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Prevention of Anaphylactic Reactions to Anaesthetic Drugs

Malcolm M. Fisher and *Gordon S. Doig*

Intensive Therapy Unit, University of Sydney, Royal North Shore Hospital of Sydney, Sydney, NSW, Australia

Contents

Abstract

Although screening tests to prevent anaphylaxis during anaesthesia have been advocated, such tests are unlikely to have significant impact on reducing the incidence of anaphylaxis during anaesthesia. This is due to the low prevalence of the disease, the diversity of drugs used in anaesthesia and the incidence of false positive and negative tests. The suggested risk factors of allergy, i.e. atopy, asthma, family history, female sex, previous exposure, vasectomy, use of zinc protamine sulfate insulin and allergy to cosmetics, eggs, fish and non-anaesthetic drugs are not valid. Although all have theoretical or real associations with anaphylaxis during anaesthesia the majority of patients with such a history undergo uneventful anaesthesia. Fruit allergy, anaphylaxis to cephalosporins and penicillin, barbiturate allergy, gelatin allergy and allergy to metabisulphite and eggs require consideration in avoiding particular drugs.

The incidence of anaesthetic anaphylaxis can be reduced by avoiding latex exposure in patients with spina bifida or latex allergy, and preventing second reactions in patients with a history of anaphylaxis, or major undiagnosed or undocumented adverse events during anaesthesia. Determining the cause of an adverse event and the drug responsible, and adequately communicating those findings can reduce second reactions. Avoiding neuromuscular blocking drugs (NMBDs) in patients who have reacted to an NMBD, and use of non-intravenous techniques should also reduce the incidence of second reactions.

Desensitisation, and blocking with monovalent quaternary ammonium compounds may allow improved safety of NMBDs and pretreatment with antihistamines and corticosteroids may block or ameliorate the severity of reactions, but there is currently little evidence to support their routine use.

Anaphylactic reactions to anaesthetic drugs are rare. The reported incidences lie between the Boston Drug Surveillance figures of 1 : 900 to 1 : 22 000.[1] The mortality is 4% in large series and an additional 2% of patients experience significant brain damage.[2] Such reactions are an increasing cause of litigation against anaesthetists in Australia.

In all the published studies neuromuscular blocking drugs (NMBDs) are the most common cause of anaphylaxis during anaesthesia. Reactions to induction agents, antimicrobials, latex and blood volume replacement solutions comprise the preponderance of the remainder[3] and for them the incidence varies between countries, depending on usage and possibly the degree of sensitisation in individual populations. Virtually every drug used in anaesthesia has been reported to cause a reaction and in addition anaphylaxis to skin preparations, opioids, protamine sulfate, vascular graft materials, atropine, neostigmine, dyes, contrast media, local anaesthetics and tumour identifying dyes are occasionally reported.

Prevention of anaphylaxis to anaesthetic drugs would require the determination of which patients had a high risk of reaction due to antibodies to the drug, or other factors in their pre-operative history. Considering the large numbers of drugs, diagnostic reagents, devices containing latex, antiseptics and blood products that are routinely used in anaesthe-

sia, and the accuracy of diagnostic tests for the antibodies, this is unlikely to be possible.

In this article we consider the feasibility of strategies which have been proposed to reduce the number of anaphylactic reactions occurring during anaesthesia.

1. Strategies Which May Prevent First Anaphylactic Reactions During Anaesthesia

1.1 Screening Tests for Anaesthetic Allergy

The greatest experience in diagnostic tests for reactivity to anaesthetic drugs involves the four drug groups most likely to produce reactions: induction agents, NMBDs, colloid blood replacement solutions and antimicrobials.[2-4]

The development of tests for the detection of allergy to these drugs has led to suggestions that patients presenting for anaesthesia, particularly those in 'high-risk' groups, should be tested preoperatively.[5] Surprisingly, the expensive and less accurate radioimmunoassay (RIA) tests were advocated for this purpose. In 1989, a recommendation of the Sheriff of Aberdeen prompted a suggestion that commercial RIA tests for thiopental sodium, suxamethonium chloride and alcuronium chloride should be used in routine pre-operative screening, initially only in 'at risk' patients, but subsequently on every patient for whom anaesthesia was planned.[6] However, the only practical example of a test that has actually been introduced into routine use is the skin prick test screening kit for chymopapain.

1.2 Is Screening for Anaesthetic Allergy Valid?

In order to determine whether a screening test should be considered for routine use, Whitby[7] proposed the following validity criteria. If these criteria can be met, it may be reasonable to apply the use of routine screening for anaphylaxis to anaesthetic agents.

1.3 Criteria for a Screening Test for Anaesthetic Allergy

1.3.1 Abnormality Must Be Adequately Defined

Some disease processes and abnormalities, such as acute myocardial infarction, are adequately defined by internationally accepted criteria, are diagnosed using standardised techniques and follow a uniform disease process. Anaphylactic reactions to anaesthetic agents, however, are more complex. The reactions themselves are not homogeneous, manifesting themselves clinically through various combinations of the classic signs and symptoms of anaphylaxis. Furthermore, each distinct or unique presentation can be due to a number of different mechanisms, particularly non-immune mechanisms, and in spite of a wealth of both anecdotal evidence and case series, the tests used in diagnosis are not standardised and still attract controversy.[8,9]

1.3.2 An Appropriate Population to Screen Must Be Identified

A screening test's performance, with regards to minimising false-positive and false-negative results, depends on the prevalence of the disease in the population of patients actually screened. As prevalence increases, false-positive and false-negative rates decrease.

