

Epidemiology of perioperative anaphylaxis

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■ Key points

Anaphylactic reactions may be either of immune (allergy, usually IgE-mediated, sometimes IgG-mediated) or non-immune origin.

The incidence of anaphylactic reactions during anaesthesia varies between countries ranging from 1/1250 to 1/18,600 per procedure.

In France, the estimated incidence of allergic reactions is 100.6 [76.2–125.3]/million procedure with a high female predominance (male: 55.4 [42.0–69.0], female: 154.9 [117.2–193.1]).

The proportion of IgE-mediated allergic reactions seems to be relatively similar between countries, ranging from 50 to 60%.

Substantial geographical variability regarding the different drugs or substances involved is reported.

Reactions involving neuromuscular blocking agents are a major cause in several countries but are less frequently reported in the United States or Denmark.

Reactions involving antibiotics, dyes or chlorhexidine are reported with a high and sometimes increasing frequency in most series.

Reactions to latex are rapidly decreasing as a result of primary and secondary prevention policy. Regional differences are a strong incentive for repeated epidemiological surveys in different countries.

■ Points essentiels

Les réactions anaphylactiques peuvent être d'origine immunologique (allergique, médiées par les IgE ou les IgG) ou non immunologique.
L'incidence des réactions anaphylactiques au cours de l'anesthésie varie entre 1/1250 et 1/18 600 selon les pays.
En France, l'incidence estimée des réactions allergiques est de 100,6 [76,2-125,3]/millions de procédures avec une nette prédominance féminine (homme : 55,4 [42,0-69,0], femme : 154,9 [117,2-193,1]).
La proportion des réactions IgE-médiées semble être relativement similaire entre les différents pays, allant de 50 à 60 % des réactions.
Une grande variabilité géographique est décrite au regard des substances incriminées.
Les curares sont une cause majeure de réaction allergique mais sont moins fréquemment impliqués aux États-Unis et au Danemark.
Les réactions impliquant les antibiotiques, les colorants ou la chlorhexidine sont décrites avec une fréquence élevée, voir croissante dans la plupart des séries.
Les réactions au latex décroissent rapidement suite aux politiques de prévention primaire et secondaire.
Les différences régionales sont un argument fort pour conduire des études épidémiologiques répétées dans différents pays.

Introduction

Knowledge about the epidemiology of anaphylaxis has substantially improved within the last decades with the collection of data coming from a large number of publications referring to clinical practice, clinical and administrative databases or surveys conducted in specific populations. Although rare, anaphylaxis appears to be more frequent than initially assumed, and variation in incidence seems related to age [1], causes and geographical area [2]. Many studies suggest a rise in the incidence of anaphylaxis [2-5]. However, this increase remains controversial and could result from better identification and reporting of anaphylactic reactions [2,5].

Although data on the incidence of drug-induced anaphylaxis are relatively limited, these reactions are a recognized cause of morbidity and death in anaesthetic practice [6]. This review will briefly summarize the main information available in the literature on the epidemiology of perioperative anaphylaxis with specific considerations regarding differences between geographical areas.

Definition

The surveillance of perioperative anaphylaxis represents a statistical challenge, because these reactions are rare, random, and mostly independent from the successive exposure of patients to a low risk intervention [7]. Another weakness of any review of epidemiologic studies is the lack of consensus definition, the

heterogeneous use of terms in the literature, the comprehensiveness of the evaluation, the type of medications/disinfectants used by region and the absence of clear insight into underlying pathophysiologic mechanisms. Severe immediate perioperative hypersensitivity reactions frequently result from the presence of allergen specific IgE (or IgG) antibodies, but reactions may also be related to other mechanisms including complement activation, direct histamine release or direct activation of the recently identified mast-cell specific MRGPRX2 receptor [8].

Incidence

For this review, a literature search was performed in the NCBI PubMed database with MeSH terms relevant to different epidemiologic aspects of perioperative anaphylaxis including triggers, geographical differences and trends. Retrieved results were then reviewed to summarize the current knowledge of anaphylaxis epidemiology (table 1).

Since the pioneering work conducted in Australia [9], the United Kingdom [10] and France [11], several series from different countries have estimated the incidence of clinical anaphylaxis during anaesthesia to be in the range of 1 in 1250 to 10,000 anaesthetics [12].

