Prevention of drug hypersensitivity reactions: pre-screening and premedication

Short title: Prevention of drug hypersensitivity reactions

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ABSTRACT

Drug hypersensitivity reactions (DHR) are heterogeneous in their pathomechanisms, clinical presentation, severity and outcomes. Novel DHR mechanisms, phenotypes and endotypes have been described. The key to prevention from further exposure to the culprit drugs involves correct identification of the putative drug through a combination of *in-vitro* and/or *in-vivo* tests, accurate drug allergy labelling and reporting, and electronic decision support systems within electronic medical records to prevent future accidental prescribing. Pre-screening and premedication, the focus of this review, may be a useful adjunct to preventive measures in certain situations. Following an index iDHR, pre-screening may be useful in perioperative anaphylaxis, iodinated (ICM) and gadolinium-based contrast media (GCM) where the culprit and potential alternative agents are skin tested. In certain non-immediate DHR, pharmacogenomic pre-screening may be used prior to prescribing high-risk drugs (e.g. carbamazepine and allopurinol) where specific HLA genotypes are associated with severe cutaneous adverse reactions. Pre-medication with antihistamine and systemic corticosteroids is another therapeutic strategy to prevent infusion reactions for certain biologicals and chemotherapeutic agents, in cases of perioperative anaphylaxis, ICM and GCM DHR, and clonal mast cell disorders. Rapid drug desensitization may also be used to induce temporary tolerance in situations where there are limited alternative drugs.

Key words: Anaphylaxis, desensitization, pharmacogenomic testing, Stevens Johnson syndrome, toxic epidermal necrolysis.

Abbreviations Used

ADA	Anti-drug antibodies
BA	Biologic agents
BTR	Breakthrough reactions
CRS	Cytokine release syndrome
DHR	Drug hypersensitivity reactions
DRESS	Drug reaction with eosinophilia and systemic symptoms
GCM	Gadolinium based contrast media
HLA	Human leukocyte antigens
Immunoglobulin	Ig
ICM	Iodinated contrast media
IL-6	Interleukin-6
iDHR	Immediate drug hypersensitivity reaction
niDHR	Non-immediate drug hypersensitivity reaction
NK	Natural killer
NMBA	Neuromuscular blocking agents
NSAID	Non-steroidal anti-inflammatory drugs
RDD	Rapid drug desensitization
SCAR	Severe cutaneous adverse reactions
sIgE	Specific immunoglobulin E
SJS	Stevens Johnson syndrome
TEN	Toxic epidermal necrolysis
TNF	Tumour necrosis factor

Introduction

Drug hypersensitivity reactions (DHR) are heterogeneous in their pathomechanisms, clinical presentation, severity and outcomes.[1,2] Severe cutaneous adverse reactions (SCAR) e.g. Stevens Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) are potentially life-threatening niDHR (non-immediate drug hypersensitivity reaction) associated with a high risk of morbidity and mortality.[3,4] Anaphylaxis to a variety of drugs[5] including beta lactam antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), perioperative anaesthetic agents, chemotherapeutic agents and biologics are increasingly recognized to be mediated by a variety of mechanisms not limited to immunoglobulin (Ig)E.[6] Prevention from further exposure involves correct identification of the putative drug through *in-vitro* and/or *in-vivo* tests,[7] accurate allergy labelling and reporting, and electronic decision support systems within electronic medical records[8] to prevent future accidental prescribing. In this review, we focus on the roles of pre-screening and pre-medication in the treatment and prevention of future DHR.

Novel mechanisms of drug hypersensitivity reactions

Gell and Coomb's classification categorizes hypersensitivity reactions (HSRs) into four subtypes (Type I-IV) according to the type of immune response and the effector mechanism responsible for cell and tissue injury:[9]

This classification has some limitations in clinical practice as HSRs to novel drugs such as chemotherapeutic and biological agents (BA) may involve other mechanisms.[6] Apart from modulating the immune system, these are potentially immunogenic drugs leading to the formation of specific anti-drug antibodies (ADA) that may cause HSRs. For example, IgE-mediated allergy may occur in a "non-classical" manner at the first administration of

cetuximab,[10] rituximab[11] and taxanes.[12] This is because patients may have pre-existing antibodies specific to the drug, due to sensitization through tick bites (in the case of cetuximab) or through shared epitopes (in the case of rituximab and taxanes). The mechanism underlying cetuximab-induced anaphylaxis has modified our concepts about IgE antibodies against carbohydrates, not considered pathogenic previously.

