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Perioperative Hypersensitivity Reactions: Diagnosis, Treatment and Evaluation

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Opinion statement

Perioperative hypersensitivity reactions are difficult to diagnose as symptoms are hard to differentiate from the effects of anaesthesia on the cardiovascular and respiratory systems. There are numerous non-allergic differential diagnoses, and subsequent investigations should aim to determine the mechanism behind the reaction. In many cases, an allergic mechanism cannot be ruled out and systematic investigations should be performed of all drugs and substances the patient was exposed to prior to the reaction. Serum tryptase taken at the time of reaction compared with the patient's own baseline level is helpful in determining whether an IgE-mediated mechanism is likely. In these cases, the culprit drug should be identified to ensure future avoidance of the culprit whilst causing only the necessary restrictions to the choice of future anaesthetic drugs. In recent years, a number of "hidden" and rarely documented allergens have been identified in the perioperative setting and, therefore, *all* exposures should be identified and tested. Investigations are highly specialised and comprise skin testing, in vitro testing and in some specialised centres, recently, also provocation. A combined approach with cooperation between anaesthesiologists and allergists is necessary to ensure the highest standard of care for patients in this complicated setting.

Introduction

Hypersensitivity reactions in the perioperative setting present a challenge for anaesthetic personnel and for the allergist given the task of subsequent allergy investigations. The diagnosis may be missed due to the usual signs and symptoms during anaesthesia, which may be difficult to distinguish from allergic symptoms. Also, multiple simultaneous exposures, both obvious intravenous administrations but also less obvious "hidden" exposures, make it impossible to identify the culprit in the clinical setting and illustrate the need for a

"detective" approach to ensure identification of all relevant exposures.

The reported incidence of perioperative hypersensitivity varies with definitions used, but in large retrospective multicentre surveys, an incidence of around 1:10,000 anaesthetics have traditionally been quoted [1]. However, prospective studies suggest that this is an underestimate and quote incidences of 1:3180 anaesthetics [2] and 1:1480 anaesthetics [3], respectively. A recent British multicentre "snapshot" study over 2 weeks in 12 British hospitals identified 1:353 incidents fulfilling the criteria for referral for allergy investigation [4]. Due to differences in methodology in the quoted studies, the true incidence of confirmed perioperative hypersensitivity remains undetermined, but it is likely that these reactions are more common than initially thought.

Suspected perioperative hypersensitivity reactions can be very dramatic; re-exposure to the culprit allergen may be severe and even lethal; and therefore, the need for standardised investigation of these complicated reactions is obvious. Optimal patient management requires prompt diagnosis and correct treatment of the reaction followed by investigations aimed at (1) establishing whether the mechanism is allergic or not and (2) identification of all potential allergens and investigation of these, using a combination of tests which will identify the culprit, whilst avoiding undue warnings against drugs not implicated in the reaction. This is a highly specialised task and requires specialist knowledge and experience. Formalised cooperation between anaesthesiologists, who can interpret the clinical reaction, read the charts, comment on potential hidden exposures, suggest relevant differential diagnoses and give advice for future anaesthesia, and allergists/immunologists who can plan, perform and interpret allergy testing is therefore necessary to ensure the highest standard of care in this setting.

Mechanisms and differential diagnoses

Traditionally, the mechanism behind suspected perioperative hypersensitivity reactions has been determined on the basis of investigation results, with test positive reactions being classified as IgE mediated and test negative reactions as non-IgE mediated [5, 6]. However, this classification is probably oversimplified, as there are a number of non-allergic differential diagnoses in perioperative hypersensitivity, which are rarely mentioned in the current literature. For an alternative classification, see Fig. 1.

Suspected perioperative hypersensitivity reactions with skin involvement and involvement of one or more other organ systems are more likely to have an underlying allergic mechanism, especially when supported by an elevated serum tryptase at the time of reaction. IgE-mediated reactions are usually identified by the combination of elevated serum tryptase and positive skin testing and/or in vitro tests. However, in a number of patients, all tests are negative despite a suspected allergic mechanism. Some may be non-IgE mediated such as IgG-mediated reactions, which have been described for dextrans [7]. Alternatively, a non-allergic mechanism may be suspected. Clinically, non-allergic reactions typically have single-system involvement without elevation in serum tryptase at the time of reaction. Examples of such non-allergic differential diagnoses are shown in Table 1.

