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Special Article

Comparative epidemiology of suspected perioperative allergic reactions

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Summary:

Suspected perioperative hypersensitivity reactions (POH) are rare reactions but contribute significantly to the morbidity and mortality of surgery and surgical procedures. Recent publications have highlighted the differences between countries concerning the respective risk of different drugs, but also the changes in patterns of causal agents and the emergence of new allergens. This review will summarize the main recent information available in the literature on the epidemiology of POH, with specific considerations regarding differences between geographic areas for the most frequently involved offending agents.

Key words:
Perioperative anaphylaxis, Epidemiology, Antibiotics, Neuromuscular blocking Agents, Sugammadex, Latex, Chlorhexidine, Blood Products

Key Points:

- Perioperative hypersensitivity reactions may be allergic or non-allergic.
- The incidence of perioperative hypersensitivity reactions (POH) of all severity grades varies between countries and ranges from 1 in 18,600 to 1 in 353 procedures.
- The proportion of presumed POH being IgE-mediated allergic reactions seems to be relatively similar between countries around 50 to 60%.
- Mortality ranges from 1.4 to 4.8% depending on series and countries.
- Substantial geographical variability regarding the causative drugs or substances involved is reported.
- Reactions involving neuromuscular blocking agents (NMBA) are the first or second cause in several countries.
- Reactions involving antibiotics are increasing and represent now the most frequent incriminated drugs in several countries.
- Reactions involving dyes or chlorhexidine are reported with a high and increasing frequency, whereas reactions to natural latex (NRL) are rapidly decreasing in most series
- Regional differences and progressive changes in the various substances incriminated are a strong incentive for repeated epidemiological surveys in different countries
- Building a worldwide network dedicated to the investigation of perioperative hypersensitivity reactions will enable a higher standard of patient care and provide valuable data on geographical differences and new or emerging allergen source

I. Introduction

A perioperative hypersensitivity (POH) reaction is, in most cases, a completely unexpected and unpredictable critical event presenting suddenly without any warning. Reactions may be either of allergic or non-allergic origin **(Ref on nomenclature to be inserted here)**. Severity ranges from mild to severe reactions, and, in extreme cases, may be fatal despite prompt recognition, prolonged adequate resuscitation and treatment. Following the pioneering work conducted in Australia [1], the United Kingdom (UK),[2] and France,[3] our knowledge about the epidemiology of anaphylaxis has substantially improved; data is now available from large numbers of clinical practice publications, clinical databases and allergen surveys from many different countries.[4-15]

Although the surveillance and analysis of rare and random adverse drug reactions represents a statistical challenge, we now have a clear evidence that differences between countries do exist. Several factors may contribute to these differences, such as gene-environment interactions, but also differences in anaesthesiology practice, variability in clinical recognition of potential POH reactions and subsequent referral or variability in the comprehensiveness of the allergy evaluation. We have learned, however, to take advantage of these differences to increase our knowledge about hypersensitivity reactions,[16] either concerning the respective risk of different drugs or the changing patterns of causal agents and the emergence of new allergens. Recent publications have highlighted these changes in the respective risk of antibiotics,[10, 17] neuromuscular blocking agents (NMBA) and sugammadex, [6, 9, 10, 17, 18] natural latex, [17] dyes [10, 17, 19] and chlorhexidine. [10, 20] This review will summarize the most important recent information available in the literature on the epidemiology of POH, with specific consideration to geographical differences for the most frequently involved offending agents.

II. Incidence and mortality (global) – similarities and regional differences (global)

Several series from different countries have estimated the incidence of POH to be in the range of 1 in 18,600 to 1 in 353 anaesthetic procedures with substantial geographical variability.[9, 17, 18, 21-29 15] In the recent 6th National Audit Project (NAP6) of the Royal College of Anaesthetists the incidence of severe life-threatening anaphylaxis, i.e. grade 3 and 4 POH, was estimated at 1 in 10,000 anaesthetic procedures. Because of methodology limitations the true incidence of severe reactions was estimated to be 70% higher. [10]

Anaphylaxis is often thought to be allergic, that is mediated by drug-specific IgE antibodies **(Ref on bja mechanisms to be inserted here)**. However, other immune and non-immune mechanisms such as IgG antibodies, non-specific direct histamine release, contact phase or complement activation and off-target occupation of the mast cell MRGPRX2 (Mas-related G-protein coupled receptor member X2) receptor may be involved,[30, 31] and account for 40% of the cases in some series.[17, 18, 32] Moreover, POH might even occur independently of mast cell and basophil activation, for example by interference with enzymes such as cyclo-oxygenase COX1. The incidence of presumed IgE-mediated reactions during anaesthesia has been estimated to be in the range of 1 in 5,000 to 1 in 13,000.[1, 33] However, data should be

interpreted cautiously, as a positive skin test does not necessarily reflect a genuine IgE-mediated reaction.[34]