Patients reactive to some monoclonal antibodies or other chemotherapeutic drugs have positive skin tests to the specific drug or detectable serum drug-specific IgE. [13,14] However, BA such as infliximab, natalizumab and adalimumab are also able to induce the development of IgG ADA that directly activate basophils and neutrophils (via FcgammaRII) and indirectly (via release of anaphylotoxins) through mast cells.[15,16] IgG-mediated reactions, that occur after at least one drug administration, may be clinically indistinguishable from IgE-mediated events. The distinction between IgE and IgG mediated reactions is that skin prick tests are negative for IgG mediated reactions. BA and chemotherapeutics may induce HSRs in an antibody-independent mechanism, such as cytokine release syndrome and complement activation (for aggregates or additives such as lipid excipients). These types of reactions usually occur at the first/second drug administration, are usually self-limiting, but could clinically overlap with IgE and IgG-mediated reactions. Thus novel drugs may induce HSR through novel mechanisms, increasing the need for precision in the diagnosis and prevention of DHR.[17] Of note, Pichler had already proposed, in 2006, a novel and specific classification for adverse drug reactions to BA[18] including five types of adverse side effects: -alfa (cytokine release syndrome),- beta (hypersensitivity), - gamma (immune or cytokine imbalance syndromes), - delta (cross reactivity) and -epsilon (non-immunological side effects).

More recently, a classification of immediate HSR based on phenotypes, endotypes and biomarkers has been proposed, applying a precision medicine-like approach to drug allergy.[19] Phenotype may be defined as the set of observable characteristics, including the timing of onset, the symptom spectrum and severity, and the exposure pattern. Endotype refers to the effector cells and molecules involved in the HSR. The same phenotype of reactions can be sustained by different endotypes. In addition, a drug may induce HSR via different mechanisms that in some patients may co-exist (overlapping endotypes). Biomarkers, represented by objectively measurable *in vivo* and *in vitro* parameters include skin testing (prick and intradermal test, patch test), serum drug-specific IgE, basophil activation test with the evaluation of surface markers of basophils activation (CD63 and CD203), tryptase and in some cases cytokines (interleukin-6 [IL-6], tumour necrosis factor [TNF]). The evaluation of biomarkers useful for the identification of underlying mechanisms is key in assessing the feasibility of drug provocation test and of desensitization to prevent further reactions in patients without any alternative therapy.

Pre-screening

Perioperative anaphylaxis

In patients without a relevant history of a previous reaction, European Academy of Allergy Asthma and Clinical Immunology (EAACI) guidelines do not recommend routine preoperative testing for sensitization to any drug(s) or product(s) used in anesthesia.[20,21] A thorough history taking for perioperative reactions remains key to diagnosis. The incidence of perioperative anaphylaxis is reported to be around 1:10,000 [22] to 1:20,000 [20]. Prospective studies suggest a higher incidence of 1:1480 [23] to 1:3180 [24] and Savic et al. even indicated that 1:353 procedures could meet the criteria of a potential perioperative anaphylaxis,

suggesting a potential underreporting or referral bias.[25,26] This low incidence does not justify pre-operative allergy evaluation in all patients.

The predictive values of allergy tests, in particular *in vitro* tests in the general population are unknown and false positive or false negative results could negatively influence anaesthesia, the procedure, or its timing. The sensitivity for IgE-mediated reactions varies. Specific IgE (sIgE) determination is only available for a limited number of perioperatively used drugs (succinylcholine, rocuronium, atracurium, chlorhexidine, latex, ethylene oxide, morphine, cefazolin in the research context)[27] and are inadequate to predict non-IgE-mediated reactions. Moreover, studies indicate that sensitization to ammonium epitopes, as a marker for sensitization to neuromuscular blocking agents (NBMAs), can be as high as 5% to 10% in the general population[21] and argues against screening in the general population.[28] In addition, patients with positive sIgE but negative skin tests for certain NMBAs have been reported to successfully receive this specific NMBA.[29] Specific IgE values for cefazolin, currently only available in a research context, were demonstrated to be similar in cefazolin allergic patients compared with exposed controls, although a ratio of specific over total IgE of 1.42×10^{-3} had an improved sensitivity and specificity (of 49% and 94% respectively)[27] Sensitivity and specificity of chlorhexidine sIgE was 94.7% and 90.1% respectively for a receiver operating characteristic analysis optimized threshold of 0.20 kUA/L,[30] indicating substantial false negative and positive results might arise from routine screening. Thus the determination of specific IgE should not be applied in isolation and performed as a pre-emptive screening tool in the general population. It should only be embedded in an allergy workup in patients with a prior reaction.[28] These specific IgE tests are not widely available in the United States.