The positive predictive value of a diagnostic test is a fraction describing the proportion of test-positive patients who actually have the disease under question. It is an estimate of the probability of having the disease if the test is positive and can be expressed in terms of the sensitivity (sens) and specificity (spec) of the test and the prevalence (prev) of the disease in the population being tested (equation 1):

$$\text{Predictive value} = \frac{\text{Sens} \times \text{prev}}{\text{Sens} \times \text{prev} + (1 - \text{spec}) \times (1 - \text{prev})} \quad \text{(Eq. 1)}$$

The numerator (sens × prev) is the fraction of truly at-risk patients in the population who are detected (predicted) by the test, and the denominator (sens × prev + [1–spec] × [1–prev]) is the fraction of

the population who are found positive by the test. The equation tells us that the predictive value of a test depends not only on the properties of the test itself (namely sensitivity and specificity) but also on the prevalence of the disease in the population to which the test is applied. When the prevalence of a disease is high, the predictive value is maximised, but when prevalence is low, fewer patients who return positive test results actually turn out to have the disease of interest.

The yield of true positive results for any screening test can be increased by selecting patients for testing based on known risk factors that increase the prevalence of disease in the screened group.

1.3.3 Incidence or Prevalence Must Be Established in a Group Similar to One to Be Screened

Most published incidences of anaphylaxis to anaesthetic drugs lie between the Boston Drug Surveillance figures of between one event in 900 anaesthetics and one event in 22 000 anaesthetics.[1] These estimates are not based on prospective studies that follow all anaesthetic cases, but rather they are obtained from the retrospective analysis of databases of reported possible reactions. Because of the process used, it is highly likely that some reactions and deaths due to reactions are misclassified, leading to a much wider variance than that already obvious from the published figures themselves.

The reported incidence of anaphylaxis during anaesthesia will depend on the number of subjects with antibodies to the anaesthetic drugs and the number of those subjects who are exposed to the drug to which they are allergic. It is likely that the prevalence of antibodies to drugs used in anaesthesia is higher than the incidence of reactions, because of patients with drug-specific antibodies who have never received the culprit drug.

1.3.4 Method of Choice for Screening Must Be Established

Two tests have the potential for use as screening tests for anaesthetic anaphylaxis, *in vitro* RIA tests for drug-specific IgE antibodies and skin testing. Both have been shown to be valid in determining the drug responsible for anaphylactic reactions but both have limitations.

Skin testing produces the greatest number of positive results when compared with RIA in patients who have anaphylactic reactions.[3,10] While figures for the sensitivity and specificity of these tests have been published they are not included as the publications have limited validity. The problem in assessment of the reliability of the tests is that when a single test is negative it is impossible to determine whether it is a false-negative test or whether the patient does not have antibodies to the drug unless the drug is actually administered to the patient.

In practice, the enormous advantage of skin testing is that it can be performed anywhere whereas RIA is available only in specialised laboratories in a few countries.

The validity of a screening test is established by comparison of results with a 'gold standard' diagnostic process. The quality of the 'gold standard' diagnostic process will clearly influence the results of the validation.

The measures usually used for evaluating the performance of a diagnostic test are sensitivity and specificity. Sensitivity is defined as the percentage of the true positive cases in a sample that are found positive by the test. Specificity is defined as the percentage of the true negative cases that are found negative by the test. A test with low sensitivity leads to a high false-negative rate. A test with low specificity results in a high number of false-positive results.

Establishing the performance of a screening test requires the test to be used in a series of subjects with a known ('gold standard') reaction status. The patients referred by anaesthetists for diagnostic testing of suspected anaphylactic reactions constitute a large sample in whom there may be a reasonable proportion of true reactors, but there is no independent and internationally accepted standardised approach to the diagnosis. One approach might be to re-test only those patients thought most confidently to be reactors, but this would not be a representative sample, and they may, in any case, acquire or lose reactivity in intervals between testings, although this is unusual. Only one of 21 patients tested 5–27 years after a reaction with skin and RIA testing was found

to have lost reactivity, and no new sensitivities were found.[11]

The low prevalence of anaesthetic anaphylaxis in the population at large means there should be little difficulty in obtaining true negative (non-reactor) patients or volunteers. For skin testing, the criteria for positivity are based on dilutions of drugs that do not cause wheal and flare reactions in people with no history of a reaction. For RIA testing, one uses sera from non-allergic controls, or cord serum, which does not contain IgE. However, there are some ethical and logistical difficulties in testing large numbers of non-reactors simply to validate a test. Because a history of exposure to inciting agents can be inaccurate, the 'gold standard' diagnostic criteria would involve actual exposure to the inciting agent. The best way to validate any screening test would be to conduct a prospective study of all patients exposed to the drug during routine anaesthesia. Due to the low incidence of allergy such a study would have to be very large.

In a prospective comparison of two NMBDs, involving 3381 patients, Beemer et al.[12] found significant differences in minor anaphylactoid effects but no anaphylaxis. Fisher and Baldo[10] calculated that a 1 **:** 5000 incidence of reactions over 7 500 000 exposures would be needed to establish an accuracy with 5% confidence limits.

The clinical reality of detecting potential anaphylactic reactions is not based upon obtaining the absolute truth, but on obtaining a high degree of clinical safety for each individual who is referred. This is determined, not by a single test or criterion, but by a weight of evidence that includes a mixture of clinical judgement, test results and understanding of the natural history of anaphylaxis: the mixture varies from patient to patient and clinician to clinician. The actual diagnosis of anaesthetic reactions is judged against the total weight of evidence, combined with the risk of subsequent possible reactions to anaesthetics not on any single, standard diagnostic test. For example, after a florid case of classical anaphylaxis when only one agent has been given, negative tests to that agent will be viewed with extreme suspicion and common sense dictates that the suspected agent be avoided. Likewise, if several agents have been given, the tests will be needed primarily to determine which agent most likely caused anaphylaxis. The identification of the agent confirms the suspicion of anaphylaxis itself. If the clinical evidence of anaphylaxis is less certain, the tests become more important, not only in establishing the culprit agent, but in making the diagnosis of anaphylaxis itself. The clinically more difficult cases need to rely more on history, clinical presentation, judgement and banks of tests rather than on any single one.

An inherent weakness in the use of skin or RIA tests alone as predictors of risk of anaphylaxis, in a population with no history of a reaction, is that the value of the description of the reaction (history) in determining the clinical relevance of the tests is lost. This is apparent in the three published studies of skin and RIA testing conducted in French patients with no history of a reaction (see table I).[13-15]

The essential conclusion of the studies was that there were too many false positives to make the tests useful. The criteria used for positivity were more liberal than those used in diagnostic prick testing after anaphylaxis.