The most powerful incidence estimate was reported in France, where a combined analysis of 3 different independent databases, using a capture-recapture method allowed a nationally based estimation of the incidence of immediate allergic (IgE-mediated) reactions of all grades 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 (1 in 10,000), a result which is very similar to that reported in the NAP6 study.[10, 35]

Perioperative hypersensitivity reactions, including anaphylaxis, occur in a monitored setting, and recent studies have shown that recognition of anaphylaxis was generally very prompt.[36, 37] If anaesthesiologists were considered reluctant to administer epinephrine (adrenaline) in Denmark,[38] this doesn't seem to be the case in the UK and France.[36, 37] In both countries, most patients with severe reactions were adequately managed with rapid administration of adrenaline, however fluid administration was sometimes regarded as insufficient. Despite an adequate resuscitation, per case mortality was estimated at 1 in 26.6 cases in the UK, a result very similar to that observed in France for mortality related to NMBA anaphylaxis.[36, 37] In addition, even after well treated anaphylactic reactions, adverse sequelae were seen in one-third of cases.[37]

A very similar perioperative mortality rate ranging from 4 to 4.76% has been recorded for all causative drugs in the United States (US) and Japan, respectively.[39, 40] This contrasts with the low rate of 0 to 1.4% recently reported for Western Australia (2000-2009).[23]

III. Causal Agents

III.1 : NMBAs and Sugammadex

In many countries, NMBAs are by far the most frequently incriminated culprit, and represent the first[1, 6, 14, 17, 18, 41, 42] or the second [10, 11] most common cause of POH.

Significant differences are observed concerning the frequency of alleged IgE-mediated reactions to NMBAs between countries. Reactions have been reported with a high frequency in France,[17, 18, 35, 43-45] Australia and New Zealand,[6] the UK,[10] Norway,[5] Belgium,[41, 42] South Korea[46] and Spain.[11, 25] The incidence of IgE-mediated reactions has been estimated at 184.0/million (95% CI 139.3-229.7) anaesthetics, reaching 250.9/million (189.8-312.9) for women in France. [35] POH reactions to NMBAs seem to be less frequent in Sweden,[16] Denmark,[4] and the US.[47-49] While the incidence seems to remain quite stable in France,[32] a significant decrease has been observed in Norway since the withdrawal of the antitussive pholcodine, which may play a role in NMBA sensitization.[50, 51]

Structure-activity studies have established that the IgE recognition site of NMBA involves the tertiary and quaternary substituted ammonium ions and its molecular environment.[52, 53] This could explain the frequent but not constant skin cross-sensitivity between the different NMBAs observed in patients allergic to NMBAs, as well as its variability between patients.[54]

An alternative explanation for cross-sensitivity in drug naïve patients could relate to off-target occupancy of the MRGPRX2 receptor by various NMBAs.[31, 34] Cross-sensitivity to all NMBAs is unusual, concerning only around 7% of patients in the last French study.[17] Patients suffering from anaphylaxis to succinylcholine cross-react with cis-atracurium in 10% of cases and with rocuronium in 20% of cases. Cross-sensitivity is most frequently observed with rocuronium and less frequently with cis-atracurium.[6, 17, 41, 55] Cross-sensitivity between cis-atracurium and atracurium is frequent but not constant, observed in around 50% of patients suffering from anaphylaxis to one of these two drugs.[17, 55] These cross-sensitivity results strongly support the absolute necessity of a systematic cross-sensitivity investigation in patients who survive anaphylaxis to a NMBA in order to identify a possible safe drug for the future.[30, 56, 57]

Differences have been reported regarding the relative risk of allergic reactions with the various NMBAs available.[58] Several studies report succinylcholine and rocuronium to be associated with a higher risk of anaphylaxis, whereas pancuronium and cis-atracurium are reported to be the NMBAs associated with the lowest incidence of anaphylaxis.[6, 8, 35, 41, 43, 44, 46, 59] This was not found in the NAP6 survey where only succinylcholine was considered at higher risk, while the risk shared by the other NMBAs was considered to be similar. However, in the UK, the market-share of cis-atracurium was only 1.6%, and 40.6% for rocuronium.[10] Thus, comparison of the respective allergic risk of rocuronium and cis-atracurium in this report cannot be accurately assessed.

