Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) Perioperative Anaphylaxis Investigation Guidelines

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Introduction

Perioperative anaphylaxis is associated with significant morbidity and mortality. The Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) identified the need for a consistent and evidence based approach to the investigation of patients who have had perioperative anaphylaxis to ensure their safe future management and have published these guidelines to promote this approach.

These guidelines are intended for use by specialists involved in the investigation of perioperative allergy. They have been approved following peer review by members of ANZAAG and are available on the ANZAAG website, http://www.anzaag.com/anaphylaxis-management/testing-guidelines.pdf

These guidelines are based on the best available evidence, which for many of the perioperative agents is based predominantly on expert opinion and requires validation. The use of a standardised approach to testing will facilitate the collection of comparable data from multiple centres enabling validation of the investigative process.

Definition of anaphylaxis

Anaphylaxis is ‘‘a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance’’[1].

General considerations

Skin prick testing (SPT) and intradermal testing (IDT) are the primary tools used for the identification of immediate hypersensitivity reactions. They are both designed to trigger localised mast cell degranulation that is manifest by a wheal and flare response. SPT is most frequently used for investigation of food and aeroallergen allergy. It is not useful for delayed type hypersensitivity testing. IDT is useful for delayed type hypersensitivity testing due to the ability to perform a delayed read[2].

International guidelines for perioperative allergy testing are available which outline performance of SPT initially with a process of escalation to maximal IDT concentrations[3 4]. Fisher described the use of intradermal testing without preceding SPT to identify the

causative agent in anaphylaxis to anaesthetic agents in 1981[5]. Since this time, IDT has been the most common technique used to investigate perioperative allergy in Australasian centres. Reasons for this approach have included the greater sensitivity of IDT compared with SPT[3 4 6] and the poor negative predictive value of SPT for drug hypersensitivity testing compared with IDT. The use of IDT at the outset aims to minimise the occurrence of false negative skin test results and provide optimal guidance for subsequent choice of anaesthetic agents. If SPT is performed and is negative, then the practitioner should always consider performing IDT.

Skin testing by the inexperienced practitioner

Skin testing was developed as a tool to determine the drug or drugs responsible after an episode of suspected perioperative anaphylaxis. It is only in this context that the specificity and sensitivity of intradermal testing has been determined, whilst the positive and negative predictive values are influenced by the history and other tests including serum tryptase and specific IgE. Skin testing was not developed as a screening tool.

The process of testing, an understanding of the factors that might affect the result, the use and significance of positive and negative controls and the interpretation of the history and results requires some degree of experience and knowledge in order for safe recommendations to be made about the future use of drugs.

ANZAAG members may be asked by anaesthetists unfamiliar with skin testing to advise on the use of skin testing in the immediate preoperative period to screen a patient for allergy to perioperative agents. For the safety of patients, ANZAAG does not recommend occasional testing by inexperienced users.

Indications for skin testing

It is recommended that skin testing be performed in all cases with a strong clinical history supporting the diagnosis of perioperative anaphylaxis[7 8]. Skin testing may also be considered in individuals with a less severe immediate hypersensitivity reaction.

Where there is an acute elevation in serum tryptase contemporaneous with an anaphylactic reaction skin testing is recommended. If the clinical picture is strongly suggestive of anaphylaxis skin testing is recommended even in the absence of an elevated tryptase[9].

It is recommended that patients be referred for assessment and testing prior to surgery where there is suspicion of a previously uninvestigated perioperative anaphylactic reaction[10]. This may only be practical when the surgery is elective.

Skin testing is not validated as a screening tool and should not be performed in the absence of a personal history of perioperative anaphylaxis[11].

Contraindications and precautions

Conditions which contraindicate or preclude skin testing

- the absence of healthy skin
- severe dermatographism
- patients who have previously had a severe non-immediate hypersensitivity reaction including, but not limited to, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis or leucocytoclastic vasculitis on histological examination or DRESS (drug reaction with eosinophilia and systemic symptoms)[12]

Relative contraindications or precautions

- recent antihistamine use (see 6.3.1)
- severe asthma
- patients on beta-blockers and angiotensin converting enzyme (ACE) inhibitors
- skin testing should not be carried out on limbs affected by lymphoedema, paralysis or neurogenic abnormalities
- pregnancy

Drugs which may interfere with skin testing results

There are several classes of drugs that might reduce skin reactivity and the cessation of these drugs should be considered prior to testing. These drugs include H1 receptor blockers (antihistamines), H2 receptor blockers, corticosteroids, antidepressants and antipsychotics with antihistamine activity.

H1 receptor blockers (antihistamines)

There is clear evidence that H1 receptor antagonists interfere with skin responsiveness and in most patients these drugs can be stopped prior to skin testing. First generation antihistamines generally have a short duration of action, but newer antihistamines have a much longer half-life. It is recommended that the ASCIA guidelines[2] for cessation of antihistamines are followed (see Appendix 1). In general, cessation of antihistamines one week prior to testing is adequate.

It should be noted that many over-the-counter cough and cold remedies, nasal sprays and eye drops contain antihistamines.

H2 receptor blockers

Ranitidine, famotidine and cimetidine have limited effect on skin reactivity, but this effect might be enhanced with co-administration of H1 antihistamines. Cessation on the day of testing is probably adequate[13].

