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Review

Diagnosis of Immediate Perioperative Hypersensitivity Reactions and the Role of Drug Provocation Testing

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Abstract

Perioperative hypersensitivity (POH) constitutes an unpredictable but significant risk during anesthesia with an estimated incidence of 1:5.000 to 1:10.000 and an estimated mortality of 3.4-3.8%. Accurate diagnosis is crucial to prevent re-exposures to the causative agent and to clear other drugs for use in future procedures. In this narrative review we summarize recommendations for the treating anesthesiologist and review established diagnostic investigations. Finally, we examine the rationale for implementing drug provocation tests as the final investigation.

Keywords: **Allergy, anaphylaxis, perioperative hypersensitivity, POH, diagnosis, drug provocation testing, drug challenge, review.**

Introduction

Perioperative hypersensitivity (POH) reactions are a heterogeneous phenomenon with varying clinical presentations and several pathophysiological mechanisms which have not yet been fully elucidated[1]. Depending on the definition used and varying according to geographical location, the incidence of POH is frequently estimated at 1:5,000 to 1:10,000 procedures[2-4]. Anaphylaxis resulting from POH has been documented as being more severe when compared to other settings (e.g. in IgE-mediated food allergy)[5]. For instance, the estimated mortality rate in the United States and the United Kingdom is reported to be 3.4-3.8% whilst the Australian and New Zealand College of Anesthesiologist consistently reports POH (together with pulmonary aspiration) to be the primary cause of mortality 'attributable to anesthesia or factors under the control of the anaesthesiologist'[6]. While overall POH occurs more frequently in females, fatal POH is more prevalent in males. A correct diagnosis and identification of the causative agent(s) are essential to prevent dangerous re-exposures and clear other drugs for future anesthetics. However, it is important to note that current diagnostic methodologies may not aways be adequate, often resulting in diagnostic uncertainties. These diagnostic uncertainties carry the risk of subsequent re-exposures or to suboptimal subsequent anesthesia when all potential culprits are needlessly avoided. This narrative review aims to describe the implementation of full-dose drug provocation testing (DPT) as a method to achieve greater diagnostic certainty in POH based on the authors' experience in a specialized POH reference center.

Mechanisms

The term "hypersensitivity" is defined as all unexpected but reproducible reactions to exposure to a defined substance that is tolerated by normal subjects and that go beyond the primary pharmacological actions[1]. While this definition of a drug hypersensitivity reaction (DHR) does not specify the underlying pathophysiological process, it excludes predictable reactions caused by the pharmacologic effect of the drug combined

with comorbidities and/or drug-drug interactions, e.g. an excessive dose of multiple anesthetics in a frail patient leading to hypotension. DHR are characterized by involvement of the immune system or inflammatory mechanisms and can be further subdivided mechanistically in allergic or non-allergic reactions and based on chrono-morphologic criteria in immediate (IDHR) or non-immediate (NIDHR) reactions. An allergic (or immunogenic) DHR implies involvement of the adaptive immune system. Mechanistically, allergic reactions are classified according to the Gell and Coombs classification. Type 1 allergic reactions are antibody (IgE)-mediated. These reactions are characterized by their rapid onset (i.e. as IDHR), often manifesting as anaphylaxis. Following exposure to an antigen, specific B lymphocytes transform into plasma cells and produce antigen-specific IgE (sIgE) antibodies. These circulating sIgE antibodies bind to high-affinity IgE receptors (FcεRI) on mast cells and basophils. A subsequent exposure to the antigen cross-links sIgE/FcεRI complexes present on the effector cell membrane and causes degranulation. Some research suggests that IgG also plays a role in allergic anaphylaxis but data in humans are still limited[7].

An antigen-specific IgE binds only a specific part of the antigen, also known as epitope or antigenic determinant. Different antigens may possess shared or analogous epitopes, a factor that can give rise to the occurrence of cross-reactivity between antigens. While drug molecules contain potential epitopes, they are too small to effectively cause sIgE/FcεRI crosslinking and must be attached to a larger carrier molecule (haptenization).

A non-allergic reaction may be initiated through non-specific activation of mast cells/basophils, for example by off-target occupancy of the Mas-related G-protein coupled receptor (MRGPRX2) or after complement activation by binding of the anaphylatoxin C3a and C5a to the C3aR and C5aR on mast cells and basophils. Alternatively, non-allergic reactions may be mast cells/basophil independent through enzyme interference, for example cyclooxygenase 1 (COX 1) or angiotensin-converting enzyme (ACE) inhibition.