It will be clear from the foregoing descriptions and discussions that no single measure or test can

Table I. Prospective studies of neuromuscular blocking drug allergy in patients with no history of anaesthetic anaphylaxis

Study	n	Population	Tests	Results	Conclusion
Maria et al.[15]	300	Preoperative	Prick test	11 positive for atracurium besilate 1 positive for suxamethonium chloride	Atracurium besilate causes false-positives
Porri et al.[13]	114 females	Preoperative	Prick test	7 positive or doubtful	Results uninterpretable
Porri et al.[14]	258	Health centre attendees	Prick test and RIA	24 positive to one or other test	Too many false-positives

n = number of patients; **RIA** = radioimmunoassay.

tell us the absolute truth. If there were one that did, there would be no need for any others. In addition, the availability of RIA testing is largely restricted to France, although there are non-validated commercial kits available for detection of drug-specific antibodies. In reality, skin tests, with all their limitations, are the only tests available outside of Europe.

1.3.5 There Must Be Diagnostic Facilities Available for Follow-Up and an Acceptable Form of Treatment

In screening for possible HIV infection, a highly sensitive, relatively cheap diagnostic test is applied to patients considered to be at risk of infection. If positive results are obtained from this initial sensitive test, a highly specific test is used to rule out false-positive results. If a patient returns positive results to the second highly specific test, therapy can be commenced.

In the case of screening for possible reactivity to anaesthetic agents, the only feasible highly sensitive screening test (a skin test) has a small rate of false-positives. In terms of safety, a false-positive test is of less practical importance than a false-negative test. A false-positive test is an inconvenience to patient and anaesthetist, whereas a false-negative test may lead to administration of an unsafe drug.

Under most circumstances of screening, the positive tests lead to further tests to verify the result. In anaesthesia screening, this would not be possible. The only other single test, the RIA test, has limited availability and is less sensitive and less specific than the skin test.

As mentioned earlier, there is no universally acceptable 'gold standard' approach to detect false positive results nor can false-positive results be minimised by screening high risk patients or by using a combination of screening tests: one with high sensitivity followed by a second with high specificity. The only logical follow-up in response to the detection of a positive screening test is to postpone surgery until a further barrage of investigations can be undertaken in order to more accurately identify alternate agents to which the patient may not be allergic. If the surgery is elective, this may simply result in an inconvenience; however, if the surgery is truly an emergency, cancellation may not be an option.

1.3.6 The Natural History of the Disease Must Be Influenced by Treatment

The detection of a positive skin test prior to anaesthesia gives a number of options for treatment. Use of alternative techniques such as regional block or volatile agents may avoid the need for intravenous agents. However, selection of alternative agents is fraught with hazard, and this is particularly so for NMBDs. The incidence of cross-sensitivity between NMBDs is about 60% by skin testing and up to 80% by RIA testing and while some pairings are common, the patterns of cross-sensitivity vary considerably between patients.[16-18] Furthermore, in some patients with multiple sensitivities, drugs which show negative responses using an intradermal test protocol may still provoke reactions.[19,20]

1.3.7 The Resources Must Be Available

The total costs of screening comprise up-front costs of applying the test and down-stream costs associated with the follow-up actions that are required for people who screen 'positive'. The costs of the resulting actions are the product of the cost of any precautionary action that needs to be taken and the number of patients for whom a positive result in the screen indicates that precautions are necessary. The desired effect is to avoid a specified adverse outcome. The chance that a patient who screens positive is at risk of the adverse outcome is given by the predictive value of the screening test. The cost per avoided adverse outcome is therefore the quotient of the cost of each precaution and the predictive value of the screen. For example, let us examine the costs associated with the proposal to reduce mortality by RIA testing of every patient presenting for surgery. The cost of a set of RIA tests (say a conservative $A50) would be incurred for every patient who presented in order to prevent a maximum of three deaths per million patients. The anaphylaxis attributable mortality rate of three deaths per million patients assumes that 1 in 20 000 patients has an anaphylactic reaction, with a resultant case-based mortality rate of 6%. Considering only the costs of performing the RIA itself, the minimum up-front

cost per death avoided would therefore be in excess of $A16 million.

There are at least two reasons why the actual costs would be more: (i) the RIA tests are only about 80% sensitive, so that the yield of avoided deaths would be reduced to 2.4 per million; and (ii) precautionary action would have to be taken, not only for the 40 patients per million identified by RIA as at risk, but also for the 99 900 patients who are not at risk, but for whom risk is falsely indicated because of the specificity of the RIA, which may be as high as 90%. Even if the cost of precautions was negligible, spending $A16 million per death avoided may be difficult to justify, because more lives could probably be saved by spending the same total amount of money in other ways. For example, far better cost effectiveness could be achieved by restricting the anaesthetic options to those that carried the least risk of anaphylaxis and investing in education to improve awareness and preparedness for dealing, not only with anaphylaxis, but also with all life-threatening emergencies. At best, it is important to note that any comprehensive evaluation of lives saved and costs of screening must consider the cancellation of surgery and extra testing involved when each false-positive patient is identified.

1.3.8 A Way of Managing Borderline Findings Must Be Defined

Borderline and negative findings, as with all immunological investigations, are very much less reliable than positive findings.

In practice, those who investigate anaesthetic reactions, while using set criteria for positivity for research and publication, warn off any drug that might provide a borderline positive reaction. This would simply not be feasible in a screening situation and it is extremely unclear as to what should be done in borderline situations. In the circumstances of anaphylaxis to anaesthetic drugs, a false-positive test may merely result in an inconvenience due to postponed surgery. A false-negative test, or ignoring a borderline positive result, may actually be dangerous.

1.3.9 Summary

As illustrated by the application of Whitby's proposed validity criteria for the application of screening tests,[7] at present, routine screening of patients for anaesthetic allergy cannot be justified, and it is unlikely to be so in the future. This is of some relevance medico-legally. In Australian and UK medico-legal cases involving anaesthetic allergy, the allegations of negligence usually include 'failure to perform tests to establish the safety of the drugs to be administered'. According to Whitby's criteria, such allegations can be thus be rejected, unless an at-risk group can be identified.