Between 2009 and 2011, the Japanese Society of Anaesthesiologists (JSA) conducted a survey on intraoperative complications and reported a total of 237 cases of anaphylaxis during

TABLE I
Epidemiologic studies of perioperative anaphylaxis

Selected studies	Location	Time period	Patients (n)	IgE-mediated (%)	Causal agents	Estimated incidence All mechanisms	Estimated incidence IgE-mediated	Mortality (%)
Savic, Kaura et al., 2015 [86]	UK	2015 (2 weeks)	13	–	All cause	1:353–1:2297	–	
Reddy, Cooke et al., 2015 [17]	New Zealand	2006–2012	21	+	NMBAs		Atracurium 1:22,451 Succinylcholine: 1:2,080 rocuronium: 1:2,499	
Mirone, Preziosi et al., 2015 [18]	Italy	2010–2014	193	28.5	All cause	–	–	
Cho, Ju et al., 2015 [87]	South Korea	2005–2014	19		NMBAs	–	2.6: 100,000	
Guyer, Saff et al., 2015 [36]	USA	2003–2012	73	18	All cause	–	–	
Gonzales-Estrada, Pien et al., 2015 [37]	USA	2002–2013	30	57	All cause	–	–	
Reitter, Petitpain et al., 2014 [26]	France	2000–2011	2022	–	NMBAs	–	–	4.1
Opstrup, Malling et al., 2014 [88]	Denmark	2004–2012	22	+	Chlorhexidine	–	–	
Krishna, York et al., 2014 [62]	UK	2005–2012	161	64	All cause	–	–	–
Antunes, Kochuyt et al., 2014 [19]	Belgium	2007–2011	119	63.9	All cause	–	–	
Gibbs, Sadleir et al., 2013 [29]	Australia	2000–2009	264	–	All cause	1:11,000		0–1.4
Dong, Mertes et al., 2012 [15]	France	2005–2007	1253	63	All cause	–	–	–
Gurrieri, Weingarten et al., 2011 [22]	USA	1992–2010	38	47.4	All cause	–	–	–
Mertes, Alla et al., 2011 [1]	France	1997–2004	2516	72.18	All cause	–	1:1280	–
Mertes, Malinovsky et al., 2008 [71]	France	2004–2006	16	–	Dyes	–	–	–
Lobera, Audicana et al., 2008 [21]	Spain	1998–2002	48	56	All cause	–	–	–
Chong, Caballero et al., 2008 [89]	UK	2005–2006	23	–	All cause	–	–	–
Light, Lovell et al., 2006 [30]	UK	1967–2000	998	49	NMBAs	–	–	9
Harboe, Guttormsen et al., 2005 [16]	Norway	1996–2001	83	71.1	All cause	–	–	–
Charuluxananan, Punjasawadwong et al., 2005 [90]	Thailand	2004	–	–	All cause	2.1:10,000		
Mertes, Laxenaire et al., 2004 [91]	France	2001–2002	712	69	All cause			
Mertes, Laxenaire et al., 2003 [44]	France	1999–2000	789	66	All cause	–	–	–
Escolano, Valero et al., 2002 [92]	Spain	1996–1997	32	62.5	All cause	1:10,263		
Laxenaire, Mertes et al., 2001 [93]	France	1997–1998	467	–	All cause			
Garvey, Roed-Petersen et al., 2001 [23]	Denmark	1998–2001	68	–	All cause	–	–	–
Dietrich, Spath et al., 2001 [75]	Germany	1995–1996	3	+	Aprotinin	–	–	–
Laxenaire, 1999 [94]	France	1995–1996	1648	42	All cause	–	1:13,000	–
Thacker and Davis, 1999 [95]	New Zealand	1976–1995	151	–	All cause	–	–	–
Dietrich, Spath et al., 1997 [96]	Germany	1988–1995	7	+	Aprotinin	–	–	–
Dormans, Templeton et al., 1997 [97]	USA	1989–1997	24	–	Latex	–	1:2,900	–

TABLE I (Continued).