Sensitisation may occur during previous anaesthesia but the majority of patients are drug naïve, that is, do not report previous exposure.[41, 53] This suggests that there must be alternative, probably environmental factors, that play a role in cross-sensitizing patients to NMBAs. A possible sensitisation resulting from exposure to compounds containing tertiary and/or quaternary ammonium groups such as cosmetics or disinfectants has been hypothesized.[53] 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,[60] although the clinical significance of this increase remains to be demonstrated. An attractive alternative hypothesis arises from the work published by Florvaag and colleagues who provided repeated evidence for a connection between the consumption of pholcodine, an opiate antitussive, and IgE-mediated anaphylactic reactions to NMBAs.[61-64] Nevertheless, patients with a genuine pholcodine allergy can have congruent negative skin tests and basophil activation tests to NMBAs, suggesting that allergy to this opioid does not preclude the use of NMBAs.[42] Johansson et al, also demonstrated, retrospectively, that pholcodine withdrawal from the Swedish market was associated with a decrease in the prevalence of sensitisation against ammonium ions in the general population.[65] Their observations have led to the withdrawal of pholcodine from the Norwegian market. This resulted in a progressive decrease in IgE antibodies to quaternary substituted ammonium ions in the population as well as in the number of reports of allergic reactions to NMBAs.[50, 51] A prospective 4 year case-control study (the ALPHO study) designed to confirm this possible link between pholcodine exposure and sensitization to NMBAs in France was initiated in 2015.

The NMBA reversal drug sugammadex was launched in the US (December, 2015) much later than in Europe (2008) or Japan (2010). This was because the Food and Drug Administration (FDA) delayed approval of sugammadex because of concerns about hypersensitivity reactions. Since the use of sugammadex in Europe is limited (probably due to its high cost), occurrence of immediate sugammadex-induced anaphylaxis seems rare.[10] In contrast, the incidence of sugammadex-induced anaphylaxis was recently reported as approximately 1 in 2,500 administrations (0.039%) based on a retrospective observational study conducted in a single Japanese hospital.[66] Sugammadex usage in Japan in 2010, in terms of monetary value, was more than four times higher than that in Spain, the country with the second-highest usage in the world.[9] The popularity of sugammadex in Japan is such that it has been administered to approximately 10% of the total Japanese population during the eight-year period since its release.[67] This evidence suggests that the difference in sugammadex-induced anaphylaxis between countries can be explained by the difference in the total amount of sugammadex used. The authors of the Japanese study referred to a previous observational study reported from two institutions in New Zealand, showing that the estimated incidence of anaphylaxis due to succinylcholine and rocuronium was 0.048% and 0.04%.[8] The authors from Japan concluded that the incidence of sugammadex-induced anaphylaxis is roughly equivalent to that of succinylcholine- and rocuronium-induced anaphylaxis.[66] Based on this speculation, one can estimate that the total incidence of intraoperative anaphylactic events will increase by at least one-third with the full-scale introduction of sugammadex.[68]

Two recent reports conducted in healthy non-anaesthetised subjects receiving sugammadex at doses of either 4 or 16 mg kg^{-1}, or placebo, repeated twice at weekly intervals, have shown an unexpectedly and dose-related high rate of immediate hypersensitivity reactions following sugammadex administration. The incidence of confirmed hypersensitivity was determined to be 0.7% in the 4 mg kg^{-1} group, 4.7% in the 16 mg kg^{-1} group, and 0% in the placebo group in the first study.[69] In the second study, the incidence of hypersensitivity was 6.6% of the 4 mg kg-1 group, 9.5% of the 16 mg kg-1 group, and 1.3% of the placebo group.[70] This high rate of reactions contrasts with the number of reactions reported in clinical practice and highlights the need for a careful survey of sugammadex-related hypersensitivity reactions. In addition, based on current knowledge, sugammadex use should be avoided in the treatment of suspected rocuronium allergy.[71]

Although the mechanism of sugammadex-induced anaphylaxis remains elusive, various hypotheses have been proposed. Since sugammadex is a modified structure of γ-cyclodextrin which is also used for food additives, exposure to γ-cyclodextrin may be the sensitizing trigger.[72] Cyclodextrin is frequently used in foods and cosmetics because it can change the physical properties of various compounds by their inclusion inside the cyclic structure. As a result, the average person is considered to ingest about 4 g of γ-cyclodextrin per day from food.[73] Therefore, even people who have never received sugammadex may be sensitized by food and cosmetics. Indeed, none of 12 patients who suffered from anaphylaxis to sugammadex had a history of a previous sugammadex exposure.[74] If this hypothesis is correct, the incidence of sugammadex-induced anaphylaxis may vary from country to country,

because the use of food containing cyclodextrins in each country are likely to be different. Another hypothesis is that sugammadex causes anaphylaxis only after it complexes with rocuronium. This hypothesis is based on several clinical cases.[75-77] Rocuronium and sugammadex alone had negative results by skin test, but positive when combined. These cases suggest that sugammadex may change its structure and become an antigenic determinant by forming a complex with rocuronium.

III.2: Hypnotics:

Historically hypnotic agents were responsible for a significant proportion of cases of perioperative anaphylaxis, but discontinuation of agents using Cremophor EL as a solvent and declining use of thiopental has dramatically changed this.