1.4 Suggested Risk Factors for Anaesthetic Allergy

Suggested risk factors for anaphylactic reactions are shown in table II. Although these risk factors occur more frequently in reactors (i.e. those who have an anaphylactic reaction to the drug) than non-reactors who have no adverse response, their prevalence in the general population is such that the majority would not greatly improve the performance of a screening test.

1.4.1 Latex Allergy

A number of factors have been identified as predisposing to anaphylaxis to latex. Children with spina bifida are a major at-risk group for latex allergy, with an incidence up to 25%.[21] Patients with latex allergy have an increased incidence of allergy to exotic fruit, particularly mangoes, bananas, papaya, avocados and kiwifruit, compared with patients with pollinosis and patients not allergic to latex.[22-24] More recently, tomatoes and potatoes have also been shown to have an association.[25]

An incidence of latex allergy in fruit-allergic patients has been reported from 30 to 80% depending on the country and methods of detecting allergy.[23] A Spanish study showed 85.9% of patients who were allergic to fruit had a positive skin test or RIA sensitivity to latex, although a history of 'clinically relevant' latex allergy was only found in 6 of 49 patients.[26]

The association is very strong: either allergy may precede the other.[27] Sicherer[28] found the incidence

Table II. Possible predisposing factors to anaesthetic anaphylaxis

At-risk group	Drug or drug class
Definite risk	
Spina bifida	Latex
Health workers with glove dermatitis	Latex
Penicillin anaphylaxis	Cephalosporins, penicillins
Allergy to eggs/soybean emulsion	Propofol
Gelatin allergy	Plasma volume expanders
Allergy to exotic fruit	Latex
Metabisulphite allergy	Metabisulphite-containing drugs
Barbiturate allergy	Thiopental sodium
Previous anaesthetic anaphylaxis	All drugs
Previous unexplained adverse reaction during anaesthesia	All drugs
Effect insufficient for intervention	
Multiple exposures	Thiopental sodium
Fish allergy	Protamine sulfate
Zinc protamine sulfate insulin exposure	Protamine sulfate
Vasectomy	Protamine sulfate
Penicillin allergy	Cephalosporins
Allergy	All drugs
Atopy	All drugs
Asthma	All drugs
Female sex	NMBDs
Allergy to NMBDs	Propofol
No or insignificant effect demonstrated	
Previous exposure	NMBDs
Family history of anaesthetic anaphylaxis	All drugs
Previous minor reaction	All drugs
Allergy to cosmetics	NMBDs
Allergy to NMBDs	Propofol
Anaphylaxis to non-anaesthetic drugs	All drugs
Chronic fatigue syndrome	All drugs
Multiple chemical sensitivities	All drugs

NMBDs = neuromuscular blocking drugs.

of allergy to fruit in patients who were allergic to latex to be 35%, and the incidence of latex allergy in patients who were allergic to fruit to be 11%.

Italian health workers with a history of glove-related symptoms had a 10.5% incidence of positive tests for latex allergy.[29] A history of atopy increases the risk of latex allergy in hospital workers: in one study 34% of physicians with a history of atopy had latex allergy.[30]

There is a strong case for delaying surgery where possible to determine if latex sensitivity is present in spina bifida patients, patients with fruit allergy and health workers with contact-glove allergy.

A questionnaire is not sufficiently reliable to detect latex allergy and it must be supplemented with tests.[31] Fisher[32] described two patients who had anaphylaxis to latex who knew they were allergic but did not tell the anaesthetist when specifically asked about allergies. It may be that a specific inquiry about fruit or latex allergy should be part of the routine pre-operative interrogation.

The laboratory tests for latex allergy involve skin prick tests with various reagents and RIA tests. For comprehensive reviews of the type and value of the tests see Hepner and Castells,[33] and Hamilton et al.[34]

In addition to detecting patients at risk, anaphylaxis to latex may be reduced by avoiding latex exposure in spina bifida patients from birth[35,36] and avoiding exposure to latex in operating rooms, particularly by provision of a latex-free environment.[33] The comprehensive French recommendations for anaesthetic allergy endorse the test of placing a rubber glove on the patient, and progressive challenge.[4] We have confirmed the diagnosis by prick testing through a latex surgical glove. These options may be useful if no facilities are available and surgery cannot be delayed.

1.4.2 Penicillin Allergy

The risk of anaphylaxis to cephalosporins in patients with a history of penicillin allergy is probably over-rated.[37] The antigenic determinants in both drug groups are complex, involving nucleus, side-chains or combinations.[38]

The reported incidence of anaphylactic reactions to cephalosporins is 0.0001–0.1%. Up to 8% of all patients with allergy to cephalosporins have a history of penicillin allergy and there is an 8-fold increase in the risk of allergy to cephalosporins in patients with a history of allergy to penicillin.[39] A Canadian study of a surgical population suggested that a history of drug allergy was probably true in 50% patients.[40] A meta-analysis of a history of penicillin allergy showed a positive likelihood ratio

of 1.9 and an absence of a history a negative likelihood ratio of 0.5.[41] Goodman et al.[42] administered cephalosporins to 413 patients with a history of penicillin allergy, excluding those with a history of penicillin anaphylaxis, and produced one possible minor reaction. In another study, 41 well characterised penicillin allergic patients were skin tested with three cephalosporins and when all tests were negative, were given therapeutic doses uneventfully. The investigators suggested that the results showed a low risk when cephalosporins with different side chains were used.[43]

Conversely, Kelkar and Li[39] recommended using drugs without a β-lactam nucleus. Others recommend drugs which do not share cross-sensitivity with penicillin (monobactams, aztreonam).[44] We have been unable to find evidence of clinical cross-reactivity between penicillins and second-, third-, or fourth-generation cephalosporins. The decision to administer a cephalosporin to a patient with a history of allergy to penicillin is probably based as much on the medico-legal consequences of ignoring what is on the package insert as evidence of significant risk.