Pre-screening for perioperative anaphylaxis includes a pre-operative questionnaire that aims to identify relevant pre-existing allergies (including latex).[20] In addition, a history of an unexplained perioperative anaphylaxis is considered an important risk factor for a future event and should always prompt an allergy workup.[31] A baseline serum tryptase should be drawn after any episodes of perioperative anaphylaxis. Secondary prevention using skin testing with all perioperative agents (including disinfectants, relevant excipients) given before the reaction, with or without additional *in vitro* tests (sIgE determination and/or basophil activation testing) and drug provocation tests where appropriate, are recommended by allergy practice guidelines.[20,32,33,34,35] Such a workup aims to identify potential culprit(s), cross-reactive molecule(s), and provide safe alternatives using an evaluation of all potential causes. The negative predictive value of an allergy workup for perioperative anaphylaxis is high and estimated to be around 96%,[36,37,29.38] although large series are awaited. Cases of repeat anaphylaxis were demonstrated to be due to incomplete referral information,[38] underlying clonal mast cell disorder,[37,38] or accidental re-exposure as shown for chlorhexidine in up to one-third of allergic patients. [39] Routine screening for underlying clonal mast cell disorders, associated with a higher risk for severe perioperative reactions to either specific and/or non-specific triggers,[32,40] is not recommended. However, cases experiencing NMBA-induced anaphylaxis despite negative skin testing for NMBAs have been reported[36,41] indicating the need for continued vigilance, including consideration of IgE-independent anaphylactic reactions mediated through activation of the mast cell receptor Mas-related G-protein coupled receptor member X2, MRGPRX2 False negative skin tests at first evaluation or re-sensitisation have been put forward as an explanation. Whether additional drug provocation testing for NMBA, the current 'gold standard' in a drug allergy workup, would also apply to patients with negative skin testing for NMBA, remains to be determined.[42] Drug provocation testing for NMBAs is carried out in a few highly specialized centres, up to 1:10 of the therapeutic dose.

This is limited by the sensitivity of the drug provocation test at this dose and risk of requiring mechanical ventilation at higher doses. Thus, most centres would for practical purposes defer the use of the skin test negative NMBA until the next surgery requiring anaesthesia.

Iodinated and gadolinium based contrast media

Radiocontrast media may be iDHR and niDHR, with iDHR, being further classified into non-IgE and IgE-mediated reactions.[43,44,45] The latter constitutes a minority of iDHR, especially those with a severe clinical presentation.[46,47,48,49]

Routine pre-screening using intradermal skin testing for RCM hypersensitivity without any history of DHR was found not be to be useful.[50] Currently, primary prevention via screening for potential iDHR and niDHR after iodinated contrast medial (ICM) or gadolinium based contrast media (GCM) using *in vitro* or *in vivo* tests is neither advised nor possible. In patients who have experienced a DHR after ICM, skin testing has been demonstrated to have a high negative predictive value, around 93%, mostly for iDHR and less for niDHR.[47,49,51,52,53] Pre-screening for RCM DHR includes a questionnaire.

Pre-prescription pharmacogenomic screening

Long before the classification of DHR phenotypes-endotypes-biomarkers,[6,54] many pharmacogenomic studies had revealed strong associations between SCAR and genes encoding human-leukocyte antigens (HLAs) in drug- and ethnicity-specific patterns.[55] HLA-B*57:01 genotype testing prior to new prescriptions of abacavir, HLA-B*15:02 prior to carbamazepine, and HLA-B*58:01 prior to allopurinol prescriptions[56,57] have become standard of care in some countries in Asia. The cost-effectiveness of pre-testing is dependent on various factors including HLA-gene frequencies, geographical and ethnic differences, cost of the genotype

test, country-specific healthcare financing and subsidy models, and availability of low-cost alternative drugs.[58]