Antidepressants and antipsychotics with antihistamine activity

Many tricyclic antidepressants including doxepin, imipramine and amitriptyline, and some tetracyclics including mirtazapine and mianserin have a variable antihistamine effect. Antipsychotics (also called neuroleptics and psychotropics) including olanzapine and quetiapine also have antihistamine effects.

Whilst they might interfere with skin reactivity abrupt unsupervised cessation is inadvisable. This must be taken into account in the interpretation of the results if they are not ceased prior to testing.

Topical corticosteroids

The application of topical corticosteroids at the site of testing does have an effect on skin reactivity. They should be ceased one week prior to testing[14].

Drugs that have no effect on skin testing interpretation

Montelukast

Montelukast is a leukotriene receptor antagonist used in the management of asthma. It

blocks the action of the inflammatory mediator leukotriene, and therefore might be expected to impair the response to skin testing.

However, there is little evidence that montelukast interferes with the interpretation of skin tests[15 16] and therefore cessation is not required.

Oral and inhaled corticosteroids

Short and long term systemic corticosteroids do not need to be stopped prior to testing[17]. There is little evidence regarding the effect of inhaled corticosteroids, but as their systemic absorption is limited, there should be little effect on skin testing[13].

Drugs which may increase the morbidity of skin testing

Beta-blockers and angiotensin converting enzyme inhibitors

The rationale for recommending cessation of these drugs is related to the theoretical concern that a severe reaction occurring during testing may be more difficult to treat due to the pharmacological effects of these drugs.

Abrupt cessation of these drugs may predispose to morbidity. The risk of a systemic reaction to intradermal testing is low. On the balance of risk, it is recommended that these drugs be continued.

Minimum facilities required for the performance of skin testing

A number of guidelines outline the steps required for the management of anaphylaxis[18-20]. Although systemic reactions in association with skin testing are rare[21], centres conducting testing must be skilled and equipped to rapidly administer initial treatment measures in the event of anaphylaxis. In accordance with these guidelines, the ability to administer adrenaline intramuscularly is essential. Testing facilities must also be able to deliver intravenous fluids, supplemental oxygen and have sufficient facilities and trained staff to perform cardiopulmonary resuscitation and assist ventilation if required.

Obtaining consent for skin testing

ANZAAG recommends the following topics are discussed when obtaining informed consent from a patient prior to skin testing:

- a description of the test
- the risks of the test
- the risks of not having the test
- an explanation of false positive and false negative results and their implications
- discussion with regards to the medications that can interfere with the results

The patient should have an opportunity to ask questions before giving consent.

Additional consent should be sought for:

- the acquisition and retention of a photographic or video record
- the use of data/information for publication and/or teaching

Procedure

Timing of skin testing

Skin testing is ideally delayed for 4 to 6 weeks following a suspected anaphylactic reaction[3] [6] [22]. Under certain circumstances testing may need to performed prior to this time. If testing is performed prior to 4 to 6 weeks only positive skin tests can be taken into account[3] [22]. There is little published data to provide guidance on early skin testing. The significance of a negative skin test performed prior to 4 to 6 weeks, including results of cross sensitivity amongst neuromuscular blocking agents (NMBAs), needs to be interpreted with caution[22] [23]. If testing is performed prior to 4 to 6 weeks then repeat testing after 4 to 6 weeks may be considered[3].

Preparation of dilutions

Skin testing commonly requires the preparation of multiple dilutions of perioperative agents to ensure the patient is tested to the range of likely allergens to which they were exposed. Ideally, resources would allow that the testing dilutions be prepared, drawn up and labeled in a sterile environment in the pharmacy, with expiry dates for the injections applied

accordingly. However, in the majority of centres there is no provision for this method of preparation therefore the testing dilutions must be drawn up by the practitioner.

Preparation of drug dilutions by the practitioner performing the testing requires that all dilutions must be prepared, labeled and dispensed prior to patient attendance to ensure that multiple dosing cannot occur. All required injections should be drawn up, labeled and capped ready for individual patient use. The testing work surface should be separate from the one on which the dilution bags are stored. Only the drugs for the patient being tested should be on the testing work surface.

Drug stability in solution and the risk of bacterial colonisation must be taken into account. Most anaesthetic drugs including midazolam, opiates and muscle relaxants are suitable for use for up to 24 hours after dilution if stored at less than 25^{o}C. However, it is recommended that propofol be used within 6 hours of dispensing[24]. Amoxycillin mixed with normal saline is reported to be suitable for use for up to 8 hours[24]. On this basis, it is recommended that all drug dilutions used for skin testing are mixed and delivered within 6 hours.

Site of skin testing

The forearm and the back are both appropriate testing sites, with the skin on the back demonstrating slightly larger SPT reaction to allergen, but not histamine[25]. When using the forearm, testing should be performed at least 5cm from the wrist and 3cm from the antecubital fossa[26].

Skin prick testing

Devices

Some devices are designed to prick through a drop of allergen on the skin and some pick up a drop from a bottle and deliver the allergen as the device is pricked through the skin. The former are recommended as more appropriate for drug allergy testing.