In the most recent GERAP survey of anaphylaxis in France, hypnotics were responsible for 2.2% of cases, with propofol and ketamine being responsible for 5 reactions each and midazolam a single reaction.[17] The recent NAP6 survey in the UK identified only a single case of hypnotic anaphylaxis.[10] This reaction was to propofol, and the authors highlighted the relative safety of propofol given that approximately 2 million patients are administered propofol annually in the UK.[10]

There has been ongoing debate about whether it is safe to administer propofol in cases of egg, soy and peanut allergy. Studies in Denmark and Spain in recent years would suggest that it is.[78, 79] There has been a case report of anaphylaxis to propofol in a patient without clinical history of soy allergy but latent sensitisation demonstrable by positive specific IgE (sIgE).[80] A single report of a child with egg allergy that experienced urticaria and erythema after propofol and had a borderline positive skin test[81] led Harper[82] to suggest that propofol is safe for use in adults with peanut, soy or egg allergy.

III.3: Opioids :

Opioids include (a) the natural occurring opiate alkaloids derived from opium (the liquid released by scratched immature seed-pods of the opium poppy, *Papaver somniferum*) such as morphine and codeine, (b) semisynthetic opioids such as pholcodine, hydrocodone, hydromorphone and diamorphine and finally (c) synthetic compounds that are chemically not related to opiates such as methadone, pethidine, fentanyl and tramadol. Many natural and (semi)synthetic opioids are potent non-specific liberators of histamine. Non-allergic histaminic reactions are much more prevalent than IgE-mediated hypersensitivity to these drugs and they probably result from off-target occupation of the MRGPRX2 receptor[83, 84] rather than from binding to the opioid μ-receptor.[85] Moreover, data suggest that many patients labelled with opioid/opiate allergy, do not have a genuine IgE-mediated allergy.[86, 87] The reason for this mislabelling is often the uncertainties associated with the use of skin tests[88] with these potent non-specific histamine releasers and unavailability of validated or reliable sIgE assays.[89] Indeed, allergic reactions to these substances are exceedingly rarely reported, despite their ubiquitous use during anaesthesia.[4, 5, 10, 11, 41, 90, 91]

III.4: Local anaesthetics:

Local anaesthetics are very commonly used in the perioperative environment, yet no cases of proven local anaesthetic allergy were reported in the NAP6 survey[10] or two other recent studies of perioperative anaphylaxis.[17, 92]

True hypersensitivity reactions to local anaesthetic drugs are considered to be rare.[93-95] Many reports of allergy prove to be spurious, often related to side effects of injections in awake patients (*e.g.* vasovagal reactions) or adverse effects of rapid absorption of vasopressor or toxic serum levels of local anaesthetic. Excipients in local anaesthetic preparations may also be responsible for suspected local anaesthetic hypersensitivity reactions, such as chlorhexidine in urethral gels. Delayed hypersensitivity can also occur with local anaesthetics. The ester group of local anaesthetics (*e.g.* procaine, tetracaine) is considered to be more antigenic than the amide group (*e.g*. lidocaine, bupivacaine, ropivacaine). The para-aminobenzoic acid metabolite of esters is thought to responsible for much of the antigenicity of this group.[30, 96] Assessment of suspected immediate hypersensitivity to local anaesthetics should involve skin tests and subcutaneous challenge tests.[92, 94]

III.5: Antibiotics:

Antibiotics, mainly β-lactam antibiotics such as amoxicillin/clavulanic acid, cefazolin and cefuroxime constitute another significant cause of perioperative anaphylaxis.[4, 5, 10, 11, 17, 18, 35, 41, 42, 47, 49, 90, 91, 97, 98] In most patients, diagnosis of β-lactam allergy is readily established by skin tests and they still merit a place as the primary diagnostic tool[99-101] However, for some compounds there appears to be room for considerable improvement, mainly in optimizing the concentration of drug to be used for skin test.[102] The potential and limitations of *in vitro* tests in the diagnostic management of β-lactam antibiotics have been reviewed recently.[103]

The NAP6 allergen exposure survey[104] demonstrated that the choice of antibiotic prophylaxis was influenced by preoperative penicillin allergy history in 25% of the patients who received teicoplanin or vancomycin, and thereby probably contributing to the high incidence of teicoplanin-induced anaphylaxis in the UK.[10] Other frequently applied alternatives are vancomycin and clindamycin. With the knowledge that history of penicillin allergy is wrong in more than 90% of cases, effective de-labelling is mandatory to optimize appropriate antibiotic administration.[105, 106] Obsolete historic data and statistics suggesting extensive cross-reactivity between penicillins and first-generation cephalosporins such as cephalotin and cephaloridine continue to influence modern practice. Therefore, many patients with unverified β-lactam allergy are labelled as “pan-β-lactam” allergic, leading to the withholding of penicillins, cephalosporins and monobactams. However, during the last few decades, evidence has accumulated that this “pan-β-lactam” allergy label is false in most cases. For example, cefazolin allergy is generally selective,[102] and rarely associated with cross-reactivity to penicillins or other cephalosporins. It appears that cefazolin is generally safe in patients with an IgE-mediated or non-IgE-mediated penicillin allergy, especially when the history is vague.[107, 108] (v **Ref paper on penicillin here)** Cefazolin does not share an R1- and R2-group with any other β-lactam antibiotic.[109] There is limited data on cefazolin safety in patients with a

history of a significant reaction to penicillin or positive skin testing to penicillin. There is no evidence that the administration of a "test dose" of an antibiotic reduces the severity of an ensuing reaction,[10] and current guidelines are advising against this practice.[110] In contrast, there are different arguments for antibiotics to be systematically administered before induction of anaesthesia.[10] This is likely to improve the detection of unknown allergies, simplify treatment and orientate the diagnostic investigation.