A positive identification of non-IgE-mediated or non-allergic reactions would require specific drug provocation, which is not presently a standard investigation in perioperative hypersensitivity, and these are therefore often diagnoses of exclusion. Opioids, neuromuscular blocking agents (NMBAs), iodinated contrast media and perhaps combinations of several histamine-releasing substances may induce non-specific histamine release by direct stimulation of mast cells or

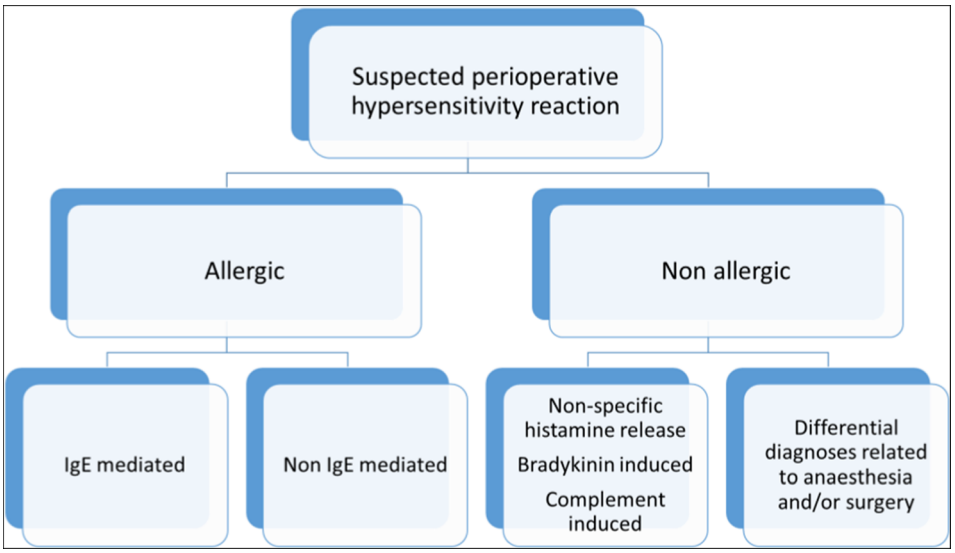

Fig. 1. Suggested classification of mechanisms behind perioperative hypersensitivity reactions.

Table 1. Differential diagnoses to perioperative hypersensitivity

Isolated bronchospasm without elevation in serum tryptase
Undiagnosed or insufficiently treated asthma
Superficial anaesthesia
Irritation from misplaced endotracheal tube
Hyperreactive airways, e.g. smokers and viral infections
Isolated hypotension without elevation in serum tryptase
Major bleeding
Relative overdose of anaesthetic agents
Vasodilatory effect of neuroaxial blockade (spinal/epidural)
Treatment with tricyclic antidepressants
Amniotic fluid embolism/pulmonary embolism
Bone cement implantation syndrome
Other types of shock
Isolated angioedema or laryngeal/pharyngeal oedema without elevation in serum tryptase
Contact dermatitis to perioperative exposures (delayed onset 8–12 h postoperatively)
ACE inhibitor-elicited angioedema (onset 1–8 h after surgery)
Oedema due to handling of difficult airway, rarely subcutaneous emphysema
Hereditary angioedema
Isolated skin symptoms without elevation in serum tryptase
Flare-up of urticaria/angioedema in patients with existing urticaria/angioedema
Non-specific histamine release causing transient rash, flushing and itching
Combination of tachycardia, skin symptoms and hypotension without elevation in serum tryptase
Non-specific histamine release
Excessive dosing of oxytocin
Mesenteric traction syndrome
Others
Mastocytosis patients may develop hypersensitivity/anaphylaxis with or without specific allergy

basophils [8••, 9]. These reactions are non-specific, non-allergic and usually less severe than IgE-mediated reactions, either involving only the skin or sometimes inducing tachycardia and a degree of hypotension. These reactions respond well to antihistamines and may be reduced, or prevented, by pretreatment with antihistamines and attention to slow injection of lower doses and concentrations of histamine-releasing drugs [10]. Reactions related to release of bradykinin, complement and other mediators exist, but knowledge of these is limited, and further research is needed into mechanisms of both non-IgE-mediated and non-allergic reactions.

