

The preoperative detection of risk of anaphylaxis during anaesthesia

M. M. FISHER*

Departments of Anaesthesia and Medicine, University of Sydney and Intensive Therapy Unit, Royal North Shore Hospital, Sydney, New South Wales, Australia

SUMMARY

In 144 patients who were referred to an anaesthetic allergy clinic because of perceived risk of anaphylaxis during anaesthesia, the only 'at risk' group that could be identified was patients with a history of unexplained severe adverse reaction during previous anaesthesia. Twenty-two of 45 patients with such a history had positive skin tests to an anaesthetic drug. Twenty-one positive tests were to neuromuscular blocking drugs and one to an opiate. In 18 of these patients the medical records were available and an adverse event had been recorded consistent with anaphylaxis. On the contrary, investigation of patients without a previous adverse reaction did not appear to be of value. These findings suggest that those patients with a history of a severe undiagnosed adverse event during previous anaesthesia should be investigated with preoperative skin-testing before undergoing further elective surgery.

Key Words: anaphylaxis, anaesthesia, prevention, intradermal testing

Anaphylaxis during anaesthesia is a rare but serious problem. Although recommendations for preoperative investigation of patients deemed to be at risk have been suggested¹, the infrequency of the reactions, absence of validated risk criteria and absence of in vitro tests with high sensitivity make screening unlikely to show cost benefit². This paper describes the experience of an anaesthetic allergy clinic in the investigation of patients who were referred because of perceived risk of anaphylaxis during anaesthesia rather than because of an observed adverse event, with the aim of determining whether any 'at risk' groups who may benefit from preoperative skin testing could be identified.

METHODS

A total of 144 patients were referred to an anaesthetic allergy clinic over a 28-year period because of a perceived risk of anaphylaxis during anaesthesia. The patients were referred because of either a family history of anaphylaxis during anaesthesia, severe allergic history, a history of multiple chemical sensitivity syndrome

and/or chronic fatigue syndrome, allergy to a drug or food which might be relevant to anaesthesia, a past history of a severe reaction during anaesthesia with limited or no information available, or other conditions felt to predispose to anaphylaxis.

These patients differed from our standard referrals, which usually involve an adverse event directly observed by the referring anaesthetist.

Of these 144, 142 patients were intradermally tested for drugs that might have been used at a previous anaesthetic (if those drugs were available) and for all other commonly used anaesthetic drugs including propofol, midazolam and neuromuscular blocking drugs (NMBDs). Where possible, the drugs which the referring anaesthetist was planning to use were also tested. The method of intradermal testing has been described previously³.

Two patients with a history of suxamethonium apnoea were not intradermally tested: both were homozygotes on blood testing.

In the patients with a history of a previous reaction (not observed by the referring anaesthetist), efforts were made to obtain the anaesthetic record by contacting the hospital at which the reaction allegedly occurred.

After testing, all patients were given a letter stating the reason for referral and the results of our testing. They were also instructed to ask their anaesthetist to provide details of subsequent anaesthesia, so that we could determine whether any subsequent allergic reactions occurred.

* M.B., Ch.B., M.D., F.J.F.I.C.M., F.R.C.A., Clinical Professor, Departments of Anaesthesia and Medicine and Senior Staff Specialist, Intensive Therapy Unit.

Address for reprints: Professor Malcolm Fisher, Intensive Therapy Unit, Royal North Shore Hospital, St Leonards, N.S.W. 2065.

Accepted for publication on July 31, 2007.

RESULTS

The results are shown in Table 1. Of the 45 patients with a history of a previous adverse reaction, 22 had positive skin tests, one to an opiate and 21 to NMBDs. The medical records of the anaesthesia at which the possible reaction occurred were obtained in 36. Of these, nine showed no record of an adverse event during anaesthesia and 18 had reactions recorded that were consistent with anaphylaxis. Seven patients had minor adverse events documented. The records of the other two patients could not be found. One hospital had no record of the patient having attended. Only five of the 45 patients had any written information regarding the adverse event that led to referral. Feedback on subsequent anaesthesia was received for 36 of these patients, all of whom had an uneventful anaesthetic.

One patient of 15 with a family history of an anaphylactic reaction during anaesthesia had a positive intradermal test. The records of the reaction were obtained and the adverse event was postoperative vomiting.

Three of the patients with an allergy to a drug or food with possible relevance to anaesthesia had positive intradermal tests to the known allergen (ampicillin, pethidine, atropine) and no patient had a positive intradermal test to anaesthetic drugs.