Upon activation of mast cells and basophils, irrespective of the underlying mechanism (allergic or non-allergic), the release of mediators such as histamine, tryptase, platelet-activating factor (PAF), prostaglandins and leukotrienes occurs. The consequence of these processes is the induction of vasodilation, an increase in vascular permeability, a decrease in cardiac contractility and the occurrence of bronchospasm. This results in a reduction of pre-load and cardiac output, hypoxemia and potentially airway compromise through angioedema. The (most severe) outcome of these reactions is a profound distributive shock, which may precipitate cardiac arrest.

POH reactions are IDHRs that occur in the perioperative setting and may be allergic or non-allergic. Distinctive attributes of POH are its elevated morbidity and mortality rates and the complexity of diagnosis. During surgery and under general anesthesia there are many confounding factors which could potentially explain, mimic, mask and/or exacerbate hypersensitivity-related symptoms as well as many different and concurrent exposures which must be investigated as potential culprits. The diagnosis of POH and the identification of the culprit agent is based on clinical picture, in vitro - and in in vivo diagnostics.

Culprits

All administered drugs have the potential to cause POH. Additionally, related compounds including latex, contrast media, dyes, colloid fluids and especially disinfectants may also cause POH.

Neuromuscular blocking agents (NMBAs) are the most frequent culprit in our region at 42-60% of identified culprits[8,9]. Suxamethonium and rocuronium have the highest incidence of hypersensitivity[10]. Sugammadex has been reported to cause POH about one in 2500 administrations, a rate similar to rocuronium and suxamethonium[11]. Interestingly, POH may be caused by sugammadex molecule on its own as evidenced by its administration in awake subjects or by the rocuronium-sugammadex complex[12-14].

The incidence of hypersensitivity to antibiotics (15-25% of identified culprits in our region)[8,9] such as cefazolin and amoxicillin/clavulanic acid is increasing. In some regions (Spain, US, UK) antibiotics already are the leading cause of POH[15].

Conversely, the incidence of hypersensitivity to latex has decreased sharply with latex's share among identified culprits falling from nearly 20% to only 2%[8,9].

Propofol rarely causes POH and it should not be avoided in patients allergic to egg or soy[16].

Hypersensitivity reactions to other anesthetic agents (e.g. midazolam and ketamine) have been described but account for almost none of the POH reactions in France and none in the United Kingdom and Flanders[2,8,9].

Opioids rarely cause IgE-mediated POH but natural opioids (e.g. morphine or codeine) may directly cause mast cell activation through the opioid and MRGPRX-2 receptor on mast cells. This is rare for synthetic opioids (e.g. sufentanil or tramadol)[17].

Non-steroidal anti-inflammatory drugs (NSAID) can cause non-specific POH through COX 1 inhibition resulting in exacerbations of respiratory disease, urticaria, or angioedema. More rarely, NSAID may cause specific IgE-mediated POH.

Hypersensitivity reactions to local anesthetic drugs are similarly rare[10]. Many adverse reactions following local anesthetic administration are side-effects of injections in awake patients (e.g. vasovagal reactions) or local anesthetic systemic toxicity.

Reports of hypersensitivity to modern colloids are rare. Epidemiological studies from France and the United Kingdom report only one and three cases of gelatine hypersensitivity, respectively.

Finally, some exposures are 'hidden': impregnated catheters or prothesis, undocumented use of disinfectant, dye, contrast, … Among these, chlorhexidine and patent blue dye are not infrequent culprits responsible for 9% and 5% of POH cases respectively in a United Kingdom epidemiological study[2].

Ultimately, however, a culprit cannot be identified in 30% of POH cases despite a full diagnostic work up.

Clinical Presentation

The manifestation of symptoms of POH is typically rapid, occurring within minutes of intravenous administration. Consequently, an interval of one hour between administration and the onset of symptoms is regarded as the cut-off point for identifying intravenously administered drugs as potential causative agents. While IDHR may affect the cutaneous, circulatory, respiratory and gastrointestinal systems, gastrointestinal symptoms such as acute nausea and vomiting are less relevant in POH. The potential cutaneous manifestations encompass urticaria, generalized erythema, pruritus and angioedema. Intraoperatively, the unconscious patient does not perceive these symptoms and objective signs are often masked by surgical drapes. Potential circulatory symptoms include distributive hypovolemic shock with hypotension, tachycardia and cardiac arrest. Potential respiratory symptoms include bronchospasm and upper airway obstruction. The manifestation of these symptoms may occur in isolation or in various combinations. The clinical classification of POH is determined by the modified Ring and Messmer Classification[18,19] (see Table I).

Reactions classified as grade 1 are limited to the skin and mucosa. Any involvement of the circulatory or respiratory system must therefore be classified as grade 2 or higher.