NSAID hypersensitivity reactions have been classified into various phenotypes including NSAID exacerbated respiratory disease (NERD), NSAID exacerbated cutaneous disease (NECD), and NSAID induced urticaria angioedema (NIUA).[59] More than 100 genetic variants have been identified in association with NERD, the majority mediated by single nucleotide polymorphisms (SNPs) of genes that regulate mRNA and protein expression responsible for prostagladin and leukotriene metabolism e.g. *LTC4S*, *ALOX5*, *CYSLTR1*, *CYSLTR2*, *TBX*, *EP2*, and *COX2*. Epigenetic mechanisms e.g. dysregulation of CpG methylation has been shown to play a role in NERD pathogenesis. However, a wide variety of different biomarkers in serum, urine, sputum, nasal polyps have been shown to be associated with NERD alone, making endotype-genotype correlations challenging.[59,60] Pre-screening is currently impossible.

Immediate reactions to beta-lactam antibiotics have to date been found to be associated mainly with the IgE pathways (IL13, IL4R, LGALS3, and NOD2) and antigen presentation (HLA-DRA),[61] although HLA-DRB1∗10:01 has also been found to be a risk factor for immediate DHR (iDHR) to penicillins.[62] Thus, much more remains to be known before pharmacogenomics and endotyping can be used to correlate with different phenotypes of a variety of DHR. Current studies have not supported avoiding beta-lactams in individuals with a family history of beta-lactam allergy.

Pre-medication

The Joint Task Force on Anaphylaxis Practice Parameters 2020 using the GRADE methodology conditionally recommends that:[35]

- Evidence supports a role for antihistamine and/or glucocorticoid premedication in specific chemotherapy protocols
- Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication in patients receiving low- or iso-osmolar contrast material to prevent recurrent RCM anaphylaxis.

Premedication for infusion reactions for biologicals and chemotherapeutic agents

Premedication with antihistamines, acetominophen and corticosteroids is a common practice to prevent infusion reactions in the majority of monoclonal antibodies, especially if intravenously administered, with no impact on the efficacy of the drug itself. Premedication is also included in some desensitization protocols. Dexamethasone is the most frequently used corticosteroid in the prevention of chemotherapeutic agent-induced HSR, due to its potency, long duration of action and antiemetic function; together with diphenhydramine, the most commonly employed histamine-1 (H1) receptor antagonist for the prevention of hypersensitivity reactions. Cetirizine appears to be a viable substitute for diphenhydramine for the prevention of infusions reactions with cetuximab, paclitaxel, and rituximab infusions in adults, although confirmatory prospective studies are needed.[63]

The combination of corticosteroid and antihistamine seems to induce fewer reactions overall and fewer severe infusion reactions, at least for some products such as cetuximab. [64] However, the optimal prophylaxis and its efficacy depends on the nature of the event and its underlying mechanisms. Premedication with corticosteroids and antihistamines at commonly used doses

is not sufficient to prevent the ADA-mediated hypersensitivity reactions, especially if ADA belongs to the IgE isotype e.g. first dose cetuximab-related reactions. High dose of intravenous corticosteroid did not consistently prevent HSR in patients with antibodies to infliximab.[64,66,67]

Premedication may prevent or dampen inflammatory reactions, such as cytokine release syndrome (CRS) induced by monoclonal antibodies used in cancer therapy.[68] A protective role of anti-tumour necrosis factor alpha agents towards CRS induced by rituximab and muromonab has been reported in small oncology case series.[69,70] The value of premedication may decrease after the first or second infusion for those drugs that are more frequently complicated by infusion reactions at the first or second dose. Discontinuation of premedication in paclitaxel-treated breast cancer patients who have not experienced a HSR with the first two doses of the chemotherapeutic drug, is not associated with increased rate of reactions and related rescue medication use during subsequent infusions.[71] Similarly, a recent observational study suggests that premedication with antihistamines may not be necessary after the second infusion of cetuximab if patients did not develop any symptoms with the first two infusions.[72]

Paclitaxel and the semisynthetic taxane docetaxel associated immediate infusion reactions, usually during first or second exposure,[71] are markedly reduced to 2-10% by premedication with corticosteroid and H1/H2 antihistamine.[73] The high proportion of immediate HSRs was supported by the complement activation property of Cremophor EL and polysorbate 80, solvents of paclitaxel and docetaxel, respectively.74,[75] However, approximately 1-2% of patients had serious immediate HSR despite premedication. Majority of the patients successfully resumed taxanes with increased premedication and slower rates of infusion or graded challenge, while few patients had more severe HSR, including death.[76]

Thus the modified strategy for premedication (with reduced doses of dexamethasone and/or antihistamines or without any dose) upon the first two infusions, allows us to avoid unnecessary drug administration, steroid-related adverse effects, and potential medication errors with multiple sequential drug administrations. Whether similar strategies can be used safely for other monoclonal antibodies and chemotherapeutics needs to be studied further, given the heterogeneity of infusion reactions.