III.6: Hevea latex:

Since the discovery of the vulcanization process by Goodyear and Hayward in the mid XIXth century, NRL from *Hevea Brasilensis* has been used in medical devices for its elastic properties. The first cases of allergy to NRL were reported in 1927 by Stern[111] and Grimm.[112] In 1984, Turjanmaa reported the first cases of perioperative anaphylaxis attributed to NRL in healthcare workers (nurses) who underwent surgery.[113] In 1989, Slater reported the case of NRL allergy in two children with spina bifida.[114] In 1990, Moneret-Vautrin confirmed an increased risk in patients with a spina bifida associated with the detection of specific IgE against NRL and recommended a NRL-free environment for these patients during surgery.[115]
The number of reported cases of allergy to NRL rapidly increased in the 1980s and reached its peak during the 1990's. The prevailing hypothesis to explain this rapid increase in NRL sensitization is that the implementation of high hygiene standards following the HIV epidemic led to an increased demand of NRL gloves. In order to respond to this demand, producers had to change their manufacturing process by reducing the leaching steps of NRL, leading to the release of higher protein content products. High protein content increased antigen exposure and extractable proteins leading to NRL sensitization.[116] Moreover, donning glove powder absorbs most NRL proteins and facilitates their airborne dissemination increasing the risk of sensitization for healthcare workers and patients.[117]
Several populations at risk have been identified including children with spina bifida,[118, 119] those with a history of multiple surgeries, especially during childhood,[120] healthcare workers,[121] and non-healthcare workers frequently exposed to NRL.[122] Atopy has been associated with a higher risk of NRL allergy in the general population and among healthcare workers.[123] However, a recent population-based study showed no significant association between atopy and NRL allergy when exposure is low.[124] Some allergies to fruits and vegetable have been associated with a higher risk of NRL allergy, but this may reflect cross-sensitisation that is not always clinically relevant. Chestnut, avocado, banana and kiwi are the most frequently associated with NRL allergy a condition referred as the latex-fruit syndrome.[125, 126]
Two Italian studies from the same group reported an increased risk of NRL sensitization in pregnant women when compared to women having gynaecological surgery.[127, 128] Although interesting, these results need to be confirmed.
The incidence of NRL-related perioperative IgE-mediated reactions was estimated at 59.1 reactions (44.8–73.6) per million anaesthetics in France between 1997 and 2004 with an increased incidence in women (91.0 (68.9 – 113.4)).[35] More recent studies in many countries have demonstrated a marked decrease in NRL anaphylaxis when compared to other causes of

IgE-mediated POH. In a large multicentre study of over 31,000 paediatric anaesthetic procedures performed in Europe between 2014 and 2015, only one complication was attributed to NRL allergy.[129]

This reduction of NRL sensitization, that has been observed in the general population,[130] can be attributed to the efforts made by manufacturers and healthcare providers during the last ten years to reduce NRL exposure.

Primary prevention is based on increased awareness of the risk of NRL allergy, NRL avoidance in at-risk populations, particularly children, the use of powder-free latex gloves and the recognition of clinical signs. Interestingly, in Thailand, where the sensitization to NRL was previously low, the continued use of powdered gloves led to an increased sensitization to NRL in healthcare workers.[131]

III.7: NSAIDS:

NSAIDS are cyclooxygenase (COX) inhibitors commonly used in perioperative settings parenterally during general anaesthesia and postoperatively for analgesia. They are a rare but well recognised cause of POH.[17, 132]

Hypersensitivity to multiple NSAIDs with dissimilar structures is mediated by inhibition of the COX-1 isoenzyme**(Cross-ref bja mechanisms to be inserted here)**. It is most likely to feature exacerbations of respiratory disease in susceptible patients, urticaria or angioedema.[133, 134]

Less commonly, true anaphylaxis does occur to NSAIDs and is the result of an IgE-mediated allergic reaction to a particular NSAID. In this situation, cross-reactivity may occur to NSAIDs that belong to the same chemical subgroup of NSAIDs, but the majority of NSAIDs will be non-reactive.