Reactions classified as grade 2 involve the respiratory and/or circulatory systems resulting in mild to moderate symptoms that do not require urgent treatment in themselves (e.g. wheezing, mild drop in blood pressure). Do note that in the context of POH these symptoms should be promptly treated with adrenaline as they may progress rapidly.

Conversely, grade 3 reactions are characterized by the onset of severe respiratory and/or circulatory symptoms that necessitate urgent intervention.

When POH results in cardiac arrest, it is classified as grade 4 (successful resuscitation) or grade 5 (fatal). In the 6th National Audit, 15% of POH patients in the UK suffered cardiac arrest[20].

The term 'anaphylaxis' is used when two or more organ systems are involved in a hypersensitivity reaction, regardless of severity or mechanism (allergic of non-allergic). Hence, the term 'anaphylactoid reaction' is no longer required[21].

The treatment for POH is dependent on the clinical presentation and -from grade 2 onwards- consists mainly of timely administration of adrenaline and fluids. The dose of adrenaline is based on the grade of the reaction[22] (see Table II).

Differential Diagnosis

POH is a clinical diagnosis, but it should be noted that many other pathologies may present with similar symptoms[15]. Isolated bronchospasm may be caused by a number of factors including, but not limited to, asthma, COPD, insufficient anesthetic depth, irritation from endotracheal intubation, aspiration or hyperreactive airways. Similarly, isolated hypotension may be caused by other

Table I. — Classification of clinical manifestations of perioperative hypersensitivity reactions according to a modified Ring and Messmer classification. Adapted from Kroigaard et al[48].

Grade	Clinical manifestations
I	Generalised cutaneous signs: erythema, urticaria with or without angioedema
II	Moderate multiorgan involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity (cough, ventilatory impairment)
III	Severe life-threatening multiorgan involvement that requires specific treatment: collapse, tachycardia or bradycardia, cardiac arrhythmias, bronchospasm; the cutaneous signs may be absent or occur only after the arterial blood pressure recovers
IV	Circulatory or respiratory arrest
V	Death due to a lack of response to cardiorespiratory resuscitation

Table II. — Mainstays of treatment of perioperative hypersensitivity grade 2-4 reactions in adults. Abbreviated from Garvey et al[22].

	I.V. adrenaline	I.V. fluid (crystalloids)
Grade II	20µg bolus Inadequate response at 2 min Escalate to 50 µg Repeat every 2 min If no i.v. access 300 µg i.m.	500 ml rapid bolus Review response Repeat as needed
Grade III	50µg bolus OR 100µg bolus if inadequate response to other vasopressors or bronchodilators Inadequate response at 2 min: Escalate to 200 µg Repeat every 2 min	500 ml rapid bolus Review response Repeat as needed up to 30 ml.kg^{-1}
Grade IV	1mg Repeat as per ALS guidelines Suggest external cardiac massage if: systolic < 50mm Hg or end-tidal CO_2 < 20mm Hg	
Refractory anaphylaxis	Where inadequate response >10 min after symptom onset: Adrenaline: double epinephrine dose If inadequate response after more than three boluses adrenaline: add adrenaline infusion 0.05–0.1 µg kg^{-1} min^{-1} Hypotension — consider adding: vasopressin 1–2 IU with or without infusion 2 IU h^{-1} glucagon 1–2 mg (if on beta-adrenergic receptor blockers) norepinephrine infusion 0.05–0.5 µg kg^{-1}min^{-1} Suggest ECLS: where available Bronchospasm — consider adding: inhaled or i.v. bronchodilators	

types of distributive shock (excessive anesthetic depth, neuraxial blockade), hypovolemic shock or other types of shock. Isolated skin symptoms may occur in chronic urticaria patients without hypersensitivity reactions. Isolated angioedema or soft tissue swelling may occur in chronic angioedema patients or be caused by airway manipulation or ACE-inhibitors.

However, the concurrent occurrence of these symptoms significantly increases the likelihood of a hypersensitivity reaction. The immediate hypersensitivity clinical consensus score (IHCCS) standardizes the interpretation of the clinical presentation[23] and is based on the presence and severity of symptoms in three categories (cardiovascular, respiratory and dermal/mucosal) augmented by additional points granted according to timing and combinations of symptoms. This results in a clinical grading scale which categorizes suspected perioperative hypersensitivity reactions from unlikely (IHCCS < 8) to almost certain (IHCCS > 21). Table III-V display the IHCCS symptom/sign definition, point allocation and interpretation.