Perioperative anaphylaxis

There is no evidence supporting the use of premedication with antihistamines or corticosteroids to prevent perioperative anaphylaxis.[20,33,35,77] It is generally accepted that antihistamines or corticosteroids will not mitigate IgE-mediated reactions.[78] Although evidence is only indirect,[79] guidelines indicate the use of H1 antihistamines can be considered[20]or recommended[34] in cases where non-allergic histamine release is suspected. Slower administration of incremental doses of drugs associated with non-allergic histamine release such as opioids, NMBAs, vancomycin has also been proposed.[33] No evidence favouring premedication with a single dose of corticosteroids for preventing immediate hypersensitivity reactions was found.[20] Finally, in cases with ethylene oxide allergy, known to be difficult to completely avoid, premedication with antihistamines, corticosteroids and omalizumab has been reported to be successful.[81] The mainstay of prevention of perioperative anaphylaxis remains careful evaluation of prior unexplained perioperative anaphylaxis, and proper avoidance in case of an allergy (especially for potential 'hidden' allergens such as chlorhexidine or excipients).

Iodinated contrast media

Premedication before ICM administration has been used for decades although the evidence for its efficacy is almost absent. The rationale stems from the ability of ICMs to directly (without

IgE) mediate basophil and mast cell degranulation.[81,82,83] The incidence was higher with the use of high-osmolar ionic monomers that have been abandoned, compared with the current low-osmolar non-ionic ICMs.[82] Premedication with H1- and/or H2-antihistamines could mitigate these histamine-mediated adverse effects. Corticosteroids exert an anti-inflammatory effect on various cells, including mast cells.[84] Most studies evaluating premedication in ICM-mediated iDHR using corticosteroids, H1-, H2-antihistamines, ephedrine, alone or in combination have methodological concerns.[85] Only two randomized, double blind, placebo controlled trials have been performed.[86,87] Bertrand *et al.* evaluated hydroxyzine 100 mg versus placebo 2 hours before (a currently abandoned) ICM in patients without a prior iDHR, demonstrating a reduction of iDHR from 12.5 to 1% ($p<0.0001$).[86] Lasser *et al*. reported a reduction in iDHR using methylprednisolone 32 mg at 12 hours and 2 hours before ICM administration compared with placebo (1.7% versus 4.9%, $p=0.005$). However, no significant reduction in patients experiencing moderate to severe iDHR was observed and in those with a prior iDHR, no difference was reported.[87] Premedication has not been shown to reduce the incidence of moderate to severe reactions or reaction-related deaths, and there is no evidence that premedication reduces incidence of iDHR in patients with a prior severe iDHR.[88] None of these studies included prior skin testing, as recommended currently by the EAACI. [89]

Guidelines no longer support the routine administration of glucocorticoids and/or antihistamines to prevent anaphylaxis in patients with prior ICM DHR, [35] but recommend allergy evaluation and identify safe alternatives in patients at risk,[90] or to consider premedication in the absence of alternatives although evidence for efficacy is lacking in these high-risk patients.[91] The side-effects of premedication with first generation H1 antihistamines and corticosteroid,[92,93] delay in radiological diagnosis and prolonged hospitalization needs to be weighed against the benefits.[94]

Changing the ICM that resulted in the initial iDHR within the same class has been shown to be more effective than premedication in high-risk patients.[95,96] and has been included as a potential strategy in the ACR guidelines 10.3.[91] However, the evidence is weak given the retrospective nature of the studies, absence of randomization and absence of prior allergy evaluation. Moreover, it has been demonstrated that patients with immediate skin test positivity for the index ICM often have one or few of other ICMs which skin test positive. Alternative ICMs which are skin test negative are often tolerated , [46 ,47,51,85] hence changing the type of ICM is an option. [97]