In patients with a history of cephalosporin allergy, other cephalosporins carry an unknown and as yet unpredictable risk,[39] and on that basis are best avoided, although we can find no cases of reactions to second-, third- or fourth-generation cephalosporins in patients who reacted to first generation cephalosporins. Caution should also be exercised with penicillins, whose side chains may be identical to those of the cephalosporin.[39]

1.4.3 Metabisulphite Allergy

There are no reported cases of anaphylaxis to metabisulphite in patients undergoing general anaesthesia. An anaphylactoid reaction due to metabisulphite during epidural anaesthesia has been described.[45] One study of large volumes of local anaesthesia for Bier block suggested that metabisulphite was related to an increased incidence of anaphylactoid reactions on release of the cuff.[46]

We were unable to exclude or confirm metabisulphite as a cause of some reactions during local anaesthesia.[47] If the investigations of a patient with alleged allergy to a local anaesthetic preparation containing metabisulphite show the local anaesthetic is not the culprit, we recommend avoiding local anaesthetics containing additives. We prefer to avoid local anaesthetics containing metabisulphite in patients with chronic fatigue syndrome (CFS) and multiple chemical sensitivities (MCS). If patients have a history of allergy to metabisulphite, local anaesthetics from multi-dose bottles containing vasoconstrictors (with the exception of prilocaine and felypressin) should be avoided and a careful check of other drugs used as preservative be undertaken.

1.4.4 Gelatin Allergy

Anaphylaxis to gelatin in vaccines and sweets has been increasingly reported.[48] Some patients who react to the gelatin-based plasma volume expanders show positive skin tests, and may therefore have anti-gelatin antibodies. It is logical to avoid these solutions in patients with gelatin allergy.

1.4.5 Thiopental Sodium Allergy

Thiopental sodium anaphylaxis on first exposure is unusual. At least six uneventful exposures are usual and up to 37 uneventful exposures have been reported prior to an exposure that produces the reaction.[49,50] However, as with other risk factors, the overwhelming majority of patients who have multiple exposures to thiopental sodium, do so without any adverse reactions. Thiopental sodium may show cross-sensitivity to other barbiturates and should be avoided in patients with such a history.

1.4.6 Protamine Sulfate Allergy

There are three proposed risk factors for protamine sulfate allergy: vasectomy, zinc protamine sulfate insulin exposure, and fish allergy.[51,52] Anaphylaxis to protamine sulfate has been described in patients with each predisposing factor. Vasectomised patients have an increased incidence of anti-protamine sulfate antibodies,[53] but in a small comparative trial of protamine sulfate administration to vasectomised men with antibodies and non-vasectomised men there were no reactions.[54] A study of adverse reactions (not anaphylactic) to protamine sulfate during cardiac catheterisation showed a 4-fold increase in adverse reactions when patients

on protamine sulfate insulin were compared with those on non-protamine sulfate insulins.[55] A prospective study of 3245 cardiac surgical patients showed that fish allergy, vasectomy, or protamine sulfate insulin did not constituted risk factors.[56] This is fortuitous, as there are few alternatives to protamine sulfate.

1.4.7 Propofol Allergy

There is no convincing evidence to support allergy to eggs or soybeans, which are present in the propofol vehicle, predisposing to propofol reactions. There is one case in the literature of allergy to propofol in a patient allergic to eggs.[57] However, it is possible that the early manufacturer's recommendation to avoid propofol in such patients has meant few patients with such a history have been exposed. It is therefore prudent to avoid propofol in patients with a history of egg or soybean allergy.

In a French study, two of 14 patients who reacted to propofol had evidence of IgE to NMBDs and it was postulated that propofol should be avoided in patients allergic to NMBDs, and that the phenyl nucleus and isopropyl groups led to abnormal linkages to IgE[58] In our series, over 60 patients allergic to NMBDs have received propofol uneventfully. Analogous situations occur with the IgE RIA for thiopental sodium showing false-positive tests for NMBDs due to the nitrogen groups on the thiopentone nucleus: this appears to be an *in vitro* phenomenon with no clinical expression.[59] In the four patients we studied with positive skin and RIA tests to thiopental sodium and an NMBD administered prior to a reaction, inhibition showed the presence of two antibodies. Similarly the ability of the morphine quaternary ammonium group to bind to NMBD IgE antibodies is not associated with anaphylaxis to morphine in NMBD reactors.[60] The occurrence of positive skin tests to propofol in NMBD-sensitive patients should lead to its avoidance.

1.4.8 Allergy to Cosmetics

There is no evidence to support the suggestion that allergy to cosmetics predisposes to NMBD reactions[61] in spite of structural similarities.

1.4.9 Anaphylaxis to Drugs not Used in Anaesthesia.

With the exception of cross-sensitivity to barbiturates, there is no evidence of increased risk of anaphylaxis during anaesthesia in patients who have had anaphylaxis to drugs not used in the operating room.

1.4.10 Female Sex

In series of reactions to NMBDs there is a preponderance of female patients, of the order of 4 : 1.[16,62,63] This figure is changing over time in Australia and is probably influenced by women receiving more anaesthetics than men.

1.4.11 Previous Exposure

It has been suggested that patients who have previously been exposed to anaesthesia may constitute a high-risk group, but the utility of this risk factor depends on the type of anaesthetic drug previously used. Indeed, with NMDBs, there is a low incidence of previous exposure. The highest incidence of previous exposure to NMBDs in a series of reactors is as low as 45%, reported from Wellington, New Zealand.[63] Furthermore, in interpreting the figures on previous exposure, one has to consider whether the information on previous exposure is actually available at presentation to the anaesthetist. Of the patients seen in our allergy clinic, only 20% brought a definite documented history of exposure; a further 20% could have had a relaxant anaesthetic though no records were available, or were known to have been exposed to another muscle relaxant for which a skin test was positive.[64,65] Taking both the definite and possible exposures together, the maximum possible incidence of previous exposure of 40% is not too different from the 45% reported from Wellington.[63] It is apparent that under most circumstances the IgE antibody to NMBDs is not formed in response to exposure to NMBDs. The antigen that produces NMBD antibodies is unknown.