Grade 2-4 reactions and grade 1 reactions accompanied by generalized erythema or urticaria should be referred for further investigation. As the clinical context is crucial in POH diagnosis and to calculate the IHCCS, the referring anesthesiologist should provide all relevant information regarding symptoms, anesthetic techniques and timeline of events. Belgian anesthesiologist are advised to use the online survey available on https://www.besarpp.be/en/allergy. The timing of referral is important as the recommended time for testing is 1-4 months after the event[15]. However, earlier testing may be possible if required for urgent surgery and while late testing may negatively impact sensitivity, there is no upper limit for time passed between reaction and testing which precludes investigations[24]. See Garvey et al for a medical algorithm regarding the following diagnostic tests in POH diagnosis[25].

In Vitro Diagnostics

Tryptase

Tryptase is a preformed mediator present in the secretory granules of mast cells and basophils[26]. α- and β-protryptase monomers are released spontaneously at baseline by resting mast cells which results in a baseline serum tryptase level (bST). Following activation, mast cells release additional α-tryptase and β-tryptase homotetramers, as well as α/β-tryptase heterotetramers. During mast cell activation, an acute increase in serum tryptase levels (aST) can be measured, for example by using the FEIA ImmunoCAP technique (available from Phadia Thermo Fisher Scientific, Uppsala, Sweden). The optimal time frame to measure aST is between 30 minutes and 2 hours following the onset of symptoms. While the bST level remains relatively constant for a given individual over time, it exhibits significant variation between individuals. Consequently, it is imperative to

Table III. — Definition of clinical terms as used in the international clinical consensus score for perioperative hypersensitivity[23].

Clinical term	Definition
Hypotension	A fall in systolic blood pressure to <70 mm Hg (at induction or during maintenance of anaesthesia) or by >20% from a previously stable value (during maintenance of anaesthesia)
Severe hypotension	A fall in systolic blood pressure to <60 mm Hg (at induction or during maintenance of anaesthesia) or by >40% from a previously stable value (during maintenance of anaesthesia)
Cardiac arrest	The requirement for cardiopulmonary resuscitation not explained by the surgical pathology, complications of the surgical procedure, co-existing medical problems or drugs, malignant hyperthermia or technical anaesthetic problems
Tachycardia	An otherwise unexplained increase in heart rate of 50% or more from a previously stable value
Bronchospasm	The onset of wheeze on auscultation, any manifestation of otherwise unexplained increased airway resistance, or both
Severe bronchospasm	Bronchospasm associated with SpO2 <85%
Urticaria	A skin rash characterized by raised pink or white raised areas of skin (wheals)
Angioedema	Dermal or mucosal swelling

Table IV. — The clinical scoring system used by the international clinical consensus score[23].

1. Cardiovascular (choose hypotension, severe hypotension or cardiac arrest and then any other items that apply	Points
Hypotension	4
Severe hypotension	6
Cardiac arrest	9
Tachycardia	2
A poor or unsustained response of hypotension to standard doses of sympathomimetics used to treat pharmacological hypotension during anaesthesia (e.g. ephedrine, phenylephrine, metaraminol)	2
A point-of-care echogardiogram showing a hyperdynamic and poorly filled heart	2
Recurrence or worsening of hypotension after a further dose of a drug given before the initial event	1
Cardiovascular confounders (in the presence of hypotension or cardiac arrest choose any that apply)	
Excessive dose of anaesthetic drugs	-2
Surgically induced hypovolemia or relative hypovolemia from prolonged fasting/dehydration	-1
Acute illness predisposing to hypotension	-1
Medications affecting cardiovascular responses during anaesthesia	-2
Neuraxial regional anaesthesia (epidural/spinal)	-1
Onset of hypotension after development of increased peak airway pressure during mechanical ventilation of the lungs	-2
2. Respiratory (choose bronchospasm or severe bronchospasm and then any other items that apply)	
Bronchospasm	2
Severe bronchospasm	4
Recurrence or worsening of bronchospasm after a further dose of a drug given before the initial event	1
Bronchospasm occurring before airway instrumentation (having excluded airway obstruction)	2
Respiratory confounders (in the presence of bronchospasm choose any that apply)	
Respiratory disease associated with reactive airways	-1
Prolonged or multiple attempts at tracheal intubation	-1
Inadequate dose of drugs to obtund airway responses before airway instrumentation	-1
3. Dermal/mucosal (choose any items that apply)	
A generalised rash that is itchy in the awake patient who has not received epidural/spinal opioids	1
Angioedema	3
Generalised erythema	3
Generalised urticaria	4
Dermal/mucosal confounder	
Angioedema in a patient taking an ACE inhibitor	-3
4. Combinations (choose a maximum of 1 item)	
CVS > 2 and RS > 2	5
CVS > 2 and D/M > 2	5
RS > 2 and D/M > 2	5
CVS > 2 and RS > 2 and D/M > 2	8
5. Timing (choose a maximum of 1 item)	
Onset of cardiovascular or respiratory features within 5 minutes of possible IV trigger	7
Onset of cardiovascular or respiratory features within 15 minutes of possible IV trigger	3
Onset of cardiovascular or respiratory features within 60 minutes of possible IV trigger	2
Onset of cardiovascular or respiratory features more than 60 minutes after possible IV trigger	-1

Table V. — Clinical grading scale for interpretation of clinical score for suspected perioperative hypersensitivity reactions[23].