Devices can either be designed for 1 allergen at a time and single use, e.g. Stallergenes prick lancet and ALK Spain SPT lancets, or multiple allergens at a time and single use. Single allergen metal lancets produce the most reproducible results, are best tolerated and may be the easiest to use, especially in relatively inexperienced hands [27 28].

Intravenous needles have been reviewed and whilst results are reasonably reproducible and

sensitive there is a higher risk of bleeding and excessive depth of penetration.

Scratch testing is not recommended as it is difficult to standardise the amount of allergen delivered and it requires excessive trauma to perform, increasing the risk of non-specific results. There is also a higher risk of a systemic allergic response.

Technique

1. Apply a drop of the solution to the skin.
2. Pass the pointed end of the lancet through the drop, perpendicular to the skin surface.
3. Apply enough pressure to the skin to cause a depression of 2-3 mm in the skin and hold for 1 second.
4. Position each test at least 2cm apart to reduce interference from adjacent positive tests.

Bleeding should not occur. Each lancet should be used only once.

Some practitioners will prick as each drop is placed on the skin prior to applying the next allergen, some will apply all the solutions and then prick. Either approach is acceptable, however pricking each allergen immediately after application may reduce the risk of spreading if the patient moves.

To reduce the risk of contamination allergen and control solutions should be blotted after 1 minute (e.g. with a tissue) rather than wiped off.

Intradermal testing

Devices

IDT is typically performed using a 0.5 or 1.0 mL syringe with an attached 26 to 30 gauge hypodermic needle[26]. A 29g needle is most commonly used by the authors.

Technique

The needle is directed at an angle of 5-10^0 to the surface of the skin[26 29]. A volume of 0.02 – 0.05 ml of drug is injected intradermally[3 4 7 26 29 30], raising a small bleb measuring 3 to 4mm in diameter[3 7]. Caution must be taken to exclude any air bubbles prior to injection.

Position each test at least 2cm apart to reduce interference from adjacent positive tests[26].

Controls for skin testing

Negative controls are necessary as some people will display dermatographism and react to the physical trauma of skin testing rather than the allergen. This may produce a wheal of substantial size which makes results of skin tests to other substances uninterpretable[2 6]. The negative control should be saline[6 7 12 31].

Positive controls are necessary to demonstrate an appropriate response to histamine release by mast cells. There may be a reduced or absent response if the patient has taken antihistamines or drugs with antihistamine effects or if their skin is non-reactive[2 6]. The positive control should either be histamine 10mg/mL by SPT or morphine 10mcg/mL by IDT[2 3 6 26 32].

Measurement of skin test responses

The histamine skin prick control should be read at 10 to 15 minutes[2]. All other results are read at 15 to 20 minutes[2-4 7 33].

Whilst a positive response often involves a wheal and flare response, only the wheal requires measurement.

There is no single wheal measurement method that is used universally. Methods of wheal measurement include measurement of the longest diameter, the sum of the longest diameter and its orthogonal diameter divided by two (the mean), products of the diameters, planimetry, weighing of tracing paper or cellophane used to outline the wheal and computerised scanning.

ANZAAG consensus is to record the longest diameter of the wheal, its orthogonal (perpendicular) diameter and their mean in millimetres. The mean is the most commonly used measurement of wheal size. Whilst it may be intuitive that the area of the response would be the most appropriate measurement; planimetry, computerised scanning and the weighing of tracing paper or cellophane used to outline the wheal and are not commonly reported. They are technically difficult and/or time consuming.

Standardising wheal measurements will aid future analysis of data collected.

Skin prick test

The positive control must be at least 4mm in diameter[2].

The negative control must be less than 3mm in diameter[2 26].

A result is positive if the wheal is at least 3mm greater than the negative control[2 3 11 12 26].

Intradermal test

A result is positive if the wheal doubles in size or increases by 3mm[3 4 30 34].

If the reaction does not reach the above threshold but it appears to be a more significant reaction than any of the other tested drugs it may be reported as equivocal. It is possible that this is the causative agent. Consideration of the positive and negative controls should be taken into account when making this assessment.

The patient should remain under observation for 40 minutes after the commencement of any test[2].

In vitro testing

Specific IgE testing

Testing of serum for specific IgE (sIgE) antibodies is available for a limited number of perioperative agents.

These tests can be useful particularly when used in combination with the patient history and the results of skin testing but issues with sensitivity and specificity limit their value when used alone. The use of sIgE assays alone as a screening tool is not recommended. To identify which perioperative agent is likely to have caused an episode of anaphylaxis and which perioperative agent or agents may need to be avoided in the future, skin testing should be performed by an experienced perioperative allergy testing centre.

There are a number of sIgE tests that detect antibodies to the quaternary ammonium group found on NMBAs. They have a variety of names such as morphine, pholcodine, suxamethonium and rocuronium sIgEs. It is important to note that a positive morphine sIgE test is a marker of antibodies to the quaternary ammonium component of NMBAs and should not be interpreted to indicate hypersensitivity to morphine.

Basophil Activation Testing

Basophil activation tests have been reported in the literature to aid in the diagnosis of immediate type hypersensitivity to drugs. However, this technique is not freely available and is mostly applicable to research at this time. Further discussion of this test is beyond the scope of this document.