Thus the use of previous exposure as a risk factor may preclude detection of up to 55% of potential reactors (i.e. those who do not report a complete history at presentation). In practical terms, the knowledge of previous exposure to specific drugs in

patients presenting for anaesthesia is difficult to obtain. It is important to appreciate that unless a putative high-risk group contains most or all of the at-risk patients, selecting only that 'high-risk' group for pre-operative testing may decrease the actual number of patients screened, and the direct costs associated with the screening test itself, but may also actually increase the costs per death prevented.

1.4.12 Family History

There is one case in the literature of relatives who experienced anaphylaxis during anaesthesia (to different NMBDs).[66] We have tested identical and non-identical twins, siblings, and up to four generations of families and found no two persons sensitive to an anaesthetic drug from the same family.

1.4.13 Previous Minor Reactions

We have also not been able to find evidence of a minor reaction preceding a serious reaction, although this may be due to failure to record minor reactions.

1.4.14 Previous Reactions

A previous anaesthetic anaphylactic reaction is a significant risk factor. Furthermore, a history of an unexplained or undocumented anaesthetic event is also a risk factor.

1.4.15 Allergy and Atopy

In all large series of reactors to anaesthetic drugs and NMBDs there appear to be disproportionate numbers of females and patients with atopy, allergy and asthma.[62,63,65,67,68] Forty percent of patients who have anaphylaxis during anaesthesia have a history of allergy or atopy, which is five times higher than non-reactors.[69] A French study, however, compared groups of reactors and non-reactors, matched for age, sex and social class. Allergy and atopy were diagnosed by skin tests and the study revealed that there was no difference in the incidence of allergy and atopy between the groups.[70] In the absence of consistent evidence that patients with history of allergy or atopy have a higher risk of anaphylaxis during anaesthesia, the use of such a history to define a high-risk population for screening will not optimise the performance of a screening test. The vast majority of patients with allergy or atopy undergo uneventful anaesthesia.[69]

1.4.16 Chronic Fatigue Syndrome and Multiple Chemical Sensitivities

These patients present a major challenge to anaesthetists. The anaesthetic literature is unhelpful. A recent Ovid database search found no references when 'anaesthesia' was searched in association with either 'chronic fatigue syndrome' or 'multiple chemical sensitivities'. These patients characteristically suffer symptoms after anaesthesia without associated physical signs.[71] The symptoms cannot be explained medically.[72] Various websites recommend screening for anaphylaxis preoperatively and referral to clinics interested in anaesthetic allergy is increasing. There is no evidence that either condition predisposes to anaphylaxis during anaesthesia.

In our clinic, patients with CFS and MCS are seen but no testing is performed. It is explained to them that they will almost certainly have adverse effects from anaesthesia, but these adverse effects are not associated with excess mortality. We suggest they keep a record of the anaesthetic drugs they receive and the adverse effects that occur to show to future anaesthetists. We recommend (albeit not on a scientific basis) that as few drugs should be used as possible and drugs containing metabisulphite should be avoided. In the patients we have followed, we noted that adverse effects, which patients attribute to the anaesthetic, are common and these symptoms usually occur after discharge from hospital.

2. Prevention of Second Anaphylactic Reactions During Anaesthesia

It is in patients with a documented or suspected anaphylactic reaction during anaesthesia that the risk of anaphylaxis may be reduced. This is the only group that can be identified where the risk of anaphylaxis is sufficiently high to make investigation mandatory.

It is also likely that patients with an adverse event during anaesthesia, which has not been diagnosed or investigated, can have their risk of anaphylaxis reduced.

There are three aspects to managing this group of patients: (i) investigation of patients suspected of having a reaction and communication of the results; (ii) choosing the safest anaesthetic technique; and (iii) the consideration of other less well validated techniques.

2.1 Investigation of Patients Who Have a Suspected Anaphylactic Reaction

The following can be stated based on sufficient studies (both case-controlled and without controls) and anecdotal cases in the literature.

- Patients who have severe adverse events during anaesthesia that clinically resemble anaphylaxis or show some of the clinical features of anaphylaxis have a high incidence of positive skin tests to a drug administered within 10 minutes of the reaction (85–90%).[63,73-76]
- Patients who undergo uneventful anaesthesia are unlikely to have positive skin tests to anaesthetic drugs.[77]
- Depending on the method of detection and the drug reacted to, 60–90% of patients with positive skin tests will have evidence of IgE antibodies to a drug used during the anaesthetic or, in the case of NMBDs, to morphine, suxamethonium chloride or an alternative NMBD.[3,58,78-82]
- If patients are selected who have suspected anaphylaxis and elevated mast cell tryptase levels, the incidence of positive skin tests will be increased (94–96%).[83]
- If subsequent anaesthesia is performed avoiding drugs that have tested positive with skin test and RIA, the anaesthesia is usually, but not invariably uneventful, if the results of that testing are known to the anaesthetist.[10,19,74,76,84] There are few data on what would happen if skin test- or RIA-positive drugs were administered to the patients with the positive tests. The absence of positive tests in controls, the demonstration of persistence of the positive tests[11] and the results of tests in patients who have had more than one reaction,[20,85-87] suggest that anaphylaxis would occur.
- The number of positive results for RIA testing can be improved by using a morphine RIA,[60] or inhibition of the suxamethonium RIA with the culprit NMBD.[3] The results of these tests are better at detecting the responsible drug, which must be avoided, than predicting which other NMBDs are safe. In two of the only four series of patients investigated for anaesthetic anaphylaxis with data for subsequent anaesthesia, anaphylaxis occurred to a second NMBD during a subsequent anaesthetic.[19,20] A case can be made for retesting the patient prior to subsequent anaesthesia after some years as sensitivity may change. NMBDs not available at the time of the adverse anaesthetic cannot be assumed to be safe and should be tested.
- There are minor differences in the results of skin testing between prick testing and intradermal testing.[88] In prick testing the drug is placed on the skin and the skin is pricked with a fine needle through the drop of drug solution. The drug is usually (except for opioids) undiluted. In intradermal testing the drug is diluted and injected into the dermis. Intradermal testing produces more false-positive results.[74,86] Prick testing is generally believed to be safer. Prick testing is more likely to be successfully completed in children and is the method of choice for latex and cetrimide testing.
- There are also differences in approach by different investigators relating to the site of skin testing and whether the back is preferable to the forearm. There are no comparative data to support either approach.
- Anaphylaxis to local anaesthetics is extremely rare and a history of local anaesthetic allergy is usually spurious.[47] Progressive challenge is used to determine whether allergy is present or not and the safety of alternative local anaesthetics in patients with allergy.[4,47]