Non-allergic mechanisms also include causes related to surgery and anaesthesia per se, which is rarely commented on in the current literature (see Table 1). Some are relatively common occurrences such as hypotension induced by anaesthetic drugs, neuroaxial blockade or major bleeding, or hyperreactive airways triggered by airway management. Most anaesthetists will be able to interpret charts and notes retrospectively and come up with these alternative explanations when testing is negative. Rarer differential diagnoses include angioedema in patients on ACE inhibitors [11], profound hypotension in patients on tricyclic antidepressants requiring treatment with adrenaline [12] or excessive doses of oxytocin causing symptoms mimicking anaphylaxis [13]. Lastly, factors related to the surgical procedure such as amniotic fluid embolism [14], bone cement implantation syndrome [15] and mesenteric traction syndrome [16] can cause dramatic reactions mimicking anaphylaxis but without tryptase elevation.

Clinical presentation

The clinical presentation of perioperative hypersensitivity represents a spectrum ranging from mild skin symptoms to anaphylaxis. Reaction severity is preferably classified using a modification of the classification suggested by Ring and Messmer in 1977 [6, 10, 17, 18]. Reactions are often severe and, in a study from the Danish Anaesthesia Allergy Centre, reported to be life-threatening and needing treatment with adrenaline in up to 45 % of referred reactions [19].

Symptoms and signs

Skin

Skin symptoms are present in nearly 80 % of cases [5], are mostly hidden beneath surgical drapes and may be absent. A recent Belgian study reported absence of skin symptoms in 22.4 % of perioperative IgE-mediated allergic reactions [20]. Skin symptoms may initially be absent in cases presenting with circulatory collapse but may re-appear once the circulation is restored allowing perfusion to the skin [17]. Anaesthesiologists rarely have specialised knowledge of allergology/dermatology, so identifying the exact nature of skin symptoms is often a challenge to the allergist subsequently trying to determine the mechanism of the reaction. Investigation of milder cases with skin symptoms only may be relevant in some cases, and especially, patients with confirmed urticaria should be considered for investigation [4]. There are several reports of patients with severe perioperative hypersensitivity reactions who had a previous history of urticarial reactions during or after surgery [21, 22].

Localised and transient rashes/urticaria on the injection arm are caused by localised histamine release, are not considered to represent significant hypersensitivity and do not need referral for investigation [10]. Likewise, transient flushing of the face, neck and chest appearing shortly after injection of known histamine-releasing drugs such as barbiturates, NMBAs and opioids usually resolve spontaneously after 5 min or less. These reactions are caused by non-specific histamine release and may be avoided by slower injection of titrated doses when possible, e.g. for opioids. Pretreatment with antihistamines may be helpful and they do not require referral for investigation [9].

Reactions dominated by pruritus, in some cases accompanied by transient rash of face and chest, recurring at several anaesthetics without increasing in severity, are also thought to be due to non-specific histamine release. These reactions require re-assurance of the patient that reactions are mild and unlikely to increase in severity at the next anaesthetic. Symptoms usually respond very well to antihistamine treatment and most may also be prevented by pretreatment with oral antihistamines for a few days prior to subsequent procedures.

Upper airway

Angioedema presenting perioperatively as a single symptom is rarely caused by allergy. If the patient is not on medication which might inhibit skin symptoms such as antihistamines, antidepressants, high-dose corticosteroids or antipsychotics, and the serum tryptase is not elevated, it is unlikely that the underlying mechanism is allergic [Melchiors BLB, Krøigaard M, Mosbech H, Garvey LH. Is isolated angioedema in the perioperative setting a symptom of allergy?—A retrospective single-centre study. Abstract accepted for presentation at Euroanaesthesia 2016, London]. A subgroup of patients developing perioperative angioedema are on treatment with ACE inhibitors. Angioedema is a well-established side effect of ACE inhibitors, and the mechanism is not allergic but due to alterations in bradykinin metabolism [23•]. Severe angioedema presenting in the hours postsurgery has been described usually affecting tongue, throat and lips and potentially compromising the airway [11, 24]. It is likely that pressure/trauma to mucous membranes on manipulation of the airway during laryngeal mask insertion or intubation may increase severity of swelling of the soft tissues of the pharynx and larynx in these patients [23•, 24]. Recently increased risk of angioedema has also been suggested in diabetic patients on treatment with gliptins [11]. As the mechanism is not allergic, conventional allergy treatment usually does not work, but some symptom relief may be achieved from adrenaline inhalation. Recent evidence suggests that bradykinin receptor antagonists may be effective in the emergency treatment [23•].

Lower airways

In the perioperative setting, most patients are on artificial ventilation, and allergic signs and symptoms from the lower airway are prolonged expiration phase, increased peak airway pressure, decrease in oxygen saturation and rhonchi on auscultation. Patients with known hyperreactive airways such as patients with asthma and chronic obstructive airways disease usually develop bronchospasm during anaphylaxis. However, bronchospasm presenting as a single symptom in the absence of elevated serum tryptase is less likely to be allergic and can in many

cases be attributed to hyperreactive airways caused by undiagnosed or insufficiently treated asthma [25].