Testing of new perioperative agents

When a new agent is implicated as a possible cause of a perioperative allergic reaction there is a need to determine the concentrations at which it should be skin tested. It is beyond the scope of these guidelines to make formal recommendations about the process for the determination of skin testing concentrations for new perioperative agents. New drugs and agents such as antiseptics and IV fluids that cause perioperative allergic reactions are constantly emerging and the question of testing concentrations needs to be addressed.

All perioperative agents have the potential to trigger both allergic and non-specific (non-allergic) reactions on skin testing. The non-irritating concentration (NIC) has been defined as the concentration at which an agent does not generally cause skin irritation in non-allergic individuals [35]. The NIC cannot be assumed to be the same for all agents, even of the same class. Certain agents (e.g. some NMBAs) are particularly prone to directly trigger mast cell degranulation and as a result the NIC for these agents is often lower than those of other drug classes. When skin testing is performed with more concentrated preparations than the NIC a positive response is likely to be due to irritation and may not represent an allergic response. At concentrations equal to or below the NIC, a positive skin test is likely to represent a true positive skin test rather than non-specific skin irritation[4].

There are published recommendations that explore processes by which the NIC can be determined for new drugs[4 35] that may serve as a guide for practitioners considering testing new agents and these will not be reviewed in detail in this document. The publication of attempts to determine the NIC for new perioperative agents is encouraged to add to the body of available information.

Graded challenge testing

At this time, the gold standard for demonstrating tolerance to an agent which has tested negative on skin testing is graded challenge. This procedure is intended to identify safe agents for use in subsequent anaesthesia, not to confirm causative agents, and should only be undertaken after negative skin testing. Whilst a comprehensive discussion of challenge testing is outside the scope of this document, there are good review articles on this topic which offer guidance to practitioners[36]. Due to the greater risk of reaction, it is recommended that challenge testing be undertaken only in centres experienced in both allergy management and investigation.

Anaphylaxis and specific agents

Neuromuscular blocking agents

NMBAs have been demonstrated to be the most common cause of perioperative anaphylaxis in Australasia[37 38].

Where a NMBA was administered perioperatively, testing must include the specific agent administered at the time of the reaction. Due to a very high degree of cross reactivity[30 39], it is important that skin testing is also conducted for a range of alternative NMBAs. This approach allows determination of the causative drug, identification of cross-reactive NMBAs (which must be also avoided) and those that are likely to be suitable for future use[3].

When a clear culprit is identified, alternative, skin test negative NMBAs are usually, but not invariably, safe[40 41]. False negative results do occur and therefore all NMBAs must be used with caution during subsequent procedures. When a skin test negative alternative has been used safely in a subsequent anaesthetic the patient's documentation should have this information added.

Betalactam antibiotics

An episode of perioperative anaphylaxis will often require the investigation of a betalactam antibiotic. This reflects the recommendation for the use of cephalosporins (particularly cephazolin) for antibiotic prophylaxis in many parts of the world including the New Zealand[42 43] and the Australian[44] antibiotic guidelines. Betalactam antibiotics have been identified as

a common cause of perioperative anaphylaxis[30 45 46]. It is recommended that all antibiotics administered be investigated as part of testing after an episode of perioperative anaphylaxis[11].

Multiple recent articles covering the complexity of investigating betalactam antibiotics are available[11 47-50]. A full review of this issue is beyond the scope of this document. However, given the frequency of betalactam use in the setting of perioperative anaphylaxis, some important general principles are summarised below.

The clinical history is critical in the diagnosis of betalactam hypersensitivity[48]. All testing and results must take into account the clinical context. Immediate hypersensitivity reactions to betalactams can be due to reactivity to the betalactam moiety or the side chain[47 48]. Similarity of the side chains has been established to be an important determinant of cross reactivity between cephalosporins and penicillins[48 49]. Cross reactivity is not predictable on the basis of drug class or generation alone. Testing must include the same antibiotic that was used at the time of the reaction[11 47].

Skin testing remains the most important method for confirming betalactam allergy and clarifying cross-reactivity[47]. European consensus guidelines[47] for specialist centres testing for betalactam allergy and cross reactivity outline a step-wise approach. The initial step recommended is SPT including the major and minor penicillin determinants, amoxicillin and a range of cephalosporins. If negative, SPT is followed by IDT of this drug panel, with increasing concentrations to the NIC to increase sensitivity of the testing. However, there remains an important false negative rate with skin testing alone. Allergy to any of the betalactams can only be excluded after provocation testing with the specific drug that was administered at the time of the reaction. Positive oral provocation after negative skin test has been shown in some studies to occur in almost one third of patients[11].

It is not feasible or necessary to perform the formal protocol described above in all patients who have perioperative anaphylaxis in association with betalactam administration. A practical approach to these patients is to skin test the administered betalactam and the other agents administered prior to the onset of anaphylaxis. If SPT is used and fails to produce a positive result, then IDT must be performed.

Where there is negative IDT for the suspected antibiotic accompanied by a clear positive to another drug administered perioperatively (for example, a NMBA) it is reasonable to administer that antibiotic again in the future. A false negative cannot be excluded.