Thus the first valid method of preventing anaesthetic anaphylaxis is to investigate the patient who may have had a reaction. At 1 hour after the commencement of the reaction, a blood specimen should be taken for mast cell tryptase assay. This is a highly

specific and sensitive assay for mast cell activation.[83,89,90] It is also activated in anaphylactoid (non-immune) reactions but is usually associated with anaphylaxis and the detection of antibodies by skin test or RIA.[83]

False-negative tests have been described due to a postulated mechanism where the reaction involves basophils (which do not contain tryptase) rather than mast cells.[90]

A skin test should be performed 4–6 weeks after the reaction.[4,73,74,76]

The second valid method of preventing second reactions in patients with a history of anaesthetic anaphylaxis is to ensure that the results of the investigations and the results of subsequent anaesthesia are available to the patient and the anaesthetist.

We believe that the conventional warning bracelet is insufficient. Two deaths in our series were due to a drug incorrectly identified as the cause of a previous reaction.

We recommend to the patients a warning device which states: (i) 'anaphylaxis to XXXX'; (ii) the name of a safe alternative, where known; and (iii) 'see letter'.

The patient is encouraged to carry a letter stating what happened, which drugs were used, the results of investigations and a recommendation. Details of subsequent anaesthesia are added by subsequent anaesthetists.

2.2 An Appropriate Choice of Anaesthetic

2.2.1 Avoiding High-Risk Drugs

With the NMBDs, suxamethonium chloride is the most common cause of anaesthetic anaphylaxis and has the highest incidence of positive skin tests in NMBD reactors.[3] Restricting its use to patients requiring emergency intubation and not using it as a routine prelude to a long-acting NMBD appears to have reduced the incidence of reactions to NMBDs in Wellington (Galletly DC, personal communication). In the early days after the introduction of rocuronium bromide, it was suggested to be a high-risk drug. A study from Australia suggested that it was intermediate in risk when the number of NMBD-allergic patients with skin sensitivity to the drug was considered and the apparent excessive numbers of reactions were related to the unprecedented high market share and usage of the drug.[91] French studies still suggest rocuronium bromide may carry a higher risk than other NMBDs.[3] In Norway, where anaphylaxis to NMBDs is rare, rocuronium bromide was withdrawn because of the number of anaphylactic reactions (29 reports in 150 000 administrations compared with 7 in 800 000 in other Nordic countries.[92] Laake and Rottingen have analysed the data that lead to the withdrawal and were unable to show that the data represented a real increase in risk,[92] and the drug has now been approved for use in Norway.

Pancuronium bromide is the NMBD associated with the lowest incidence of anaesthetic anaphylaxis in large series.[3,10]

Three groups of patients may present who have a history of anaphylaxis under anaesthesia.

In the first group, a reaction has been documented and the patient has been investigated and the cause determined. The evidence presented earlier suggests that subsequent anaesthesia is likely to be safe. If the reaction was attributed to an NMBD there is a risk from other NMBDs (see section 2.4) and there is still a case for avoiding NMBDs and using regional block or volatile agents if such techniques are suitable. A case can be made for retesting the elective surgical patient if the testing was carried out some time ago.

In the second group if a reaction has been documented but no cause determined, the consideration of alternative techniques, or avoiding the drugs used at the culprit anaesthesia or using drugs given uneventfully subsequently (if documented) should be all that is necessary. Pretreatment could be considered (see section 2.3.1). NMBDs should be avoided if possible. If surgery is elective the patient should be retested with the drugs the anaesthetist wishes to use.

The third group of patients who have a history of a previous anaesthetic mishap about which they have no information provides a challenge. We have investigated 17 such patients preoperatively and found NMBD allergy in three. All had uneventful

anaesthesia. Thus, elective surgery should be delayed, the patient investigated and the results of the investigation and the anaesthesia documented. Some useful information can be gained from the history of the previous event. Useful information to ascertain includes where the patient was when he/she awoke, how long the patient was in hospital and whether he/she had a sore chest. For emergency surgery the principles of using alternative techniques such as regional block or volatile anaesthesia and avoiding NMBDs remain valid. Low-risk drugs such as fentanyl, midazolam, propofol and pancuronium bromide should be used in preference to thiopental sodium and suxamethonium chloride. Pretreatment should be considered.

2.3 Other Strategies for Reducing the Risk of Anaphylaxis

2.3.1 Pretreatment

Pretreatment is the use of drugs or drug combinations to prevent an anaphylactic reaction. Pharmacological pretreatment has been shown to reduce the incidence of anaphylactoid reactions to contrast media in a number of studies. Current recommendations include corticosteroids, histamine H_1 receptor antagonists and ephedrine.[93]

Whether these data can be applied for prevention for anaphylaxis during anaesthesia is not known. There has never been a convincing demonstration of IgE antibodies to radio-contrast media and the mechanism may be completely different. There have been numerous demonstrations of the ability of histamine H_1 and H_2 receptor antagonists to reduce the incidence of adverse effects due to direct histamine release during anaesthesia,[94-97] but there are no data for anaphylaxis. It is likely that such drug combinations would reduce the severity of anaphylaxis, but the current status of pharmacological pretreatment remains unproven. A combination of histamine H_1 and H_2 receptor antagonists as pretreatment reduces the mortality from chymopapain anaphylaxis.[98]

Pretreatment with high molecular weight dextran reduces the incidence of anaphylactoid reactions to dextrans, but may itself produce anaphylactoid reactions.[99]

2.3.2 Prick Testing Immediately Preoperatively

Another potential way of reducing the risk of anaphylaxis would be to preoperatively prick test the patient with the drugs to be used for anaesthesia. Whether prick testing is reliable in a 'sick' patient has not been determined. The endogenous catecholamine and corticosteroid response could theoretically reduce the reliability of the testing. A control such as morphine should be used to ensure histamine releasability and responsiveness are not impaired.