Interpretation	Total (net) score
Almost certain to be an IHR	> 21
Very likely to be an IHR	15-21
Likely to be an IHR	11-14
Possible IHR	8-10
Unlikely to be an IHR	< 8

always assess a paired tryptase sample as the aST level must be interpreted relative to the bST level. bST can be sampled 24 hours after resolution of the symptoms but this is less time-sensitive than aST sampling due to the relatively constant nature of bST levels.

An increase of aST above bST of +20% + 2µg/L has been validated in adults to confirm mast cell activation[27-30]. In children an increase of 0.71µg/L above the baseline is utilised[31,32].

While the reported specificity is high (86-95% in adults and 97% in children), sensitivity is significantly lower (75-78% in adults and 53% in children).

Tryptase has been shown to be more sensitive in IgE-mediated POHs[31,33], but it should be noted that an absence of increase in tryptase does not discriminate between IgE-mediated and non-IgE mediated hypersensitivities (e.g. MRGPRX-2)[34,35].

Other mediators such as histamine have shorter half-lives and are subject to specific preanalytical caveats, which renders them less practical to sample during a hypersensitivity reaction[27].

Specific IgE

The quantification of drug-specific IgE has been demonstrated to be a helpful tool to confirm drug sensitization. However, it is imperative to acknowledge that a confirmed drug sensitization does not necessarily imply that the implicated drug was the causative agent for the observed hypersensitivity reaction, nor does it guarantee the ability to elicit an allergic reaction in the patient[36]. Conversely, the absence of a serologically confirmed drug sensitization does not preclude the possibility of an IgE-mediated hypersensitivity reaction and a non-IgE-mediated hypersensitivity reaction can logically not be detected by sIgE quantification. Currently, sIgE quantification is typically performed using a solid-phase indirect fluorescent enzyme immune assay (FEIA), wherein a substrate is bound to the solid phase and patient serum is added. The remaining serum is then washed away, and an anti-IgE detection antibody linked to an enzyme is added. This antibody will bind to any sIgE that remains. Finally, the enzyme substrate is added, and the signal it creates depends on the amount of sIgE present.

Whilst sIgE quantification appears to be a logical proposition from a mechanistic perspective, it is important to note that the accuracy and interpretation of the results are contingent on several factors. As previously mentioned, sIgE only recognizes a specific part of an antigen, known as an epitope, and different antigens may possess similar epitopes. For example, the serological assessment of sensitization to NMBAs is primarily accomplished through the quantification of sIgE reactivity to tertiary and quaternary substituted ammonium structures, as these are the dominant epitopes of NMBAs[37]. Two such examples of this are sIgE morphine and sIgE pholcodine which can be used to depict suxamethonium and rocuronium sensitization but are not at all indicative for opiate hypersensitivity, a frequent cause of confusion[38]. For the sIgE morphine assessment (in which morphine is bound to the solid phase and patient serum is added as described above) this can be explained by the presence of a tertiary substituted ammonium group (NR3) in morphine's piperidine ring. At physiologic pH, this tertiary amine group becomes protonated (NHR3+) and serves as an epitope for certain IgE antibodies which in vivo can bind the similar quaternary substituted ammonium group (NR4+) present in NMBAs. Despite their in vitro binding of the morphine substrate, in vivo exposure to morphine in the presence of these antibodies does not cause sIgE/FcεRI crosslinking. Hence, despite its name, the sIgE morphine assessment depicts the presence of IgE antibodies which cause NMBA and not opiate hypersensitivity. Furthermore, elevated levels of total IgE have been demonstrated to compromise the interpretation of sIgE results due to non-specific binding of IgE to the solid phase. It should also be noted that sIgE assays are commercially available for only a limited number of compounds relevant to POH, including latex (and its allergenic components), morphine, chlorhexidine, NMBAs, penicillin antibiotics and cefaclor. Some sIgE

assays are available for research use only. The performance of sIgE assays varies between substances and studies with sensitivity ranging from 49% (cefazolin sIgE to total IgE ratio) to 92% (sIgE rocuronium and chlorhexidine) and specificity from 72% (sIgE rocuronium) to 100% (sIgE atracurium)[39].