Where all agents administered perioperatively are skin test negative and there is a strong clinical story to support anaphylaxis, particularly in the presence of an elevated serum tryptase, the possibility of a false negative to the antibiotic agent must be considered. These patients may benefit from further antibiotic testing.

IDT is not valid for use as a screening test to predict immediate hypersensitivity to cephalosporins in the absence of a clinical history supporting prior anaphylaxis[51].

Laboratory testing for sIgE is available for the penicillins and a limited number of cephalosporins. These tests have low sensitivity and their use is not routinely indicated.

Local anaesthetic agents

Whilst immediate hypersensitivity to amide local anaesthetic (LA) agents is rare[31 52], it is relatively common for patients to report adverse reactions following their administration. Consequently, it is important for practitioners to have an approach to testing for LA hypersensitivity. Skin testing is performed with the intention of identifying an agent that can be safely given to the patient. It is recommended that skin testing is undertaken with the suspect agent plus at least one alternative and is followed at least 30 minutes later by a subcutaneous challenge if skin testing is negative [31 52 53].

In addition, it is important for practitioners to consider excipients or other agents present in commercially available LA preparations. These may be the cause of hypersensitivity reactions, in which case the LA alone may be well tolerated. It is important to avoid skin testing with preparations containing adrenaline or other vasoconstrictors due to the high likelihood of producing false negative results. In contrast to some reports[54], the authors have not noted IDT for LA to be more uncomfortable than other agents, or associated with false positive results, even at neat concentrations.

As described above, an in-depth discussion of challenge testing is outside of the scope of this document. LA allergy is an issue that will frequently arise for anaesthetists and other practitioners undertaking perioperative allergy testing and is therefore covered briefly.

If skin testing is negative at maximal IDT concentration a subcutaneous challenge should be considered. This may be undertaken using a graded protocol or a single step delivering 1-3mls of undiluted LA subcutaneously[8 52 54 55]. The latter approach is more commonly employed by the authors. In the event of a positive skin test, an alternative, skin test negative LA should be challenged. Subcutaneous challenge carries a higher risk of anaphylaxis and must only be performed in a facility with resuscitation equipment and appropriately trained staff. As there is also the possibility of a delayed reaction when a subcutaneous challenge is performed, the patient should be followed up at 24 hours to assess for any delayed response.

Chlorhexidine

This widely used antiseptic is found in many wipes, gels, lubricants, dressing, drapes and devices in the perioperative environment and is increasing as a cause of anaphylaxis[56 57]. The widespread and often undocumented use of this agent means that it is frequently unrecognized as a possible cause of allergic reactions[58 59]. If the patient is exposed to chlorhexidine intravenously, such as with chlorhexidine impregnated central venous access devices, anaphylaxis is likely to develop rapidly[60]. If chlorhexidine is absorbed across mucous membranes anaphylaxis is often delayed, as may occur with chlorhexidine containing urethral gels. Information regarding chlorhexidine exposure is frequently incomplete at the time of patient referral[59]. Repeated episodes of chlorhexidine anaphylaxis have been reported to occur in some patients before chlorhexidine has been identified as the responsible allergen. In all cases of perioperative anaphylaxis, where it is not possible to be certain that there was no exposure to chlorhexidine, testing to chlorhexidine should be considered[58].

Drug dilutions

Dilutions and drug concentrations reported in Table 1 are drawn from published literature where possible, with references included. Where published data are lacking reported dilutions and concentrations are based on the consensus opinion of report authors based on experience gained through multiple episodes of testing.

Table 1: DRUG DILUTIONS FOR SKIN TESTING

Positive control: Histamine 10mg/ml by SPT or Morphine 10mcg/ml by IDT

Negative control: Physiological saline 0.9%

*All dilutions in Table 1 reference this concentration. This may not be the most common concentration available.

NIC: Non-irritating concentration

DRUG/AGENT	***SPT***		***IDT***				***References***	***Comments***
(Reference Concentration, mg/mL)*	***Initial***	***Maximum Non-irritant***	***Initial***		***Suggested Maximum***		***Published Maximum NIC***		
	Dilution	***Dilution***	***Concentration µg/mL***	***(Dilution)***	***Concentration µg/mL***	***(Dilution)***	***µg/mL***		
Hypnotics									
Propofol (10)	undiluted	undiluted	100	(1:100)	1,000	(1:10)	1,000	3 30 31 47 61	
Thiopentone (25)	undiluted	undiluted	250	(1:100)	2500	(1:10)	2,500	3 30 31 47 61	
Ketamine (100)	undiluted	undiluted	100	(1:1,000)	100	(1:1000)	1,000	3 31 47 62	
Midazolam (1)	undiluted	undiluted	10	(1:100)	100	(1:10)	500	3 30 47 61 62	NB: many references contain starting conc^{n} 5mg/mL