Circulation

Tachycardia classically presents together with hypotension, but in some cases, no change in pulse or even bradycardia may be observed, probably more often in patients on beta-blocker treatment.

Hypotension may present as the only symptom, can be quite dramatic and will often not respond to the usual vasopressors used during anaesthesia, such as ephedrine and phenylephrine. When anaphylaxis presents with severe hypotension, a significant increase in serum tryptase will be seen in most cases [26]. All cases of perioperative unexplained severe hypotension should be referred for allergy investigation, but an allergic mechanism is not always confirmed. Several differential diagnoses may be used as a diagnosis of exclusion if investigations are negative and serum tryptase is not elevated at the time of reaction (see Table 1). If investigations do not reveal an allergen in cases of severe hypotension with elevated tryptase, the circumstances of the reaction need to be reconsidered for overlooked allergens. These may be antibiotics/other drugs administered, but not recorded on the charts; disinfectants, dyes and other substances administered by the surgeon; and excipients like polyethyleneglycols (PEGs) and methylcelluloses [27•]. Finally, if transfusion of blood or blood products has taken place, this may be concluded to be the cause if all other causes are eliminated [28]. Unfortunately, at the present time, no diagnostic tool is available to positively confirm immunologic transfusion reactions. Lastly, patients with an underlying, undetected mast cell disorder may present with severe hypotension, not always caused by a specific allergen but by mediator release triggered by other factors in the perioperative setting such as pain, stress, prolonged pressure and extremes of temperature.

Treatment and decision-making in the operating room

Anaphylaxis is difficult to diagnose in the perioperative setting, and therefore, it has been suggested that it should be considered in all cases of hypotension not responding to the usual vasopressors [19]. The first-line treatment is adrenaline in diluted 10–50-μg *intravenous* bolus doses titrated to effect and supplemented by intravenous fluid loading [10, 27•, 29]. Unlike most other clinical settings, *intravenous* adrenaline is used perioperatively as the patient is monitored and anaesthetic personnel have the skills needed to dilute and administer appropriate dosages. Antihistamines and steroids can be administered once the patient is stabilised as they play no proven role in the emergency management. In patients presenting with skin symptoms only, however, initial treatment with antihistamines and/or corticosteroids may be sufficient, but the patient should be monitored closely for progression in symptom severity necessitating further treatment [27•].

When anaphylaxis is suspected, the perioperative setting should be ideal for prompt and relevant treatment, as patients are monitored, have iv access in place and are attended by anaesthetic personnel who are specialists in the management of medical emergencies, including anaphylaxis [19]. In the light of this, mortality from perioperative anaphylaxis should be low, but literature on

this is very limited. A recent study from Australia in the period of 2000–2009 quotes mortality to be 0–1.4 % [30•], whilst a French study of mortality from NMBAs alone in the period of 2000–2011 quotes a higher incidence of 4.1 % for this specific drug group [31]. An increased focus on teaching anaesthetists about the recognition and treatment of perioperative anaphylaxis is very important to ensure that mortality is kept as low as possible.

Some cases of perioperative anaphylaxis are very severe and difficult to stabilise, requiring surgery to be abandoned and needing subsequent observation in intensive care with continuous infusion of adrenaline for several hours. However, the majority of cases stabilise relatively quickly and it may be safe to continue surgery in these patients, when the indication for surgery is strong, e.g. surgery for malignancy or other potentially life-threatening diseases. Allergy investigations require careful planning and can rarely be carried out at short notice; in addition, skin test results may not be reliable until 4–6 weeks after the initial reaction [32]. Patients who have procedures cancelled due to suspected anaphylaxis may thus have surgery delayed substantially, which may be detrimental, and even affect long-term survival. In patients who stabilise quickly on initial treatment, the option to continue surgery should therefore be discussed in the operating room, between surgeons and anaesthetic personnel, weighing up the individual risks and potential benefit for the patient.

Postoperatively, the level of monitoring depends on the severity of the reaction and treatment response. The incidence of recurrence of allergy symptoms, termed biphasic anaphylaxis, has been quoted in international anaphylaxis guidelines to occur in up to 20 % of patients with anaphylaxis of all causes [33••]. However, this is likely to be an overestimate as more recent studies of larger groups of patients suggest an incidence of clinically important biphasic allergic reactions of <2 % [34•, 35•]. The incidence of biphasic reactions after perioperative hypersensitivity reactions is unknown but thought to be low [27•].