As with aST, the timing of sampling is of importance when quantifying sIgE. While sIgE can be measured at the time of reaction, a negative result should be repeated after a period of 4-6 weeks[15]. Conversely, sIgE levels are known to decrease over time, particularly sIgE to β-lactam antibiotics and chlorhexidine[39,40].

In an attempt to enhance the specificity of the tests and to counteract the effect of non-specific binding in patients with high total IgE (tIgE), sIgE:tIgE ratios were investigated with mixed results. For example, in the context of β-lactam antibiotics and chlorhexidine (unpublished data), there was an enhancement in diagnostic performance, particularly in terms of specificity[41,42]. However, this observation was not replicated in the case of rocuronium[43]. Consequently, sIgE is not recommended for pre-emptive screening purposes.

BAT/MAT

The basophil activation test (BAT) and mast cell activation test (MAT) are advanced diagnostic in vitro/ex vivo techniques which have been reviewed elsewhere[44-46].

To summarize, the BAT is a method of confirming drug hypersensitivity that involves the flow-assisted analysis and quantification of ex vivo-activated basophils. The BAT is a particularly interesting procedure when sIgE quantification and skin testing yield discordant results or when sIgE is not available for the investigated drug (e.g. opiates, hypnotics). BAT is performed on fresh blood (within 24 hours, preferably within 4 hours) and requires advanced equipment and experienced personnel which restricts routine use to expert centers.

Unfortunately, 15% of patients have ex-vivo non-responsive basophils and in these patients the BAT is inconclusive.

The mast cell activation test (MAT) involves the stimulation of mast cells from mast cell lines including LAD2 cells and/or cultured donor mast cells, either directly (dMAT) or indirectly after passive sensitization with patients' sera or plasma (pMAT). The pMAT has been shown to have several advantages over conventional BAT. It does not require the use of fresh blood, thereby reducing the time sensitivity of the procedure. Moreover, the pMAT uses plasma or serum that can be frozen and shipped to specialized centers. This overcomes the logistical challenges associated with the collection and handling of fresh blood. Secondly, MAT has no non-responders as the responsiveness of mast cells from cell lines and donors can be confirmed in advance.

In Vivo diagnostics: Skin Tests

Skin Tests

Skin testing comprises skin prick tests (SPT) and intradermal tests (IDT). In the SPT, the investigated drug (or a dilution thereof) is applied to the skin of the ventral forearm and then pierced by a lancet. The test is considered positive if after 15-20 minutes a wheal develops with a diameter greater or equal to 3mm surrounded by erythema.

In the IDT, a small volume (0,2mL) of the investigated drug is injected directly into the ventral forearm skin creating a bleb. The European Academy of Allergy and Clinical Immunology (EAACI) recommends considering the IDT positive if a wheal develops with a diameter at least 3mm larger than the initial bleb[15]. Another potential cutoff is an absolute diameter equaling or exceeding 5mm (for anesthetics) or 8mm (for NMBAs) or a doubling of diameter of the initial bleb[19]. An IDT should only be performed after a negative SPT.

Skin tests are considered the primary investigation in POH diagnosis due to their practical feasibility as an in vivo investigation[15]. However, it should be noted that all drugs have the potential to cause local irritation if not sufficiently diluted, which may consequently impact the specificity of the results. Therefore, it is essential that they are diluted to a standardized non-irritant concentration (NIC). Conversely, as skin tests at concentrations below NIC differ significantly from the exposure preceding the POH reaction (i.e. typically a large intravenous bolus), skin tests do not possess perfect sensitivity. The establishment of the true positive and negative predictive value (PPV and NPV, respectively) is challenging, as this would necessitate the re-exposure of patients with a positive skin test (for PPV) or the performance of a full-dose drug provocation test (DPT) for patients with a negative skin test (for NPV). The former entails unacceptable risk to patient safety, as most of these patients will have a true hypersensitivity. The latter has long been considered unfeasible, especially for hypnotics and NMBAs.

In Vivo diagnostics: Drug Provocation Testing

Rationale

Despite our best efforts and the numerous advances in the field of POH diagnosis, the current diagnostic process, which is based on the interpretation of

the clinical picture in combination with in vitro (tryptase, sIgE, BAT/MAT) and in vivo (skin test) investigations, fails to identify the causative agent in 30% of POH cases[8,9].