Selected studies	Location	Time period	Patients (n)	IgE-mediated (%)	Causal agents	Estimated incidence All mechanisms	Estimated incidence IgE-mediated	Mortality (%)
Tan, Lear et al., 1997 [98]	UK	1974–1994	37	–	Latex	–	–	–
Laxenaire, 1996 [99]	France	1992–1994	1750	57.8	All cause	–	–	–
Kwittken, Sweinberg et al., 1995 [100]	USA	1990–1991	14	–	Latex	–	–	–
Laxenaire, Charpentier et al., 1994 [72]	France	1991–1992	43	+	Colloids	–	0.219%	–
Pepys, Pepys et al., 1994 [101]	UK	1992	51	78	All cause	–	–	–
Pecquet and Leynadier, 1993 [102]	France	1987–1992	48	–	Latex	–	–	–
Clarke and Watkins, 1993 [103]	UK	1988–1992	521	–	–	–	–	–
Laxenaire, 1993 [104]	France	1990–1991	1585	52	All cause	–	–	–
Currie, Webb et al., 1993 [105]	Australia	1987–1991	57	–	All cause	–	–	–
Mitsuhata, Matsumoto et al., 1992 [106]	Japan	1952–1990	105	–	All cause	–	–	4.67
Mitsuhata, Hasegawa et al., 1992 [27]	Japan	–	28	–	All cause	1:10,000	–	4.76
Binkley, Cheema et al., 1992 [107]	Canada	–	28	61	All cause	–	–	–
Laxenaire, Moneret-Vautrin et al., 1990 [59]	France	1985–1989	1240	66	All cause	1:3500–1:6000	–	–
Moscicki, Sockin et al., 1990 [50]	USA	1980–1988	27	48	All cause	–	–	–
Assem, 1990 [108]	UK	1972–1990	105	–	All cause	–	–	–
Watkins, 1989 [109]	UK	1985–1987	241	–	All cause	–	–	–
Watkins, 1985 [110]	UK	1986–1984	106	–	All cause	1:5,000–1:10,000	–	–
Galletly and Treuren, 1985 [111]	New Zealand	1978–1985	61	84	All cause	1:1,250	–	–
Leynadier, Luce et al., 1984 [112]	France	–	55	–	All cause	–	–	–
Youngman, Taylor et al., 1983 [113]	New Zealand	1977–1983	158	–	NMBAs	–	1:5,000	–
Vervloet, Nizankowska et al., 1983 [114]	France	1976–1983	41	–	NMBAs	–	–	–
Laxenaire, Moneret-Vautrin et al., 1982 [115]	France	1975–1981	100	42	All cause	–	–	–
Sage, 1981 [116]	New Zealand	1977–1980	63	68	All cause	–	–	–
Fisher and More, 1981 [117]	Australia	1972–1980	116	82	All cause	–	1/5,000–1: 13,000	–
Clarke, Dundee et al., 1975 [118]	UK	1965–1974	100	–	All cause	–	–	–

anaesthesia. The incidence of anaphylaxis based on this survey was approximately 1/18,600. This incidence included 13 cases of cardiac arrest and one fatal case. Anaphylaxis was the most common cause of complications during anaesthesia that was independent of surgery, aesthetic management, and pre-existing comorbidities [13].

Recently, a combined analysis of 3 different French databases, using a capture-recapture method has allowed a nationally based estimation of the incidence of immediate IgE-mediated allergic reactions occurring during anaesthesia, according to sex, age, and causal substance. This report has confirmed the general view that immediate-type hypersensitivity reactions are largely

underreported, the incidence of allergic reactions being estimated at 100.6 [76.2–125.3] per million procedures [14].

The proportion of test positive and presumed IgE-mediated allergic reactions seems to be relatively similar between countries, ranging from 50 to 60% (table I).

However, substantial geographical variability regarding the different drugs or substances involved is reported. There are a large number of variables that can have an impact on the most common causes of intraoperative anaphylaxis from country to country. These variables include the ability to identify intraoperative anaphylaxis and initiate referral, the severity of the reactions that are included (or not included in the study), the type of neuromuscular blockers that are used by region, the comprehensiveness of the evaluation (i.e. inclusion of chlorhexidine, all meds given, etc.), possible sensitizing substances in a region and availability of in vitro testing to medications used and/or variance in the concentrations used for skin prick and intradermal testing.