We advise an elective allergy workup in those with a moderate to severe DHR to identify an immediate or non-immediate allergy, potential cross-reactive ICMs and safe alternatives [47,49,51,89,97]. A list of potentially cross-reactive ICMs for iDHR and niDHR and a diagnostic algorithm has been published by the EAACI.[89] For those in whom skin testing does not show evidence of an underlying allergy, an empirical change of ICM might further reduce the likelihood of recurrence of an iDHR, [89,95,96]although additional prospective studies are warranted. For those with a prior iDHR who require urgent ICM administration, premedication could be used if no valid alternatives are available and the investigation is deemed necessary, along with vigilance for a potential severe repeat reaction. The role of premedication in niDHR has not been evaluated and in case of proven ICM-mediated severe niDHR strict avoidance remain mandatory.

Gadolinium based contrast media

The incidence of GCM-induced DHR is considered lower compared to that observed with ICMs. GCM are not histamine-releasers in vitro. Mostly immediate isolated cutaneous

reactions occur, although anaphylaxis and niDHR have been reported.[45] Premedication in primary prevention is considered unnecessary. However, similar to ICM, varying approaches exist for patients who have experienced a reaction.

Firstly, premedication using H1 antihistamines and corticosteroids, analogous to protocols used for ICM premedication have been applied in GCM-induced DHR. However, breakthrough reactions despite premedication occur frequently and a recent meta-analysis suggested an incidence of 39% (95% confidence interval, 25-48%).[98] In the same meta-analysis, no conclusion could be made regarding the effect of switching to an alternative GCM or using skin testing to prevent repeat reactions due to insufficient data. Empirical switching to an alternative GCM prior to readministration with or without premedication evaluated recently in a single-arm observational study[99] in 26 patients with mild to moderate DHR reduced the expected rate of breakthrough reactions to 3.7% (no control group was evaluated). No difference within those receiving no H1 antihistamine (diphenhydramine), or H1 antihistamine and corticosteroid premedication was observed, although groups were not proportional or randomized.

Secondly, evaluation for GCM-induced DHR via skin testing to identify subgroups with an underlying GCM allergy is being performed, largely by allergy specialist groups. In the largest series to date, 18 (13.6%) of 132 patients with a potential GCM-induced DHR had positive skin tests, with most being diagnosed with an iDHR (95%).[100] All 6 patients with positive skin tests who were re-exposed to a negative skin-tested GCM tolerated the latter.

Premedication in patients with GCM-induced DHR is associated with frequent breakthrough reactions. Larger studies combining prior allergy workup, empirical switching to alternative

GCM and/or premedication are needed. For the present, a similar approach to ICM DHR is used for GCM DHR.

Clonal mast cell disorders

Patient with clonal mast cell disorders are at increased risk of anaphylaxis, theoretically during certain medical procedures, general anesthesia and radiocontrast media administrations. The value of premedication is insufficiently studied in this population and there is no evidence to support or refute premedication with antihistamines and corticosteroid prior to anesthesia in mastocytosis patients. Many groups therefore advise premedication in this condition.[40] For ICMs, observational data in mastocytosis are scarce.[40] In 457 compiled mastocytosis patients, 3 (0.6%) experienced an ICM-mediated iDHR of which one was anaphylaxis.[101] Conversely, in none of the patients experiencing fatal anaphylaxis after ICM exposure was mastocytosis identified (although only 8/34 cases underwent a bone marrow evaluation).[102] Hermans *et al*. suggested that mastocytosis patients receiving ICM, do not require premedication unless there is a history of ICM-mediated anaphylaxis or an anticipated high risk for anaphylaxis.[101] However, larger studies are required to evaluate the use or burden of premedication in this specific patient group.

Rapid drug desensitization

Rapid drug desensitization (RDD) or temporary induction of drug tolerance (TIDT) induces a temporary state of tolerance to a medication responsible for HSR. It is performed by gradual introduction of small amounts of medication in divided incremental steps over a short period of time (from several hours to a few days) until the total cumulative therapeutic dose is achieved and tolerated.[103,104] RDD to BA and chemotherapeutic agents is becoming standard of care, allowing a medication-allergic patient to receive the optimal agent particularly for cancers and

rheumatologic disorders where standard therapies have been ineffective, associated with toxicities, or where no better alternatives are available.[105,106]