DPT has been shown to detect -but not discriminate between- both IgE-mediated and non-IgE-mediated hypersensitivity reactions and full-dose DPTs are expected to possess near-perfect sensitivity and specificity. Besides reliably identifying the culprit, it can also establish safe alternatives. For these reasons DPT has emerged as the gold standard for investigating general (non-perioperative) drug hypersensitivity[47]. In the context of POH, however, the implementation of full-dose DPTs has historically been limited due to the potent effects of anesthetic agents, the perceived high risk nature of the procedure, and the necessity for close cooperation between allergologists and anaesthetists[19,48]. A worldwide survey conducted in 2019 revealed that routine DPT was performed in only two centers, while just 25 centers reported occasionally DPT procedures[49]. The indications for DPT, the drugs tested, the doses used, the responsible practitioner (allergologist, anesthesiologist, nurse) and the setting (clinic, operating room, recovery, intensive care unit) varied strongly between centers. A number of different philosophies can be distinguished: one center administers a full-dose of the drugs used in the index reactions (index drugs) while others only administer 1/10th of the dose. Another reported approach involves the administration of either a 1/10th or a full-dose of a presumed safe alternative to the drugs used in the index reaction.

Consequently, it is crucial to investigate the safety of both partial- and full-dose DPTs and DPTs with alternative drugs and index drugs. Furthermore, it is important to ascertain whether DPTs contribute to the diagnostic investigation and whether full-dose DPTs are more informative than partial-dose DPTs.

The paucity of research in this area, with only four studies published thus far, underscores the need for further investigation to address these crucial questions.

Asserhøj reported performing DPTs with propofol in 133 patients of which four were positive (symptoms similar to index reaction)[16]. DPTs were performed for all index drugs with the exception of NMBAs. The propofol DPT comprised a three-step titrated administration up to a maximum dose of 10 mg propofol. No adverse effects were reported.

Melchiors, also affiliated with the Danish Anaesthesia Allergy Center, reported conducting 49 DPTs with index NMBAs, of which a single was positive (the reaction was not described)[50]. The DPTs were performed in three ten-fold steps up to a fixed maximum dose of approximately 10-15% of the full therapeutic dose (e.g. 5mg rocuronium). The administration of the final dose was performed by an anesthesiologist over 5 to 20 minutes. No NMBA (side) effects were observed at doses of 1/1000th and 1/100th, but at the highest dose most patients experienced transient visual disturbance and two patients reported transient impaired tongue movement. No cases of respiratory distress or other severe adverse effects were observed.

Van Cuilenborg performed nine DPTs with index NMBAs (rocuronium 7, cisatracurium 1, succinylcholine 1)[51]. DPTs were performed on an awake patient cohort using a three-step protocol, with a fixed highest dose corresponding to approximately 10-15% of the full therapeutic dose. One DPT was deemed potentially positive on the basis of intermittent stridor following the administration of the lowest dose of rocuronium. All eight patients with negative DPT reported mild side effects including diplopia, ptosis, dizziness, slurred speech and difficulty closing the mouth from the second dose (approximately 5% of the full-dose) onwards. These side effects were well tolerated and no respiratory difficulties or other serious adverse effects were noted.

Tornero Molina reported on 29 patients who received full-dose DPTs with all index drugs (with negative ST) or an alternative (if skin testwas positive)[52]. The question of whether DPTs were performed systematically or sporadically remains unresolved, given that the 29 patients were included over a 10 year period. DPTs were performed by administering increasing doses starting with 1/8 or 1/4 of the total dose every 15 minutes. Patient were intubated during DPTs with remifentanil and NMBAs and in cases of severe index reactions with bronchial symptoms or glottis oedema or the need for cardiopulmonary resuscitation. Endotracheal intubation was performed after inhalational induction with sevoflurane and local anesthesia of the airway with lidocaine. One out 28 propofol DPTs was positive at a dose of 50mg. Out of 23 fentanyl DPTs, one was positive. The same patient was the only patient out of five with a positive DPT for remifentanil (doses not specified). All 23 DPTs with rocuronium were negative and no other NMBAs were tested. From the evidence that is available, albeit limited, it would appear that DPTs even with index drugs at full-dose, are safe when performed in highly specialized centers. In some cases hypersensitivity is only identified at higher doses. As previously mentioned, the utilization of DPTs as the reference test enables the evaluation of the true NPV of conventional diagnostic

modalities. In the past, attempts to establish the NPV of conventional testing for anesthetics were made through retrospective analysis of subsequent re-exposures[53-55]. However, anesthesiologists often decide not to re-administer NMBAs used during the index reaction, especially if no causative agent was identified. This introduces a significant bias in the retrospective analysis, as this group (no culprit identified, NMBA not re-exposed) is at the highest risk of containing false negatives as NMBAs are the most frequent cause of POH in our region. In order to establish the NPV for conventional testing, a prospective approach is required in which all patients are challenged with index drugs after negative conventional testing (Table VI).