Paracetamol is another rare cause of anaphylaxis,[134] particularly in the perioperative setting. The intravenous preparation may contain mannitol that has been responsible for one such reaction that goes undetected by oral drug challenge.[135] Hypersensitivity resulting from COX-1 isoenzyme inhibition is also possible at high doses.[136]

III.8: Disinfectants:

Among disinfectants, chlorhexidine is known as a major cause of POH. Since the first case of proven chlorhexidine-induced anaphylaxis reported in 1989,[137] numerous further cases have been reported mostly related to anaesthesia and surgery. Chlorhexidine products are recommended increasingly to reduce infection risks for patients. For example, national UK guidelines recommends use of 2% chlorhexidine in 70% isopropyl alcohol as the skin disinfectant of choice for central venous catheter insertion and for urethral catheterization. The use of a chlorhexidine-containing urethral lubricant for catheterization is also suggested.[138] According to the Medicines and Healthcare products Regulatory Agency licensing records, the percentage of products containing chlorhexidine has significantly increased over the past 20 years.[139] Moreover, even in non-medical environments, chlorhexidine is found in many commercially available products, including mouthwashes, antiseptic creams, tooth paste, and plasters. This increase in chlorhexidine containing

products both in medical and non-medical environments clearly identifies its popularity, which may explain the increasing susceptibility to sensitization followed by the high incidence of chlorhexidine-induced anaphylaxis.

Although chlorhexidine represented 9% of culprit drugs for POH in the NAP6 study,[10] regional differences are large in the incidence of chlorhexidine-induced anaphylaxis. Chlorhexidine is frequently incriminated in the UK,[140] Belgium,[42] Australia[141] and Denmark[4, 20] which are countries where chlorhexidine is routinely tested in all patients investigated for suspected perioperative allergy. Reactions are relatively rare in France, probably because of a limited use of chlorhexidine as a disinfectant in the operating room in this country.[18] The causative chlorhexidine-product was reportedly chlorhexidine-containing lubricant for urinary catheter (44%), chlorhexidine-impregnated central venous catheters (35%), and topical chlorhexidine (16%) in a recent review.[141] Chlorhexidine-induced anaphylaxis predominantly occur in males (~ 80%).[139, 141] This may be because of the more frequent use of urethral lubricant in males. The first case of chlorhexidine-impregnated catheter anaphylaxis was reported in 1997[142] and acute anaphylactic shock during anaesthesia has been reported in Japanese and European patients following insertion of chlorhexidine-impregnated catheters. Such adverse events prompted government warnings in Japan,[137] US,[143] and Australia.[144] These led to Japan withdrawing all chlorhexidine-impregnated central venous catheters.[145] Although it is not common, POH due to topical chlorhexidine has also been reported.[137, 146, 147] A high rate of reactions to topical chlorhexidine was reported in Japan and as a result specific recommendations regarding the maximum chlorhexidine concentration to be used were issued.[137] Additional warnings concerning urethral gels have been issued. In contrast, the guideline published by Centers for Disease Control and Prevention recommends skin preparation with a > 0.5% chlorhexidine solution with alcohol before central venous catheter and peripheral arterial catheter insertion.[148] As mentioned above, even more concentrated (i.e., 2%) chlorhexidine is recommended for the same purpose in UK.[149] Although the incidence of anaphylaxis due to topical chlorhexidine in the US is unknown, one can expect its high incidence in the United States as well. Collaborative international studies to compare the usage of chlorhexidine in each country with the incidence of anaphylaxis due to chlorhexidine would be beneficial. Taken together, the incidence of anaphylaxis due to chlorhexidine is likely to be underestimated and clinicians should be aware that chlorhexidine is one of the “hidden” causes of POH.[132] The problem of chlorhexidine allergy in the perioperative setting is discussed in greater depth in Rose et al . (**cross ref bja chlorhexidine revue to be inserted here)**

A few cases of anaphylaxis due to povidone-iodine have been also reported,[150, 151] although it is notably less than that caused by chlorhexidine.

III.9: Dyes:

Blue dyes have long been associated with cases of anaphylaxis in the perioperative period, with the first cases described in the 1960s.[152, 153] They are frequently used by surgeons in combination with radioactive isotope to facilitate mapping of lymphatic drainage and identification of sentinel lymph nodes (SLN) in cases of breast cancer and melanoma.