Investigating perioperative hypersensitivity

A detailed history of the circumstances of the reaction is imperative for successful allergy evaluation. A combined allergy and anaesthetic evaluation will lead to the best outcome for the patient. Ideally, the referral should be made by the anaesthetist who carried out the anaesthetic and who has detailed knowledge of the chronology of events and relevant exposures. Attending anaesthetists may also suggest alternative explanations for symptoms in cases where suspected allergy cannot be confirmed on subsequent investigation. Copies of the anaesthetic charts are needed for evaluation of symptoms and signs and for detailed account of exposures. However, not all exposures are drugs given intravenously and copies of the surgeon's account of the operation, separate drug charts and surgical nursing notes may be needed to get the complete picture of exposures. Sterilising agents such as ethylene oxide, disinfectants such as chlorhexidine or povidone iodine and latex are certain exposures during surgery in many countries but are rarely documented on charts and have been termed hidden allergens/exposures [27•]. Also, recently, it has been shown that even substances thought to be inert like ultrasound gels, local anaesthetic sprays, bandages or intravenous injection substances may contain

allergenic substances such as methylcelluloses, PEGs/macrogols or mannitol [36–38]. Finally, substances used by the surgeon, e.g. dyes such as Patent Blue, have been reported from many countries as an increasing cause of perioperative hypersensitivity [5, 20, 39].

Due to the many simultaneous exposures, it is not possible to guess the culprit allergen based alone on timing of administration in relation to the reaction [40, 41]. Whilst reactions to intravenous drugs, e.g. antibiotics and NMBAs, are likely to occur within minutes of administration [41, 42], other exposures may occur at the same time such as urinary catheter insertion; thus, a reaction to chlorhexidine in urethral gel may coincide with the iv administration of an antibiotic, which is then wrongly suspected as the allergen.

Centres investigating patients with perioperative hypersensitivity should be aware of the commonly used hidden exposures during surgery in their country and consider testing relevant substances in all patients. Most centres carry out latex testing in all patients regardless of reports of exposure in the referral papers. Studies suggest that allergy to chlorhexidine may have been overlooked in countries where it is used routinely [20, 39], and it is suggested to implement similar routine testing with chlorhexidine [43•]. Chlorhexidine is rarely reported on anaesthetic charts, and exposure may therefore go unnoticed due to lack of knowledge about the many potential products containing chlorhexidine [44].

Careful evaluation of the circumstances around the reaction should lead to a plan for testing all drugs and substances the patient was exposed to prior to the reaction. A large number of substances may be implicated, and in the Danish Anaesthesia Allergy Centre, time limits have been applied for the selection of substances to test. All substances given intravenously within 1 h before the reaction and all substances exposed by other routes, e.g. oral, spinal, epidural and intramuscular, within 2 h before the reaction are tested [43•]. Asymptomatic re-exposures within hours of the reaction should be interpreted with caution as a potential reaction may have been inhibited by treatment with antihistamines and corticosteroids; thus, testing should still be considered. Uneventful re-exposure days/weeks later usually means that the drug is tolerated and testing can be omitted.

Investigations of perioperative hypersensitivity reactions follow the same principles as drug allergy investigation in general and are aimed at identifying IgE-mediated reactions through skin testing (skin prick test and intradermal test) and in vitro tests such as basophil activation tests and histamine release tests [10, 27•]. The rate of positivity varies between centres due to differences in referral patterns and investigations used. Recent studies from countries with high rates of NMBA anaphylaxis quote the positivity rate to be around 63 % [5, 20]. In Denmark where NMBA anaphylaxis is rare, the positivity rate in the national reference centre is lower, at about 40–45 % (unpublished observation from the Danish Anaesthesia Allergy Centre).

For many of the investigated drugs, experience with existing tests is limited and no one single test has 100 % sensitivity and specificity. Overlooking an allergen and false negative testing are both dangerous for the patient, as it may lead to re-exposure and subsequent reactions. On the other hand, false positive testing limits choice for future anaesthesia but may also lead to wrong conclusions and generalisations. Inconclusive test results for drugs administered minutes before the reaction, or for drugs with a suspected high probability for

positive reaction, such as antibiotics or NMBAs, may be interpreted as positive, and the wrong conclusions may be drawn. Whilst timing is an important part of the evaluation, multiple drug administrations and other exposures in the perioperative environment make it hazardous to guess the culprit [39–41]. Therefore, regardless of the clinical suspicion, systematic testing of all potential culprit drugs should be carried out and conclusions drawn on the basis of *all* test results. Occasionally, patients test positive for more than one substance and therefore investigations should be completed for the remaining suspected drugs, even if one substance tests positive.