DRUG/AGENT (Reference Concentration, mg/mL)*	SPT		IDT						
	Initial	Maximum Non-irritant	Initial		Suggested Maximum		Published Maximum NIC	References	Comments
	Dilution	Dilution	Concentration µg/mL	(Dilution)	Concentration µg/mL	(Dilution)	µg/mL		
Opioids									
Morphine (10)	1:100	1:10	0.1	(1:100,000)	0.1	(1:100,000)	10	3 30 47 61	a
Oxycodone (10)	No data	No data	10	(1:1,000)	100	(1:100)	No data		No supporting data
Alfentanil (0.5)	1:10	undiluted	5	(1:100)	50	(1:10)	50	3 30 47 61	
Fentanyl (0.05)	1:10	undiluted	0.05	(1:1,000)	5	(1:10)	5	3 30 47 61	
Pethidine (50)	1:2	1:2	0.5	(1:100,000)	2.5	(1:20,000)	2.5	6 30	
Remifentanil (0.05)	undiluted	undiluted	0.5	(1:100)	5	(1:10)	5	3 30 47 61	
Non-opioid analgesics									
Parecoxib (8)	No data	No data	80	(1:100)	80	(1:100)			
Ketorolac (10)	No data	No data	100	(1:100)	100	(1:100)	No data		No supporting data
Tramadol (50)	No data	No data	500	(1:100)	500	(1:100)	No data	63	Case reports only

a The maximum NIC concentration published in the referenced papers has been clearly demonstrated by the authors to give positive results in sufficient numbers of control subjects to be used as a positive intradermal control (see section 9.6). The authors consequently do not exceed a concentration of 0.1µg/mL as maximum NIC.

DRUG/AGENT (Reference Concentration, mg/mL)*		SPT		IDT					References	Comments
		Initial	Maximum Non-irritant	Initial		Suggested Maximum		Published Maximum NIC		
		Dilution	Dilution	Concentration µg/mL	(Dilution)	Concentration µg/mL	(Dilution)	µg/mL		
Paracetamol	(10)	No data	No data	100	(1:100)	1,000	(1:10)	100,000 b	64	c
NMBA										
Atracurium	(10)	1:10	1:10	1	(1:10,000)	10	(1:1,000)	10	3 30 31 47 61 65	
Cisatracurium	(2)	undiluted	undiluted	2	(1:1,000)	20	(1:100)	20	3 30 31 47 61 65	
Mivacurium	(2)	1:10	1:10	0.2	(1:10,000)	2	(1:1,000)	2	3 30 31 47 61 65	
Pancuronium	(2)	undiluted	undiluted	2	(1:1,000)	20	(1:100)	200	3 30 31 47 61 65	
Rocuronium	(10)	undiluted	undiluted	10	(1:1,000)	100	(1:100)	50	3 29-31 47 61 65 66	d
Vecuronium	(4)	undiluted	undiluted	4	(1:1,000)	40	(1:100)	400	3 30 31 47 61 65	
Suxamethonium	(50)	1:5	1:5	50	(1:1,000)	100	(1:500)	100	3 30 31 47 61 65	

b Concentration refers to pure paracetamol which is not available in Australia or New Zealand for parenteral administration.

c MR (2015, personal communication) indicates that reported maximum IDT concentration of 1,000mcg/mL is non-irritant for preparations containing mannitol.

d The authors acknowledge that some publications (refs 29, 65, 66) recommended that the maximum concentration of rocuronium be 50µg/ml by IDT. However, our consensus opinion, based upon many years of practice, is that a maximum concentration of 100µg/ml for rocuronium is appropriate.

DRUG/AGENT (Reference Concentration, mg/mL)*		SPT		IDT						References	Comments
		Initial	Maximum Non-irritant	Initial		Suggested Maximum		Published Maximum NIC			
		Dilution	Dilution	Concentration µg/mL	(Dilution)	Concentration µg/mL	(Dilution)	µg/mL			
NMBA Reversal agents/components											
Sugammadex	(100)	No data	No data	100	(1:1,000)	1 000	(1:100)	1,000		67	
Neostigmine	(2.5)	undiluted	undiluted	2.5	(1:1,000)	25	(1:100)	No data		68	Reference for SPT only
Atropine	(0.6)	undiluted	undiluted	0.6	(1:1,000)	0.6	(1:1,000)	0.6		69	
Glycopyrronium	(0.2)	No data	No data	0.2	(1:1,000)	0.2	(1:1,000)	No data			
Local Anaesthetics											
Lidocaine	(10)	undiluted	undiluted	100	(1:100)	10,000	undiluted	1,000		3 30 47 61	e
Bupivacaine	(2.5)	undiluted	undiluted	25	(1:100)	2,500	undiluted	250		3 30 47 61	
Ropivacaine	(10)	undiluted	undiluted	100	(1:100)	10,000	undiluted	200		3 30 47 61	
Mepivacaine	(10)	undiluted	undiluted	100	(1:100)	10,000	undiluted	1,000		3 30 47 61	
Prilocaine	(10)	undiluted	undiluted	100	(1:100)	10,000	undiluted			47	

e Undiluted local anaesthetics used by authors with no noted increase in patient discomfort or unexpected positive results.