Allergic reactions involving antibiotics or dyes are reported with a high and sometimes increasing frequency in most series, whereas the epidemic of allergic reactions to latex seems now largely under control [12]. On the contrary, reactions involving neuromuscular blocking agents (NMBAs) remain a major cause in several countries [15–21] but are less frequently reported in the United States or Denmark [22,23]. Reactions involving chlorhexidine seem to be frequent in Denmark [24] and UK [25], but are relatively uncommon in France [15]. Finally, reactions involving local anaesthetics appear very uncommon in series from all countries [12].

Mortality

Although these reactions occur in a monitored setting, an unfavourable outcome may occur even when they are rapidly recognized and appropriately treated [26]. A perioperative mortality rate ranging from 4 to 4.76% has been recorded for all causative drugs in the United States and Japan, respectively [27,28]. This is in sharp contrast with the low rate of 0 to 1.4% recently reported for Western Australia (2000–2009) [29]. Mortality due to reactions involving NMBAs has been estimated at 9% in the United Kingdom [30], and 4.1% in France [26].

Causal agents

Neuromuscular blocking agents

Non-specific direct histamine release was long thought to account for anaphylactic reactions to neuromuscular blocking agents, given their simple molecular structure [31]. The possibility of an allergic reaction to succinylcholine was first demonstrated in 1967 using a Prausnitz-Küsner test [32], whereas the existence of specific IgE recognizing substituted ammonium ions was demonstrated by Baldo and Fisher using a radio-immunological technique based on a sepharose-alcuronium complex [9].

In most reports, a large proportion of reactions are skin test or IgE positive, suggesting an IgE-mediated mechanism. Nevertheless, direct nonspecific mast cell and basophil activation leading to histamine release has been reported with the use of d-tubocurarine, atracurium and mivacurium [33,34]. Significant differences are observed concerning the frequency of IgE-mediated reactions between countries. The incidence of IgE-mediated reactions has been estimated at 184.0/million (139.3–229.7) anaesthetics, reaching 250.9/million (189.8–312.9) for women in France [1]. Reactions have also been reported with a high frequency in Australia and New Zealand, the United Kingdom, Norway, Belgium and Spain (table I). They seem to be less frequent in Sweden [35], Denmark [23], and the United States [22,36,37].

Structure-activity studies have established that the IgE recognition site of NMBAs involved the substituted ammonium ions and its molecular environment [9,38,39]. This explains the frequent cross-reactivity between the different NMBAs observed in 60 to 70% of patients allergic to NMBAs observed in skin testing, as well as its variability between patients [40]. Cross-reactivity to all NMBAs is unusual, but seems to be more frequent with aminosteroid NMBAs than with benzyloquinoline-derived NMBAs [41].

Differences have been reported regarding the relative risk of allergic reactions with the various NMBAs available [42]. Several studies report succinylcholine and rocuronium at higher risk of anaphylaxis, whereas pancuronium and cis-atracurium are reported to be the NMBAs associated with the lowest incidence of anaphylaxis [17,20,43–45].

Allergic reactions to NMBAs may occur at first exposure suggesting that there must be environmental factors that play a role in cross-sensitizing patients against NMBAs. A possible sensitisation resulting from exposure to compounds containing tertiary and/or quaternary ammonium groups such as cosmetics or disinfectants has been hypothesized. This hypothesis is supported by a recent study conducted in hairdressers demonstrating a significant increase in IgE-sensitization to NMBAs and quaternary ammonium ion compounds [46], although the clinical significance of this increase remains to be demonstrated. Another attractive hypothesis arises from the work published by Florvaag et al. who provided repeated evidence for a connection between the consumption of pholcodine (PHO), an opioid antitussive and IgE-mediated anaphylactic reactions to neuromuscular blocking agents [47]. Their observations have led to the withdrawal of pholcodine from the Norwegian market which resulted in a decrease in IgEs to quaternary ammonium ions in the population and in the number of reports of allergic reactions to NMBAs [48]. A prospective 3 years-case control study (the ALPHO study) designed to confirm this possible link between pholcodine exposure and sensitization to NMBAs in France has been initiated in 2014.