The risk of false positive testing is further increased if testing with non-exposed drugs is carried out. Whilst it is important to rule out cross-reactivity for some drug groups, such as NMBAs, there is no evidence for benefit of routine testing with specific drug groups in non-exposed patients [45••].

Achieving the highest possible sensitivity in testing and thus avoiding false negative testing requires highly specialised knowledge and skills but will provide the safest choices for future anaesthesia. This may be achieved by combining results of several tests, i.e. skin prick test, intradermal test, specific IgE or other in vitro tests, and some studies suggest that *a positive result in two or more test modalities* is one way of achieving high sensitivity for drugs where drug provocation is either not possible, or considered hazardous, which applies to a large number of drugs from the perioperative setting [43•, 46].

Serum tryptase

Serum tryptase has proven to be a useful tool in the investigation of perioperative hypersensitivity reactions. One commercially available assay (ImmunoCAP, Thermofisher, Uppsala, Sweden) measures total tryptase as the sum of baseline tryptase, continuously secreted from mast cells, and beta-tryptase only released from granules in the mast cell during activation, such as during anaphylaxis. Baseline serum tryptase may decrease slightly in the perioperative setting due to the dilutional effect of intravenous fluids [47]. Baseline serum tryptase values are very reproducible in individual patients, even over time, and this have led to suggestions that relevant increases in serum tryptase may occur within the recommended normal range <11.4 μg/l [47, 48]. Recently, it was suggested to change from using an absolute cutoff for serum tryptase of 11.4 μg/l to comparing serum tryptase taken at the time of reaction with the patient's own baseline. A relevant increase in acute over baseline level of serum tryptase has been suggested to exceed 2 + 1.2× baseline level [49•]. This new diagnostic method requires a minimum of two samples from the patient, one at the time of reaction and a baseline sample. The time taken for serum tryptase to return to baseline following anaphylaxis exceeds 24 h in some patients, and thus, sampling should ideally take place several days after the reaction. In practice, the baseline sample can be taken at the time of subsequent allergy investigations [10]. Some centres, especially in the UK, advocate three samples, but this can be difficult to implement in practice, and a recent study reported that only 34 % of patients had all three samples taken [50].

In clinical practice, tryptase is very stable in both serum and plasma, and samples can be taken at room temperature and sent for analysis the next day without any special preparation. Even so, samples are not always taken at the time of suspected reactions. To improve the number of blood samples taken at

the correct time interval, it has been suggested to liase with anaesthetic departments and send out "anaphylaxis packs" with blood sampling equipment, referral papers and blood sample request forms for serum tryptase. This was initiated by the Norwegian Network for perioperative allergy, is routine in the Danish Anaesthesia Allergy Centre and has recently been introduced in the North of England with great success [10, 51].

Blood samples for tryptase should be taken 30 min to 3 h after the reaction to ensure that peak values at 1–2 h postreaction are captured. Therefore, the time of blood sampling relative to the onset of the allergic reaction should always be recorded, so it can be used for subsequent interpretation of results.

The importance of a baseline tryptase value extends beyond ensuring a return to baseline after anaphylaxis. In some patients, the baseline serum tryptase may be elevated, which may be a sign of an underlying mast cell disorder [52]. In patients with severe perioperative cardiovascular collapse even in the absence of skin symptoms, systemic mastocytosis should be considered as a differential diagnosis, especially if no allergen is found on subsequent investigation. It has recently been reported that patients with systemic mast cell disorders may even have baseline serum tryptase within the normal range, i.e. <11.4 μg/l [53]. It has recently become possible to initiate investigations for suspected mastocytosis by screening for the KIT-816 mutation in peripheral blood, and an algorithm for this has been suggested [54••].

An elevated serum tryptase taken at the time of reaction is useful in supporting the diagnosis of a suspected allergic reaction, but when it is *not* elevated, it may also be useful in helping to disprove an allergic mechanism and confirm alternative differential diagnoses (see Table 1).