Two patients with a history of allergy to eggs had negative intradermal tests to propofol and were challenged uneventfully with progressive intravenous doses. Both have received propofol a number of times uneventfully subsequently.

Three of 43 patients with multiple allergies had equivocal intradermal tests to histamine releasing NMBDs.

One other patient who was referred because of severe vomiting postoperatively had positive skin tests to NMBDs, which were probably unrelated to the adverse event.

In all, feedback was obtained on 117 subsequent anaesthetics. Of these, 115 patients had uneventful anaesthesia. Two patients had adverse events related subsequent anaesthesia, but neither was allergic in nature. Both were patients with a history of multiple chemical sensitivity, chronic fatigue syndrome and previous adverse reactions to anaesthesia. In both cases the subsequent adverse reactions occurred after discharge from hospital and neither the first nor the subsequent reactions were allergic in nature.

DISCUSSION

Intradermal testing has been demonstrated repeatedly to be a valuable test to determine the drug responsible for an anaphylactic reaction during anaesthesia. The routine use of skin testing of patients prior to anaesthesia to avoid anaphylaxis has been advocated in the past, but has only become practice in Spain after the High Court ruling deemed an anaesthetist negligent for failing to carry out allergy tests on a patient prior to undergoing general anaesthesia.

Studies of skin testing with anaesthetic drugs in volunteers suggest an unacceptably high incidence of false positive skin tests to neuromuscular blockers^{4,7}

TABLE 1

Reason for referral, results of testing and subsequent anaesthesia in patients referred to an anaesthetic allergy clinic with no documented reaction.

REASON for referral	Number	Intradermal test positive/number	Subsequent reaction/uneventful anaesthesia
Allergy to drug or food relevant to anaesthesia	29	3/29	0/24
Family history anaphylaxis during anaesthesia	15	1*/15	0/13
Multiple chemical sensitivity and/or chronic fatigue syndrome	4	1**/4	0/3
Multiple chemical sensitivity and/or chronic fatigue syndrome plus undocumented reaction	2	0/2	2/0
Other condition***	6	1/4	0/3
Multiple allergies	43	3/43	0/36
History of adverse reaction during anaesthesia	45	22/45	0/36

* Records obtained for relative and no reaction recorded in hospital records. Reaction occurred after discharge from hospital and not allergic.

** Patient with multiple chemical sensitivities developed wheals on the opposite arm when tested with propofol.

*** Included patients referred with succinylcholine apnoea (2).

Possible malignant hyperthermia susceptibility (1), mastocytosis (1), vasovagal reactions (1) and slow to wake and severe postoperative vomiting (1).

although the volunteers had not been given the test positive drugs. The false positives, in association with the low incidence of anaesthetic anaphylaxis, make it unlikely that skin testing is a useful screening test unless an at risk group can be identified. A study in Spain of 424 preoperative patients tested for 30 drugs by prick testing found 20 positive tests; 12 to NMBDs, four to iodine and two each to latex and etomidate⁸.

In a review of the literature, Fisher and Doig identified a number of risk factors for anaesthetic anaphylaxis, which included spina bifida, health workers with glove dermatitis, penicillin anaphylaxis, allergy to eggs, soybean, gelatin, exotic fruit, metabisulphate, or barbiturates and previous anaphylaxis and suggested that unexplained adverse reactions during anaesthesia could be a risk factor⁹.

This paper supports this suggestion: 22 of 45 patients with such a history had positive skin tests and the anaesthetic records indicated that anaphylaxis was a likely case in 18. After investigation and communication of the results to patients undergoing subsequent anaesthesia in 36 of these cases, all had uneventful anaesthesia. This included 14 patients with a history consistent with anaphylaxis.

Our findings suggest that patients who have a history of a severe but undocumented adverse response during anaesthesia may benefit from delaying elective surgery and using skin testing to evaluate the reaction and identify safe drugs. In our study, the reactions that led to referral occurred up to 20 years previously. Fisher and Baldo have demonstrated that antibodies to anaesthetic drugs persist for many years¹⁰. Therefore, delay of surgery and investigation should occur irrespective of how long ago the reaction occurred.

None of the other groups referred to us was shown to be at risk of anaphylaxis. We have subsequently stopped investigating these patients.