RDD can be performed in both patients with IgE and non-IgE HSR with similar success, despite different molecular mechanisms of DHR.[104] The principle of RDD is to abolish acute and late phase IgE-mediated activation of mast cell through delivering small, incremental drug doses usually beginning with 1:100,000 – 1/10 of the dose that does not cause nonspecific irritation when administered intradermally; and doubling the dose every 15-20 minutes until the full therapeutic dose is reached.[107,108] The rational for premedication depends on the nature of HSR as well as the immune-inducing and chemical properties of each agent. [109]

RDD has been shown to be an effective and safe method to re-introduce taxanes in patients with life-threatening HSR. A non-IgE mechanism was initially postulated according to the result of nonspecific induction of histamine release from basophils in one study using paclitaxel alone (without Cremophor EL) in a patient with repeated HSR after premedication and slowing the rate, and in healthy controls.[110] However, some of these HSRs may be IgE-mediated through demonstration of positive immunoblot assay and skin test results, although predictive values of these skin test results remain to be verified.[111,112,113] Different protocols to approach taxane HSR have been published; most authors have used skin testing and severity of initial HSRs for risk stratification. To maximize safety, reintroduction of taxanes in high-risk group was initially offered through RDD, with an attempt to decelerate the protocol and resume regular infusion if patients have shown to tolerate RDD very well.[113,114] With a standard protocol for RDD and premedication, approximately one-third of patients or 4-6% of RDD procedures had break-through reactions (BTR), usually with mild or grade 1 severity. Grade 2 or moderate-severe BTRs accounted for 4-6% of all patients receiving RDD. In patients with BTRs, addition of aspirin 325 mg (oral) and montelukast 10 mg (oral) have been shown to be

more effective at minimizing BTRs by inhibition of the synthesis of prostaglandins and blocking the receptor for cysteinyl leukotriene, respectively.[115] These are important mediators secreted by activated mast cells and basophils. However, one study has questioned the benefit of this premedication regimen in taxane RDD, and this needs to be confirmed in a larger sample size.[116]

CONCLUSION

Pre-screening using skin tests and intradermal tests identify the putative and alternative drugs in perioperative anaphylaxis, ICM and GCM iDHR. Pharmacogenomic tests using HLA-genotyping for high-risk drugs for SCAR are drug- and ethnicity-specific with variable cost-effectiveness depending on factors including the country's healthcare financing model and access to less costly alternative drugs. Pre-medication is effective in most iDHR to chemotherapeutic and biologic agents, but not for moderate to severe contrast media, and general anaesthetic agents induced HSR. Desensitization is effective in IgE mediated immune mediated DHR and certain non-immune mediated DHR like some types of NSAID-hypersensitivity reactions.

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Table 1: Pre-screening

Prevention of drug hypersensitivity reactions

- Primary prevention: no role
- Secondary prevention: in individuals with a previous hypersensitivity reaction

Perioperative anaphylaxis

- Evidence supports a role for
    - pre-operative questionnaire: to identify relevant pre-existing allergies (including latex)
    - baseline serum tryptase
    - skin prick and intradermal testing with all perioperative agents (neuromuscular blocking agents [NMBA], opioids, local/ regional anaesthetic agents, hypnotics, benzodiazepines, antibiotics, disinfectants, relevant excipients)
- Evidence is lacking to support
    - *in vitro* tests (specific IgE determination and/or basophil activation testing)
    - drug provocation tests (up to 1:10 of therapeutic dose of NMBA; associated with risks of hypersensitivity reaction and need for mechanical ventilation; for practical purposes, consider deferring the use of the skin test negative perioperative drugs until the next surgery requiring anaesthesia)

Iodinated and gadolinium based contrast media

- Evidence supports a role for
    - pre-procedure questionnaire: to identify exposure and clinical reactions to previous contrast media
    - skin prick and intradermal testing (for the index and alternative agents: high negative predictive value, around 93% for immediate hypersensitivity reactions, less for non-immediate reactions)
    - drug provocation tests (for skin test negative contrast media)
- Evidence is lacking to support
    - *in-vitro tests* (not commercially available)

Pharmacogenomic screening for drugs with high risk of severe cutaneous adverse reactions (SCAR)

- Evidence supports a role for testing (in most countries) for
    - HLA-B*57:01 (abacavir)
    - HLA-B*15:02 (carbamazepine)
    - HLA-B*58:01 (allopurinol)
- Evidence is lacking to support testing for other drugs e.g. beta lactams, non-steroidal anti-inflammatory drugs