Skin testing

Skin tests (skin prick test (SPT) and intradermal test (IDT)) are the most commonly used tests in the investigation of perioperative hypersensitivity [1]. However, there is a lack of standardisation of which tests and methods should be used, and of interpretation of test results, causing sensitivity and specificity of skin testing to vary between drugs and between centres. The intradermal test carries a high risk of false positive testing and in an attempt to standardise test concentrations; the European Network for Drug Allergy (ENDA) has recently published non-irritant test concentrations from existing knowledge and best available evidence in the literature [45••]. The suggested skin test concentrations for anaesthetic drugs are based on recommendations from the large anaesthesia allergy network GERAP in France [55] but also include information from a study in healthy volunteers, suggesting that IDT concentrations for some of the NMBAs should be altered [45••, 56]. Suggestion that the concentration for vecuronium at 1/10 concentration (0.4 mg/ml) is leading to false positive results has been supported by clinical practice [20, 57]. A provocation model for NMBAs would be useful in validating the skin test concentrations but is obviously problematic due to the effect of the drugs.

In many studies and case reports in the literature, reference is made to "positive skin testing" without specifying which tests are positive and at what concentration. A positive skin prick test, especially when showing dose response on increasing doses, is more likely to be a true positive, especially if IDT is also positive on low concentrations. If skin prick tests and the lower concentrations

on IDT are negative, then a positive IDT result on the highest concentration only (often 1/10 of vial strength) is more likely to be a false positive result and should ideally be confirmed/disproved by provocation. As normal practice in drug allergy is to discontinue testing with a particular drug, when a positive test result has been obtained, tests are unfortunately rarely validated against each other.

Provocation

Provocation is rarely considered in the investigation of perioperative hypersensitivity due to the pharmacological effect of most drugs and has only been recommended for, e.g. antibiotics and local anaesthetics, when skin tests were either not possible or negative [55]. However, provocation is the gold standard in drug allergy and is helpful in confirming or disproving inconclusive skin test results. It may be that the time has come to introduce provocation into the investigation of perioperative hypersensitivity in some highly specialised centres.

Specific IgE

For a limited number of drugs used in the perioperative setting, there are commercially available tests for specific IgE with varying sensitivity and specificity. Many centres use the ImmunoCAP system (Thermofisher, Uppsala, Sweden), and the specific IgE assay for chlorhexidine has been shown to have very high sensitivity and specificity [43•]. Specific IgE for latex and penicillins also show acceptable results, but for most of the remaining tests, validity is uncertain. Specific IgE can be measured at the time of the allergic reaction and has been shown to be elevated at this time for several allergens such as chlorhexidine, ethylene oxide and NMBAs [58–60]. Specific IgE levels will decrease over time on lack of exposure and may fall below the detection limit of 0.35 kUA/l, and therefore, a negative result cannot be used to rule out allergy. On re-exposure, specific IgE levels may increase again with or without a clinical reaction [58] [Opstrup MS, Poulsen LK, Malling HJ, Jensen BM, Garvey LH. Dynamics of specific IgE in chlorhexidine allergic patients with and without accidental re-exposure. Submitted January 2016].

Basophil activation tests and histamine release tests

Basophil activation test (BAT) measures the up-regulation of certain surface markers (CD63 and CD203) on the basophil in response to allergen stimulation, and histamine release test (HR) relies on measurement of histamine release in response to allergen stimulation. Both have limited availability to clinicians outside highly specialised centres, where they show some promise, and both methods rely on the availability of fresh blood for analysis, which is a limiting factor.

Causes

The literature on perioperative hypersensitivity is dominated by large multicentre studies from France where experience has been gathered over many years. In France and other countries such as Norway, UK, New Zealand, and Australia, the main causes of perioperative hypersensitivity are the NMBAs. As these drugs are structurally similar, cross-reactivity within the group is also reported in up to 60–70 % of cases [1]. A link between the availability of

pholcodine, the active ingredient in some over-the-counter cough mixtures, have been linked to higher rates of sensitisation to NMBAs in some countries [61]. The lack of availability of pholcodine in Sweden, Denmark, and USA may explain the relative rarity of NMBA reactions in these countries [62].

Antibiotics are one of the leading causes of perioperative hypersensitivity in all countries that have reported results of investigations. Main culprits are penicillins and cephalosporins, but differences in specific drugs reflect local preferences and geographical differences in bacterial resistance patterns [41].

A marked decrease in the incidence of perioperative hypersensitivity reactions to latex has been reported from several countries [3, 17] [Brandi S, Krøigaard M, Mosbech H, Garvey LH. Decreasing frequency of perioperative latex allergy in Denmark in the period 1999–2015. Abstract submitted for EAACI congress Vienna June 2016], probably due to decreased exposure to latex in the perioperative setting and the avoidance of powdered gloves in many countries.