DRUG/AGENT (Reference Concentration, mg/mL)*	SPT		IDT					
	Initial	Maximum Non-irritant	Initial		Suggested Maximum		Published Maximum NIC	References	Comments
	Dilution	Dilution	Concentration µg/mL	(Dilution)	Concentration µg/mL	(Dilution)	µg/mL		
Articaine (40)	No data	No data	400	(1:100)	4,000	(1:10)	No data		NB: applies to adrenaline-free solution only
Antiemetics									
Metoclopramide (5)	No data	No data	5	(1:1,000)	50	(1:100)	No data		
Ondansetron (2)	undiluted	undiluted	2	(1:1,000)	20	(1:100)	20	70	
Granisetron (1)	undiluted	undiluted	10	(1:100)	10	(1:100)	100	71	Case report only
Tropisetron	No data	No data	No data	No data	No data	No data	No data		
Cyclizine (50)	No data	No data	No data	No data	No data	No data	No data		
Droperidol (5)	1:2	undiluted	5	(1:1,000)	50	(1:100)	No data		NB: Droperidol reference concentration often 2.5mg/ml
Antiseptics									
Povidone Iodine (aqueous) (100)	undiluted	undiluted	10	(1:10,000)	1,000	(1:100)	10,000	3 72	

DRUG/AGENT (Reference Concentration, mg/mL)*		SPT		IDT					References	Comments
		Initial	Maximum Non-irritant	Initial		Suggested Maximum		Published Maximum NIC		
		Dilution	Dilution	Concentration µg/mL	(Dilution)	Concentration µg/mL	(Dilution)	µg/mL		
Chlorhexidine (aqueous)	(0.02%or 0.2mg/ml)	undiluted	undiluted f	0.00002% or 0.2µg/ml	(1:1,000)	0.0002% or 2µg/ml	(1:100)	0.0002% or 2µg/ml	3 30 47	
Anti/pro-coagulants										
Heparin	(5,000 U/mL)	undiluted	undiluted	50 U/ml	(1:100)	500 U/ml	(1:10)		47 73	Concentration of heparin not stated
Enoxaparin	(10,000 U/mL)	undiluted	undiluted	10 U/mL	(1:1,000)	1,000U/ml	(1:10)		47 73	Concentration of enoxaparin not stated
Protamine	(50)	data inconclusive	No data	10	(1:5,000)	50	(1:1,000)	50	30 74	
Tranexamic Acid	(100)	undiluted	No data	1,000	(1:100)	10,000	(1:10)		75	Case report only
IV antibiotics										
Ampicillin / Amoxicillin	(100)	1:5	1:5	1,000	(1:100)	10,000	(1:10)	20,000	30 47 76-78	
Cefazolin	(100)	1:5	1:5	1,000	(1:100)	10,000	(1:10)	33,000	30 35 47 76 78	

f Chlorhexidine SPT maximum NIC reported up to 0.5% or 5mg/mL

DRUG/AGENT (Reference Concentration, mg/mL)*	SPT		IDT					References	Comments
	Initial	Maximum Non-irritant	Initial		Suggested Maximum		Published Maximum NIC		
	Dilution	Dilution	Concentration µg/mL	(Dilution)	Concentration µg/mL	(Dilution)	µg/mL		
Cefalotin (100)	1:50	1:50	1,000	(1:100)	2,000	(1:50)	2,000	30 47 76	
Ceftriaxone (100)	1:5	1:5	1,000	(1:100)	10,000	(1:10)	20,000	30 35 47 76-78	
Cefuroxime (150)	1:3	1:3	150	(1:1,000)	15,000	(1:10)	20,000	30 35 47 76-79	
Gentamicin (40)	undiluted	undiluted	400	(1:100)	400	(1:100)	400	30	
Vancomycin (100)	not recommended	not recommended	0.1	(1:1,000,000)	0.1	(1:1,000,000)	0.1	30	
Benzylpenicillin (60mg/ml or 100,000IU/mL)	undiluted	undiluted	10,000 IU/ml	(1:10)	10,000 IU/ml	(1:10)	20,000–25,000 IU/ml	30 76-78	
Metronidazole (5)	No data	No data	50	(1:100)	50	(1:100)	No data		
Meropenem (100)	1:100	1:100	1,000	(1:100)	1,000	(1:100)	1,000	80 81	
Ciprofloxacin (2)	1:100	1:100	2	(1:1,000)	6.67	(1:300)	6.67	82 83	
IV fluids									
Gelatin colloids (35-40)	undiluted	undiluted	350 - 400	(1:100)	3,500–4,000	(1:10)	35,000–40,000	30	
Dyes									