Hypnotics

Reactions were quite frequent with barbiturates mainly because of their ability to elicit direct leukocyte histamine release, but true IgE-mediated anaphylactic reactions confirmed by skin tests and specific IgE assay have also been described [49,50]. Reactions are now rarely seen as a result of their decreased use [15]. Reactions were also quite frequent with hypnotics using Cremophor EL as solubilizer [51]. The use of propofol formulated in 10% soybean oil emulsion significantly reduced the rate of hypersensitivity reactions [1,15,52]. It has been suggested that propofol should be omitted in patients with allergy to eggs or soy, because of the presence of lecithins in the propofol vehicle, but this has not been confirmed in daily practice [53,54] and is not recommended in current guidelines [55].

Reactions to midazolam, etomidate or ketamine appear to be really rare [15,40], and there are no documented cases of inhalational agents causing anaphylaxis.

Opioids

IgE-mediated anaphylaxis to opioids is rare, accounting for only 1.6% of the reactions in the last large published survey in France [15]. Most immediate hypersensitivity reactions to morphine, codeine phosphate, or pethidine results from direct nonspecific skin mast cell activation. There is no evidence of cross-reactivity between the different opioid subclasses phenanthrenes (e.g., morphine, codeine), phenylpiperidines (alfentanil, fentanyl, remifentanyl, sufentanyl, and meperidine) and diphenylheptanes (methadone and propoxyphene) [56], but cross-reactivity between morphine and codeine is frequent [12,55,57].

Local anaesthetics

IgE-mediated immediate hypersensitivity reactions to local anaesthetics are extremely rare in view of their use [6,12,15,58]. Reactions to benzoic acid esters are thought to be secondary to their metabolism via plasma esterases to para-aminobenzoic acid, thus intra-class cross-reactivity may occur. The amide local anaesthetics (lidocaine bupivacaine, mepivacaine, ropivacaine) are usually used during anaesthesia, which are considered less sensitizing.

In most cases, suspected hypersensitivity reactions result from non-allergic causes including vasovagal syncope, relative overdosage due to accidental intravascular administration, symptoms from vasopressor or toxic levels due to slow metabolism and intolerance.

In case of positive skin testing to local anaesthetics, possible reactions induced by the presence of methylparaben, paraben, or metabisulfite used as preservatives must also be considered [12,55].

Antibiotics

Antibiotics represent an increasing cause of allergic reactions in the perioperative period. They account for between 40 to 50% of

the reactions reported in the United States or Spain [21,22,37]. A rapid increase from 2% in the late eighties to around 20% of the reactions now is also reported in France where antibiotics represent the second most common cause of IgE-mediated reactions (unpublished data) [59]. Penicillins and cephalosporins account for the majority of antibiotics related anaphylactic reactions during anaesthesia, and the specific drugs incriminated depend on local preferences in different countries [60]. Vancomycin and quinolones have also been incriminated in some cases, but the allergic nature of these reactions is difficult to establish in view of their direct histamine releasing properties and the limitation of skin tests with these drugs.

Latex

Latex was previously one of the leading causes of anaphylaxis during anaesthesia. In the 1980s, the HIV epidemic, led to a sudden high demand for natural rubber latex products. This resulted in the release of higher protein containing latex products on the market and was associated with a sharp increase in the number of allergic reactions to latex. Several at-risk groups including children undergoing numerous procedures, particularly those with spina bifida, adults requiring multiple procedures and health care workers have been identified [55]. Many efforts have been made in the last ten years to reduce both latex exposure and sensitization by decreasing the protein content and stopping the use of powdered gloves. This has resulted in a marked decrease of the number of reactions to latex in several countries and now latex is now only the fourth cause of reaction in the last survey conducted in France (unpublished data) [61,62].

Non-steroidal anti-inflammatory agents

Non-steroidal anti-inflammatory agents (NSAIDs) are increasingly used in post-surgical and post-procedural settings. Most reactions are non-IgE mediated resulting from Cox 1 inhibition [55]. IgE-mediated anaphylaxis, although less frequent, may occur. In this situation, the patient only reacts to one NSAID.