An increase in the incidence of hypersensitivity reactions to Patent Blue used for subcutaneous injection and sentinel node marking in breast and skin cancers is reported in most countries, and the incidence has been calculated to be as high as 1:300 exposures [63]. This is a much higher risk of reaction than any other drug in the perioperative setting and has led to suggestions that preoperative screening with skin testing may be warranted for this specific substance [64].

Chlorhexidine is used widely for disinfection prior to intravenous cannulation, surgical incision and urethral catheterisation and is an ingredient in central lines, dressings, bandages and numerous other products in the health service [44]. Hypersensitivity reactions are increasingly reported to chlorhexidine and in countries like Denmark and UK, where routine testing of all patients have been implemented in some centres, 5–9.6 % of reactions are confirmed to be due to chlorhexidine [39, 43•, 50]. Reactions to chlorhexidine range from postoperative urticaria to anaphylaxis with cardiac arrest, and a number of patients report experiencing mild reactions prior to more severe reactions [21, 22, 58]. It is likely that many reactions to chlorhexidine still go unnoticed around the world, as chlorhexidine is a hidden exposure rarely written on charts. It is strongly recommended that centres investigating perioperative hypersensitivity test all patients for allergy to chlorhexidine as exposure can probably be presumed in the perioperative setting in most countries [43•].

Allergic reactions to local anaesthetics are exceedingly rare in the perioperative setting [1, 65] [Kvisselgaard AD, Krøigaard M, Mosbech H, Garvey LH. No cases of perioperative allergy to local anaesthetics in the Danish Anaesthesia Allergy Centre. Submitted January 2016]. Outside the perioperative setting, allergic symptoms are also rare on exposure to local anaesthetics, and it is more likely that reactions are caused by other exposures such as chlorhexidine and latex [66].

Reactions to intravenous anaesthetics such as barbiturates and propofol are relatively rare. Suggestion that the use of propofol should be contraindicated in patients allergic to egg, soy and peanut due to the content of egg lecithin and soybean oil has now largely been disproved [67•, 68].

Any substance administered in the perioperative setting may potentially elicit allergic reactions. Analgesics, antiemetics, proton pump inhibitors, benzodiazepines, etc. may all be incriminated. Colloids are rare causes; previously, dextrans were incriminated, but more recently, new attention has been drawn to gelatins as these may be a cause in patients sensitised to the carbohydrate epitope Alfa-Gal after tick bites [69]. Other hidden exposure such as the sterilising agent

ethylene oxide has been shown to be a rare cause of hypersensitivity reactions [70]. Exposure to ethylene oxide is almost inevitable, and testing of all patients may be considered; however, it is unlikely to be a problem in all specialties, and high-risk patient groups should be identified and tested [59]. Recently, macrogols/polyethyleneglycols or PEGs and methylcelluloses present in gels, sprays, cements and other substances used perioperatively, without being documented on charts, have been identified as allergens [36, 37]. Although rare, reactions to these substances are probably regularly overlooked and thus under-reported, and this stresses the importance of documenting all exposures, when referring patients with suspected perioperative hypersensitivity reactions.

Risk factors and prevention

The risk of a perioperative hypersensitivity reaction is increased in patients with a history of a previous unexplained adverse reaction during anaesthesia [71]. No other risk factors for perioperative hypersensitivity reactions have been consistently reported. The severity of a hypersensitivity reaction may increase with increasing age and in patients with elevated baseline tryptase [72] as has been shown for insect venom allergy [73]. Patients with other drug allergies are not thought to be at increased risk in the perioperative setting, and the same is true for patients with multiple inhalational and/or food allergies. The latter group often report non-specific itching/rashes after surgery, which can be worrying to the patient but may be prevented or attenuated by pretreatment with antihistamines or continuation of usual antihistamine treatment.

Conclusion

Perioperative hypersensitivity reactions are rare but require prompt diagnosis and correct treatment for the best outcome. Due to the multiple simultaneous exposures and many alternative diagnoses in the perioperative setting, subsequent allergy investigation requires a systematic approach, with attention to detail and specialised knowledge of these rare reactions. Investigations of these complicated patients should ideally be carried out in few highly specialised centres with formalised cooperation between anaesthesiologists and allergists to ensure the highest standard of care.

Compliance with ethical standards

Conflict of interest
Lene Heise Garvey is a part-time post doc researcher funded by Gentofte Hospital. Dr. Garvey declares that she has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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