DRUG/AGENT (Reference Concentration, mg/mL)*	SPT		IDT					
	Initial	Maximum Non-irritant	Initial		Suggested Maximum		Published Maximum NIC	References	Comments
	Dilution	Dilution	Concentration µg/mL	(Dilution)	Concentration µg/mL	(Dilution)	µg/mL		
Patent blue (25mg/ml or 2.5%)	undiluted	undiluted	25µg/ml or 0.0025%	(1:1,000)	250 µg/ml or 0.025%	(1:100)	2,500µg/ml or 0.25%	3 47	
Methylene blue (10 or 1%)	undiluted	no data	10	(1:1,000)	100	(1:100)	100	3 47	
Steroids									
Dexamethasone (4)	1:10	undiluted	40	(1:100)	400	(1:10)	400	84-86	
Methylprednisone (40)	1:10	undiluted	400	(1:100)	4,000	(1:10)	4,000	84-86	
Triamcinolone (40)	1:10	undiluted	400	(1:100)	4,000	(1:10)	4,000	85 86	
Hydrocortisone (50)	1:10	undiluted	500	(1:100)	5,000	(1:10)	10,000	85 86	
Betamethasone (5.7)	undiluted	undiluted	57	(1:100)	380	(1:15)	400	86	
Contrast agents									
Iodinated contrast media (varies)	undiluted	undiluted	varies	(1:10)	varies	(1:10)	varies	47 87	Concentration variable
Gadolinium (0.5mmol/ml)	undiluted	undiluted	0.05mmol/ml	(1:10)	0.05mmol/ml	(1:10)	0.05mmol/L	47 88	
Others									
Clonidine (0.15)	No data	No data	1.5	(1:100)	1.5	(1:100)	No data		
Hyaluronidase (1,500U/mL)	1:10	1:10	1.5U/ml	(1:1,000)	15U/mL	(1:100)	150U/ml	89 90	

DRUG/AGENT (Reference Concentration, mg/mL)*	SPT		IDT					References	Comments
	Initial	Maximum Non-irritant	Initial		Suggested Maximum		Published Maximum NIC		
	Dilution	Dilution	Concentration µg/mL	(Dilution)	Concentration µg/mL	(Dilution)	µg/mL		
Carboxymethyl -cellulose (5)	undiluted	undiluted	5	(1:1,000)	50	(1:100)	1,000	86 91	
Syntocinon	not recommended	not recommended	not recommended	not recommended	not recommended	not recommended		92	
Carbetocin	No data	No data	No data	No data	No data	No data	No data		

Appendix

ASCIA guidelines for drug cessation - Drugs which are antihistamines or have antihistamine activity and which may interfere with skin testing.

Generic	Commercial	Withholding period (days)	Comment
Antihistamines			
Brompheniramine	Demazin*, Dimetapp*	5	Withholding period varies in individuals due to different rates of metabolism; 4 days is recommended as general advice.
Cetirizine	Alzene, Cetrelief, ZepAllergy, Zilarex, Zodac, Zyrtec	4	
Chlorpheniramine	Codral*, Demazin*, Dimetapp*, Logicin*, Sudafed*, Sinutab*	4	
Cyproheptadine	Periactin	4	
Desloratadine	Aerius	4	
Dexchlorpheniramine	Polaramine	4	
Diphenhydramine	Benadryl, Paedamin, Snuzaid, Unisom Sleepgels	2	
Dimenhydrinate	Travacalm		
Doxylamine	Dolased, Codagesic, Codalgin, Dimetapp*, Maxydol, Panalgesic, Tensodeine, Dozile, Fiorinal, Mersyndol, Restavit,	2	
Fexofenadine	Allerfexo, Fexo, Fexal, Fexorelief, Fexotabs, Tefodine, Telfast, Xergic	4	
Levocetirizine	Xyzal	4	

ASCIA drug cessation guidelines cont.

Loratadine	Alledine, Allerdyne, Allereze, Claratyne, Lorano, Lorapaed, Lorastyne	10	Usually 4 days is sufficient
Pheniramine	Avil	4	
Promethazine HCl	Allersoothe, Avomine, Phenergan, Fenezal	4	
Trimeprazine	Vallergan	2	
Triprolidine	Codral*, Sudafed*	1	
H-2 antagonists			
Cimetidine	Magicul, Tagamet	1	There may be only minimal suppression of the skin test
Ranitidine	Ausran, Rani-2, Ranital, Ranoxyl	1	
Famotidine	Ausfam, Famohexal, Pamicid, Pepcidine, Pepzan	1	
Antidepressants			
Amitriptyline	Endep		Withholding period not established, antihistamine effect variable but often significant.
Clomipramine	Anafranil, Placil, generic		
Dothiepin	Dothep		
Doxepin	Deptran, Sinequan	7	
Imipramine	Tofranil, Tolerade		
Mianserin	Lumin, Tolvon		
Mirtazapine	Aurozamine, Avanza, Axit, Mirtazon, Milivin, Remeron		
Trimipramine	Surmontil		

ASCIA drug cessation guidelines cont.

Anti-migraine			
Pizotifen	Sandomigran		
Antiemetics			
Prochlorperazine	Nausetil, Nausrelief, Prozine, Procalm, Stemetil, Stemzine		Weak antihistamine
Neuroleptics			
Chlorpromazine	Largactil		Withholding period not established, may be up to 2 weeks Antihistamine effect variable between drugs and individuals.
Clozapine	Clopine, Clozaril, Closyn		
Flupenthixol	Fluanxol**		
Fluphenazine	Modecate		
Olanzapine	Lanzek, Ozin, Zylap, Zypine, Zyprexa		
Pericyazine	Neulactil**		
Quetiapine	Delucon, Quetiaccord, Quipine, Sequase, Seronia, Seroquel, Syquel		
Risperidone	Ozidal, Resdone, Rispa, Risperdal, Rispericor, Rixadone		
Zuclopenthixol	Clopixol**		

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* Multiple preparations under this name, check label

** Antihistamine effect not formally demonstrated but thought likely due to structural and functional similarities with other drugs

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