Anaphylaxis to dyes is often delayed in onset compared to intravenously-delivered perioperative antigens,[10, 19] probably as a result of slow absorption from subcutaneous tissue and lymphatics[19, 154] and/or delay of recognition because of interference with pulse oximetry with (prolonged) artificial lowering of readings.[19, 155]

The two most commonly used blue dyes for SLN identification are patent blue V (also known as E-131, commonly used in Europe and Australia) and isosulfan blue (commonly used in the USA). The close structural relationship between these two vital dyes (isosulfan blue is a structural isomer of patent blue which is often confused with its hydroxylated relative, patent blue V), means that cross-reactivity has been described and should be assumed.[156] In contrast, methylene blue dye is structurally dissimilar and would not be expected to cross-react, though this has been described.[19, 157] Allergy to dyes is mainly documented by skin testing but BAT can help to identify safe alternatives.[158]

Controversy about the incidence of reactions to these dyes has existed for many years. Barthelmes[159] looked at several studies of isosulfan blue allergy and reported an allergy rate of 1.42% with severe reactions requiring vasopressor support in 0.44%. In contrast, their own large study of patent blue V reported a lower allergy rate of 0.86% with 0.06% severe using the same criteria. The largest series involving skin test proven hypersensitivity to patent blue V recorded a rate of 0.34%.[154] In the last survey published in France, blue dyes were the third largest cause of POH of all severity grades.[17] Similarly, the recent NAP6 survey in the UK found that patent blue V was the fourth most prevalent cause of perioperative allergy after antibiotics, NMBAs and chlorhexidine[10] and was calculated to occur in 1:6863 exposures. This is lower than the previously mentioned studies, but in perspective is a higher incidence than that calculated for antibiotics, NMBAs and chlorhexidine once exposure rates are considered. Some centres have begun screening patients using skin tests for detection of hypersensitivity to blue dyes prior to exposure[160] or advocating consenting patients specifically about risks of hypersensitivity with their use.[159-161]

Methylene blue has been considered a lower allergy risk than patent blue V or isosulfan blue but is theoretically less useful in SLN localisation due to lack of a sulfonic acid group that would allow lymphatic uptake. Additionally, methylene blue is less suitable for subcutaneous injection due to the risk of skin and fat necrosis. Some recent evidence suggests, however, it may be equally suitable at detecting SLN as patent blue V.[162] Isolated case reports of hypersensitivity to methylene blue have been published.[163-165]

III.10: Colloids:

The epidemiology of hypersensitivity reactions to colloids has changed because of the withdrawal of some colloids from the market and restrictions in the use of others. Only a few studies are relevant to the epidemiology of currently used colloids.

Synthetic colloids are associated with the higher risk of hypersensitivity reactions.[166] In a study from Barron, where human albumin was used as a reference, the estimated risk of hypersensitivity reaction to gelatin was 12 times higher, hydroxyethyl starch 4 times higher and dextrans 2 times higher per administration.[167] However, hydroxyethyl starch 130/0.4 was

not evaluated in this study and old modified fluid gelatins (Haemaccel®), with histamine-releasing properties[168], are no longer used in western countries.

Allergic reactions to dextrans are mainly IgG-mediated[166] and can be prevented in most cases by hapten inhibition.[169] Since this product is no longer used for vascular filling, these reactions are no longer seen in the perioperative setting.

Hypersensitivity reactions to newer modified fluid gelatins account for 0.6 % of perioperative hypersensitivity reactions in the last GERAP study in France and for 1.2 % in Norway[5, 17] In the UK, 2.8% of anaesthetists reported seeing a hypersensitivity reaction due to colloids.[170] In the last NAP-6 study, only 3 cases of gelatin-induced reaction were reported.[10]

In the USA, the use of hydroxyethyl starch was associated with a risk of hypersensitivity reactions with an odds ratio of 1.29 (1.02-1.62).[15] Due to the recent restrictions applied to the use of hydroxyethyl starch, hypersensitivity reactions to this fluid were not described in the last GERAP study in France nor in the NAP-6 survey in the UK.[10, 17]

III.11: Blood products:

Although usually considered collectively, hypersensitivity reactions occur to a heterogeneous group of blood components that vary in their risk of causing serious hypersensitivity reactions. The genesis of true hypersensitivity reactions to blood products is complex and is best divided into recipient-related and donor-related aetiologies. In the first of these, a recipient's antibody reacts with an antigen in the blood product. The best known of these is anti-A in a patient who is IgA deficient though many antibodies have been described including traces of drug in the unit reacting with the patient's antibodies and is the reason for measurement of a recipient's IgA level in the investigation of possible blood transfusion anaphylaxis.[171] Donor-related reactions include the transfer of antibodies or lymphocytes in the blood product that react to antigens present in the patient.[172]

The NAP6 survey identified 2 cases of anaphylaxis (one to cryoprecipitate and one to fresh frozen plasma) in an estimated 84,000 perioperative blood product administrations.[10] The authors of this survey suggest that this may reflect a local haemovigilance scheme but equally it may reflect the difficulty in diagnosing perioperative blood product reactions in the absence of a confirmatory skin test and with multiple other suspect antigens. Furthermore, shock during the administration of blood products may result from non-anaphylactic causes such as ABO incompatibility (acute haemolytic transfusion reaction), bacterial contamination of blood products, bradykinin accumulation[173] and hypovolaemia.