Table 2: Pre-medication

Prevention of drug hypersensitivity reactions

- Primary prevention: no role
- Secondary prevention: in individuals with a previous hypersensitivity reaction

Chemotherapeutic agents and biologicals (monoclonal antibodies)

- Evidence supports a role for antihistamine (e.g. diphenhydramine) and/or glucocorticoid (e.g. dexamethasone) premedication in specific chemotherapy protocols e.g. cetuximab, paclitaxel, rituximab

Perioperative anaphylaxis

- Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication in patients with previous perioperative anaphylaxis or first episode exposure to perioperative agents

Radiocontrast media (RCM)

- Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication in patients receiving low- or iso-osmolar contrast material to prevent recurrent RCM anaphylaxis

Gadolinium-based contrast media (GCM)

- Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication in patients receiving GCM to prevent recurrent GCM anaphylaxis

Clonal mast cell disorders

- Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication during certain medical procedures, general anesthesia and radiocontrast media administrations

Table 3 Rapid drug desensitization (RDD) or temporary induction of drug tolerance (TIDT)

Prevention of drug hypersensitivity reactions

- Primary prevention: no role
- Secondary prevention: indicated in individuals with a previous immediate drug hypersensitivity reaction which may be IgE-mediated or non-IgE mediated

Indication

- Evidence supports a role for prevention in hypersensitivity reactions to chemotherapeutic agents and biologicals (monoclonal antibodies) e.g. taxane hypersensitivity reactions

No evidence

- Evidence does not support a role for RDD/TIDT in
    - perioperative anaphylaxis
    - radiocontrast media (RCM) hypersensitivity
    - gadolinium-based contrast media (GCM) hypersensitivity

CME EXAM

MS# & Article title: 21-00296, Prevention of Drug Hypersensitivity Reactions: Pre-Screening and Premedication
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Learning objectives:
1. To clinically correlate the immunological mechanisms with various phenotypes and endotypes of drug hypersensitivity reactions.
2. To understand the benefits and limitation of pre-medications in the prevention of specific types of drug hypersensitivity reactions.
3. To use appropriate in-vivo, in-vitro and pharmacogenomic tests in the prevention of serious systemic drug hypersensitivity reactions.

Questions:

1. Which of the following is the possible source of sensitization for IgE-mediated allergy to rituximab and taxanes?
A. Ammonium epitopes
B. Environmental allergens
C. Shared epitopes
D. Tick bites

Answer: C
Explanation: Pre-existing antibodies specific to the drug may develop from sensitization through shared epitopes for rituximab and taxanes. Environmental allergens and ammonium epitopes are not known to be sources of sensitization.

2. Which of the following is the factor that improves the cost-effectiveness of HLA pharmacogenomic screening for drugs at high risk of severe cutaneous adverse reactions (SCAR)?
A. Low cost of the alternative drug
B. Low prevalence of SCAR
C. High cost of HLA genotype test
D. Treatment of an uncommon medical condition

Answer: A

Explanation: A cost-effective test for genetic screening for SCAR should be one where the alternative drug is low cost, the prevalence of SCAR is high, genotype test is low cost, and the medical condition is common.

3. In the evaluation of perioperative anaphylaxis, which of the following steps is the most important?
A. Basophil activation tests to all disinfectants and excipients
B. Drug provocation tests to skin test negative neuromuscular blockers
C. Pre-screening for relevant pre-existing allergies
D. Routine screening for mast cell activation syndromes

Answer: C
Explanation: All relevant allergies should be pre-screened through a questionnaire or patient interview. Basophil activation tests are not widely commercially available for all disinfectants and excipients. There is presently no role for drug provocation tests for neuromuscular blocking agents which are tested negative. There is no need for routine screening for mast cell activation syndromes.

4. An allergy work-up for iodinated contrast media (ICM) may be helpful in identifying which of the follow?
A. An alternative gadolinium contrast media (GCM)
B. Only non-immediate ICM allergic reactions
C. Patients at low risk for ICM allergy
D. Potentially cross-reactive ICMs

Answer: D
Explanation: An elective allergy work-up for ICM only identifies the culprit and cross-reactive ICM and not alternative GCMs, patients at moderate to high risk (not low risk) of ICM allergy, and both immediate and non-immediate allergy (using delayed intradermal reading).