Current Guidelines

Presently, the European Academy of Allergy & Clinical Immunology (EAACI) recommends the utilization of DPT[47]:

- To exclude hypersensitivity to the suspected culprit drug when the history is non-specific or considered at low or intermediate risk of drug hypersensitivity. Removing the drug allergy label (delabeling) is especially indicated in allergy to penicillin as part of antibiotic stewardship and reducing antibiotic resistance
- Cross-reactivity testing to find a safe alternative drug (from same or related drug group): in cases where drug skin tests/IgE/Basophil activation tests or DPT with the culprit drug is positive or not indicated, for example, due to severe reactions and high risk of allergy. Potentially safe alternative drugs should be identified on negative skin tests prior to DPT
- To establish a robust diagnosis in the event of a history suggestive of drug allergy, but where other tests have been inconclusive or unavailable
- When several drugs have been taken at the same time, to demonstrate tolerance to classes of drugs other than the identified culprit drug

In its risk stratification this guideline classifies anaphylaxis or urticaria within 1h of drug exposure as high risk. Consequently, virtually all POH reactions are categorized as high risk, for which the guideline advises full-dose DPTs to be performed with a minimum of three steps in a highly specialized center. In the case of anaphylaxis, the initial dose should not exceed 1/100th of the full therapeutic dose and the guideline recommends a minimum interval of 30 minutes between the doses, albeit without making distinctions between routes of administration.

Finally, the guideline recommends a minimum of one to two hours of observation following the administration of DPT, as severe reactions have been documented to occur within this time period.

Implementation

Presently, a systematic full-dose DPT with anesthetic index drugs has been implemented at the Antwerp University Hospital for more than two years. The establishment and maintenance of expertise is achieved through the performance of over 30 DPTs with anesthetics per year with close collaboration between allergologists and anesthesiologists within our highly specialized POH center. DPTs are only performed following a comprehensive work-up with skin tests, sIgE and BAT/pMAT where relevant. All DPTs are administered at an individualized, weight-based full-dose as some reactions only occur at doses greater than 1/10th (unpublished data). All DPTs are performed with index drugs unless skin testing or BAT was positive. In accordance with the EAACI guideline we avoid DPTs with the most likely culprit (usually an NMBA) in grade 4 reactions if all previous investigations were negative (i.e. no alternative culprit(s) was(were) identified).

In the event of an index product testing positive in skin testing/BAT, an alternative drug that has tested negative in the same test is used for DPT. All DPTs involving anesthetics are directly supervised or performed by a specialized anesthesiologist.

DPTs involving NMBAs commence in an awake state with doses up to 1/10th of the therapeutic dose calculated based on the patient's individual weight. Higher doses are administered under general anesthesia with mechanical ventilation. In the event that an inhalational agent was utilized during the index reaction prior to the onset of symptoms, it is considered a potential culprit and should not be used to maintain anesthesia during NMBA

Table VI. — Published or reported series of drug provocation tests. DPT = drug provocation tests.

Author	Patients (n)	Index or Alternative	Investigated drug(s)	Fraction of full therapeutic dose (%)	Positive DPTs (n)	Adverse events
Asserhoj[16]	133	index	propofol	+/- 5-10	4	No
Melchiors[50]	49	index	NMBA	+/- 10-15	1	No
Van Cuilenborg[51]	9	index	NMBA	+/- 10-15	0-1	No
Tornero[52]	29	Index	all involved drugs	100	3	No

DPT. Concomitant exposure to potential culprits such as chlorhexidine or latex is strictly avoided. We observe an interval of one hour between drugs and an observation of one hour after the last administration. It is imperative to note that DPTs can only be considered positive in the presence of objective signs, as a non-negligible proportion of individuals subjected to testing (3%) have reported subjective nocebo symptoms[56]. Our preliminary results (unpublished) indicate that full-dose DPTs with anesthetics can identify the causative agent in a significant group of patients where conventional tests failed to do so.

Conclusion

POH constitutes an unpredictable but significant risk during anesthesia. Following the acute management, an accurate diagnosis is crucial to prevent dangerous re-exposures to the causative agent and to clear other drugs for use in future procedures. The attending anesthesiologist should sample an aST one hour after onset of the symptoms and refer all grade 2-4 reactions and grade 1 reactions accompanied by generalized erythema or urticaria to a center specialized in POH where a full diagnostic work up, including a full-dose DPT, can be performed. When referring, the anesthesiologist should provide detailed and comprehensive information regarding all exposures, symptoms, treatment and a clear timeline of events. Belgian anesthesiologists can do this using an online form on the BeSARPP website (https://www.besarpp.be/en/allergy).

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