991;**35**:706–710.
16. Laxenaire MC, Mertes PM, GERAP. Anaphylaxis during anaesthesia. Results of a two-year survey in France. *Br J Anaesth* 2001;**87**:549–558.
17. Mertes PM, Laxenaire MC, GERAP. Anaphylaxis during anesthesia. Results of a two-year survey in France. *Anesthesiology* 2002;**96**:A1083.
18. 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**:264–269.
19. Holzman RS. Clinical management of latex-allergic children. *Anesth Analg* 1997;**85**:529–533.
20. Mavale-Manuel S, Paty E, Lebourgeois M, Scheinmann P, Blic(de) J. Allergie au latex chez les enfants asthmatiques. *Rev Fr Allergol Immunol Clin* 2003;**43**:159–164.

21. Kurup VP, Fink JN. The spectrum of immunologic sensitization in latex allergy. *Allergy* 2001;**56**:2–12.
22. Cullinan P, Brown R, Field A, Hourihane J, Jones M, Kekwick R et al. Latex allergy. A position paper of the British Society of Allergy and Clinical Immunology. *Clin Exp Allergy* 2003;**33**:1484–1499.
23. Turjanmaa K. Diagnosis of latex allergy. *Allergy* 2001;**56**:810–812.
24. Porri F, Pradal M, Lemiére C, Birnbaum J, Mege JL, Lanteaume A et al. Association between latex and repeated latex exposure in children. *Anesthesiology* 1997;**86**:599–602.
25. Poley GE, Slater JE. Latex allergy. *J Allergy Clin Immunol* 2000;**105**:1054–1062.
26. Grüber C, Buck D, Wahn U, Niggeman B. Is there a role for immunoblots in the diagnosis of latex allergy? Intermethod comparison of *in vitro* and *in vivo* IgE assays in spina bifida patients. *Allergy* 2000;**55**:476–483.
27. 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**:844–849.
28. Blanca M, Torres MJ, Garcia JJ, Romano A, Mayorga C, Ramon(de) E et al. Natural evolution of skin test sensitivity in patients allergic to β -lactam antibiotics. *J Allergy Clin Immunol* 1999;**103**:918–924.
29. Fisher M, Baldo BA. Persistence of antibodies to anaesthetic drugs. *Anaesth Intens Care* 1992;**20**:143–146.
30. Leydanier F, Dry J. Anaphylaxis to muscle-relaxant drugs: study of cross-reactivity by skin tests. *Int Arch Allergy Appl Immunol* 1991;**94**:349–353.
31. Baldo BA, Fisher MM. Diagnosis of IgE-dependent anaphylaxis to neuromuscular blocking drugs, thiopentone and opioids. *Ann Fr Anesth Reanim* 1993;**12**:173–181.
32. Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. *Br J Anaesth* 1998;**80**:26–29.
33. Thacker MA, Davis FM. Subsequent general anaesthesia in patients with a history of previous anaphylactoid/anaphylactic reaction to muscle relaxant. *Anaesth Intensive Care* 1999;**27**:190–193.