Chlorhexidine

Chlorhexidine is a skin antiseptic and disinfectant widely used in medical, procedural and surgical settings. The allergic risk associated with its use in the perioperative period has long been recognized [24,63–66]. Anaphylaxis has been reported via topical skin application, ophthalmic wash solution, chlorhexidine bath, coated central venous catheter and urethral gels [12]. Sensitization to chlorhexidine can occur from home products such as mouthwash, toothpaste, dressings, ointments and over the counter disinfectant solutions [67]. Significant geographical differences are reported concerning the incidence of chlorhexidine-induced anaphylaxis. Reactions are quite frequent in UK [62] or Denmark [24] but relatively rare in France [46] perhaps because of its limited use in the operating room.

Dyes

Due to their extensive use in sentinel lymph node mapping in cancer surgery, triarylmethane dyes, patent blue V and isosulfan blue, are now considered important allergens in the operating room. The mechanism of these reactions remains unclear; both direct mast cell and/or basophil activation and specific IgE sensitization have been implicated. Methylene blue, a smaller molecule, which differs structurally from the triarylmethane dyes, has been proposed as an alternative for lymph node mapping [68], but has also been associated with reactions [69,70]. Since surgeons will continue to use it for lymph node mapping, anaesthesiologists must be aware of this relatively frequent rate of reactions, which usually occur after a 30 to 50 minutes' delay following injection [71].

Colloids

Anaphylaxis to colloids may be difficult to diagnose since they are usually administered in hypotensive patients. The incidence has been estimated to range from 0.033% to 0.22% [72]. Gelatins and dextrans are more commonly associated with reactions than albumin and hetastarch [12].

Aprotinin

Aprotinin, a serine protease inhibitor with antifibrinolytic activity, was used intravenously or in haemostatic sealants to reduce bleeding during heart, orthopaedic and liver surgery. It was temporarily withdrawn worldwide in 2007 after studies suggested that its use increased the risk of complications or death, but regulators recommended recently that the suspension be lifted [73]. Aprotinin has long been one of the major causes of allergic reactions in cardiovascular surgery [74]. Prevalence of reactions is higher in patients with a history of previous exposure, and therefore, a re-exposure interval less than six months is considered a relative contraindication [75].

Sugammadex

Sugammadex is a synthetic γ -dextrin derivative designed to selectively bind to steroidal neuromuscular blocking agents. Multiple case reports of anaphylaxis to sugammadex have been recently reported [76-78]. Although the mechanism of the reaction is not clearly identified, elevated serum tryptase, positive skin testing and flow cytometry results have been provided to suggest an IgE-mediated mechanism in several cases [79,80].

Several reports have suggested that treatment of rocuronium-induced anaphylaxis should include the administration of sugammadex. Central to this proposal is whether or not encapsulation of rocuronium by sugammadex may prevent further mediator release from mast cells and basophils [81]. Some investigators performed laboratory experiments to answer these questions. CD63 expression, a marker of basophil activation, could not be blocked when sugammadex was added after basophils had already been activated by rocuronium [82]. Studies using a cutaneous model similarly concluded that sugammadex is unlikely to significantly modify the clinical course of an established allergic reaction [83].

In contrast to this evidence from laboratory settings, a review that summarized 11 cases from seven different countries demonstrated recovery from anaphylaxis after sugammadex administration [84]. There are several hypotheses to explain the discrepancy between evidences from clinical and laboratory settings, including that administration of sugammadex and alleviation of symptoms may have coincided with the beneficial effects of the already-instituted therapy with adrenaline injection and fluid resuscitation. A recent report that retrospectively analysed 13 cases of presumed rocuronium-induced anaphylaxis concluded that sugammadex does not modify the clinical course of a suspected hypersensitivity reaction [85]. Moreover, they cautioned against including sugammadex in anaphylaxis-treatment algorithms. Further studies are needed to settle this discussion.

Conclusion

An increasing risk of reactions to antibiotics, a decreasing risk of reactions to latex and continued demonstration of frequent reactions to NMBAs in some, but not all countries, highlight the fact that there are geographical differences and changes over time in the epidemiology of perioperative allergic reactions. New or previously undiscovered allergens such as blue dyes, sugammadex and disinfectants emerge and reactions to these agents must be monitored. These changes and differences are a strong incentive for repeated epidemiological surveys in different countries.

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