It is estimated that the incidence of hypersensitivity reactions to blood products overall is 0.6 per 1000 transfusions.[172] The risk of individual components of blood varies substantially with estimates that platelets cause 1.1 allergic reactions (of all severities) per 1000 transfusions compared to 0.68 and 0.04 respectively for plasma transfusions and red cell concentrates. Additionally, allergic reactions to platelets were likely to be more severe than with other blood components.[174] A report from France suggested that methylene blue treated FFP (introduced as a pathogen reduction strategy) could carry a higher risk of allergic reactions than non-treated units,[164] but this increased risk has not been confirmed in other studies.[175]

III.12: Others:

Aprotinin, a polypeptide isolated from bovine lung, is capable of stimulating a specific IgE antibody in humans and has been shown to cause anaphylaxis. Although the incidence seems to be low at present,[10] sporadic cases of anaphylaxis due to aprotinin contained in fibrin glue[176, 177] and aprotinin used as an anticoagulant during cardiac surgery[178, 179] have been reported. The risk of hypersensitivity reaction is low after primary exposure to aprotinin. However, application of aprotinin carries a high risk between the fourth and the 30th day after previous exposure, and cannot be recommended for the first 6 months.[178]

Protamine sulfate is a polypeptide that is used to reverse heparin anticoagulation and retard the absorption of insulin, often as neutral protamine Hagedorn (NPH). The polypeptide is extracted from salmon milt in a protein purification process. In addition to IgE-mediated anaphylaxis, protamine can produce multiple adverse reactions, including non-immune mast cell degranulation, complement activation, or IgG-mediated responses that account for the systemic effects.[180] If anaphylaxis occurs during protamine administration when cardiac pulmonary bypass is readily available, the method of managing anticoagulation and potential reversal following reheparinization is an unsolved issue.[181] Fortunately, the incidence of protamine-induced anaphylaxis appears to be low in most countries.[10, 18] Patients who receive protamine containing insulins are at the greatest risk. Indeed, an incident rate of adverse effects is reportedly 0.6% to 2% (10-30 times more than other patients) in NPH insulin-dependent diabetics undergoing cardiac surgery.[182, 183]

IV: Discussion

The overall incidence of perioperative hypersensitivity ranges from 1 in 18,600 to 1 in 353 with substantial geographical variability. Several factors may explain these differences including the definition of hypersensitivity or anaphylaxis used and the mechanism and severity of the reactions included. The recent NAP6 survey conducted in the UK included only severe grade 3,4 and 5 cases, and the incidence was estimated to be at least 1 in 10 000 anaesthetics but likely underestimated.[10] This incidence is similar to the incidence of IgE-mediated hypersensitivity reactions of all grades in France, which was based on a combined analysis of 2 different independent databases representing a cohort of 2,516 cases.[35]

There is also substantial geographical variability regarding the different drugs or substances involved. 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 possible perioperative hypersensitivity and initiate referral, the severity of the reactions that are included, the type of NMBA and antibiotics used by region, the comprehensiveness of the evaluation (i.e. inclusion of all potential allergens the patient was exposed to, such as chlorhexidine, sealants), possible sensitizing substances in a region and availability of *in vitro* testing.[32]

Hypersensitivity reactions to NMBAs remain a major cause in most, but not all countries. As stated above, reactions to NRL have been decreasing over the past 2 decades. Reactions

involving antibiotics are rapidly rising, now being more common than NRL and the most common culprit in some series.[10, 17]

This increase in antibiotic anaphylaxis may reflect the increasing antibiotic sensitisation in the population, but may also be influenced by the type of antibiotics used for prophylaxis. Thus, reactions to teicoplanin appear to be frequent in the UK but not in France.[10] Reactions to cephalosporins represent half of the reactions in France.[17] The use of teicoplanin for prophylaxis is not recommended in France, whereas it is frequently used as an alternative in cases of suspected penicillin allergy in the UK.

Reactions involving chlorhexidine are now being reported with an increased frequency.[10, 20] It may be difficult to correctly diagnose it because of a lack of exposure recognition as exposure to chlorhexidine is rarely documented on anaesthetic charts.[132] Therefore, systematic testing for a possible chlorhexidine allergic reaction seems prudent in cases of POH, even in countries where usage appears to be low.

Allergic reactions involving dyes are also being reported with a high frequency, representing now the third most commonly responsible allergen in France. Clinical diagnosis may be difficult since these reactions are usually delayed following dye injection.[19] Reactions to hypnotics, local anaesthetics and NSAIDS remain uncommon in the perioperative environment.

V/ Conclusion:

Due to the rare occurrence of POH it is mandatory that collaborations are established both within and across specialties to form specialized centres that can build up and report expertise in this highly specialized field. Building a worldwide network dedicated to the investigation of these reactions will not only enable a higher standard of patient care, but will also lead to research collaborations and provide invaluable data on geographical differences, changes in patterns of causal agents and new or emerging allergen sources.

Supplementary Materials

Methodology

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. Additional reports of interest identified by the writing group were included. Retrieved results were then reviewed to summarize the current knowledge of POH epidemiology.

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