2.3.3 Test Dose

There is no evidence that a test dose reduces the incidence of anaphylaxis and administering test dose is probably not logical. A very small dose would need to be given (we have seen anaphylaxis from <30μg in skin testing). Should the dose be small enough to prevent anaphylaxis, the next logical step would be to use a larger dose. While the proposition is that a small enough dose could be chosen to give a lesser reaction it is unlikely in reality.

2.3.4 Desensitisation and Blocking

Two other techniques have been described when a relaxant anaesthetic is necessary in a patient who has had an undiagnosed anaphylactic reaction likely to be due to an NMBD or in a patient with skin test positive to all NMBDs.

NMBDs produce reactions by cross-linking cell bound IgE molecules through their divalent substituted ammonium ions.[100]

Thomas et al.[101] were able to desensitise a patient allergic to an NMBD with increasing doses of monovalent quaternary ammonium salt, tiemonium iodide, apparently prevented anaphylaxis to atracurium besilate by using other quaternary ammonium compounds.[102] They subsequently demonstrated that monovalent haptens inhibited skin reactivity and leucocyte histamine release in sensitised patients.[103]

This option provides an intriguing possibility, which has not been evaluated. The single substituted ammonium ion of morphine binds avidly to the IgE NMBD antibody *in vitro* and this is not associated with allergy to morphine.[60] Morphine is a readily

available source of a potential blocker drug which could be used as a substitute for the usual induction agents and has the potential to block anaphylaxis to NMBDs. A large dose (2–5 mg/kg) would be necessary, making the technique unsuitable for short cases. The use of a dose of this size may produce hypotension, particularly in elderly patients using β-adrenoceptor antagonists. H_1 and H_2 receptor antagonists prevent these effects.[94]

2.4 Subsequent Anaesthesia in Patients Who Have Been Investigated

Five studies have included data on subsequent anaesthesia in patients who have had reactions and been investigated by skin testing alone or skin testing, RIA, RIA inhibition and mast cell tryptase assays in various combinations. Leynadier et al. described 27 patients with positive prick tests for an NMBD of whom 13 had experienced 19 uneventful anaesthetics when a skin test negative NMBD was used.[74] Thacker and Davis found no subsequent anaphylaxis in seven patients with negative skin tests.[19] Three of 50 patients who had severe reactions and a positive skin test to an NMBD had second reactions to an NMBD, which had an equivocal skin test or was not tested at the time of the initial reaction. The 50 patients received 83 anaesthetics and an NMBD was used in 49 patients.[19] Moscicki et al. investigated 27 patients.[84] Of 11 with negative skin tests, three had subsequent anaesthesia and of 16 with positive skin tests eight had subsequent anaesthesia and none developed anaphylaxis. The patients in this series were premedicated with diphenhydramine.[84]

A Belgian study found positive skin tests to NMBDs in 43 patients.[104] Nineteen of these patients had uneventful exposures to skin test negative NMBDs on 26 occasions.

The current data from our own series are as follows.

- Seventy-one of 72 patients with a clinical diagnosis suggesting anaphylaxis was not the cause of the adverse reaction during anaesthesia and negative skin tests received uneventful subsequent anaesthesia and one patient had a prolonged block.
- Fifty-one of 52 patients who fulfilled clinical criteria for severe anaphylaxis and had negative skin and RIA tests had uneventful subsequent anaesthesia avoiding the drugs used in the culprit anaesthetic. One patient had a second reaction. A review of this patient's records 20 years later suggested latex hypersensitivity which was not considered at the time.
- Two hundred and ninety-five of 301 patients with positive skin tests (all drugs) after a severe reaction subsequently had uneventful anaesthesia. Six had second anaphylactic reactions, two to NMBDs not tested and four to NMBDs, which gave false-negative reactions.

These data suggest that although subsequent anaesthesia is safe, NMBDs are the drugs most likely to produce reactions.

3. Conclusion

The application of Whitby's proposed validity criteria for the application of screening tests, suggests that routine screening for anaesthetic allergy cannot be presently justified. Allegations in medicolegal cases of negligence due to 'failure to perform tests to establish the safety of drugs to be administered' cannot be supported, under many, but not all circumstances. However, there are identifiable risk factors, which should influence anaesthetic drug selection and where possible lead to delay of surgery to allow appropriate investigation. Also if these same criteria are applied to patients who have a documented history of anaphylaxis during anaesthesia, or a history of an unexplained or undocumented serious adverse event during anaesthesia it is difficult to justify inaction. In these specific groups of patients there are safe, effective techniques that can be undertaken prior to subsequent anaesthesia to reduce the risk of a reaction.

The minimisation of morbidity and mortality from anaesthetic anaphylaxis is more likely to be achieved by adequate training of anaesthetists to recognise, treat and investigate anaphylactic reactions, and prevent subsequent reactions than in any

screening procedure applied to all preoperative patients.

It behoves the anaesthetist to remember that the litigation industry does not necessarily rely on scientific evidence. Most of the cases of litigation related to anaesthetic anaphylaxis with which we have been involved include the allegation that in view of some aspect of the patient's history, steps should have been taken to determine that the drugs administered were safe. The prudent anaesthetist may therefore wish to avoid, where possible, using drugs where there is a suggestion of risk from the history, however small that risk is.

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Correspondence and offprints: Dr *Malcolm M. Fisher*, Intensive Therapy Unit, Royal North Shore Hospital of Sydney, St Leonards, Sydney, NSW 2065, Australia .
E-mail: mfisher@med.usyd.edu.au