A family history of anaphylaxis has been suggested as important in one case of cousins who reacted to different NMBDs¹¹, but there are no other cases in the literature, nor in a series of over 1700 patients or in 42 blood relatives of 12 skin test positive patients, including identical twins tested prospectively¹². Chronic fatigue syndrome and multiple chemical sensitivity do not predispose to anaphylaxis during anaesthesia⁹ and although web sites devoted to these conditions advocate preoperative skin testing, there is no evidence of any benefit in this group.

In the patients investigated because of allergy to other drugs, no positive skin tests to anaesthetic drugs were found. The only allergies to other drugs or substances that suggest risk are exotic fruits and

latex, barbiturates and thiopentone, and egg/soybean and propofol⁹.

The question of egg and soybean allergy and propofol is an interesting one. As the warnings regarding possible cross sensitivity were a manufacturer's recommendation from the date of release of the drug, no convincing case has been reported. However, because propofol is so useful (in outpatient surgery in particular), it was felt reasonable to carefully challenge two people with a history that previously led to them being denied the drug. Both had no adverse effect and have since received propofol a number of times clinically without adverse effect.

Three of 43 patients with a history of multiple allergies had weak positive skin tests to NMBDs. It is not possible to determine whether these were false positive tests. The patients were given letters advising caution with these drugs with subsequent anaesthetics.

While there is an increased incidence of a history of allergy in patients who have anaphylaxis during anaesthesia compared to patients who undergo anaesthesia uneventfully¹³, the incidence of anaphylaxis is low and the majority of people with a history of allergy undergo anaesthesia uneventfully. In spite of this, it is not uncommon after anaesthetic anaphylaxis for a litigation claim to be made that the patient's allergic history should have led to preoperative skin testing. However, a history of allergy is not a predisposing factor to anaesthetic anaphylaxis¹⁴ and preoperative testing of these patients is not recommended.

The lack of documentation of adverse responses in many of the medical records obtained is of concern. Our clinic has provided all patients with a letter stating what happened, the results of investigations and recommendations as to the probable safety of alternative drugs, in addition to recommending warning bracelets in patients who had severe allergic reactions. It is difficult in Australia to obtain anaesthetic details of previous anaesthesia from hospital notes and we have therefore given information directly to patients and asked that they obtain details of subsequent anaesthesia from the anaesthetist concerned and feed this information back to us. This would enable us to update our records and modify their 'letter' if necessary. Unfortunately, the response from anaesthetists has been very disappointing. Nevertheless, availability of information regarding anaesthesia in patients at risk both reassures the anaesthetist and improves the safety of subsequent anaesthesia.

This study suggests that patients with a history of a severe undiagnosed adverse reaction during anaesthesia should have appropriate investigation such as skin testing preoperatively, and that their elective surgery should be delayed if necessary, pending the outcomes of this investigation. Further, if such patients present for urgent surgery that cannot be delayed, the safety of anaesthesia might be improved by preoperatively prick testing with the NMBD to be administered.

There does not appear to be any benefit in intradermally testing patients for anaesthetic allergy if there is no history of a previous serious adverse reaction.

REFERENCES

1. French Society of Allergy and Clinical Immunology. Reducing the risk of anaphylaxis during anaesthesia. *Ann Fr Anesth Reanim* 2002; 21 (Suppl 1):7-23.
2. Fisher MM. Skin testing in the preoperative diagnosis of anaesthetic allergy. *Ann Fr Anesth Reanim* 1985; 4:192-195.
3. Fisher MM. Intradermal testing after anaphylactoid reactions to anaesthetic drugs: Practical aspects of performance and interpretation. *Anaesth Intensive Care* 1984; 12:115-120.
4. Porri F, Lemiere C, Birnbaum J, Guilloux L, Lanteaume A, Didelot R et al. Prevalence of muscle relaxant sensitivity in a general population: implications for a preoperative screening. *Clin Exp Allergy* 1999; 29:72-75.
5. Dhonneur G, Combes X, Chassard D, Merle JC. Skin sensitivity to rocuronium and vecuronium: a randomized controlled prick-testing study in healthy volunteers. *Anesth Analg* 2004; 98:986-989.
6. Levy JH, Gottge M, Szlam F, Zaffer R, McCall C. Weal and flare responses to intradermal rocuronium and cisatracurium in humans. *Br J Anaesth* 2000; 85:844-849.
7. Berg CM, Heier T, Wilhelmsen V, Florvaag E. Rocuronium and cisatracurium-positive skin tests in non-allergic volunteers: determination of drug concentration thresholds using a dilution titration technique. *Acta Anaesthesiol Scand* 2003; 47:720-724.
8. Tamayo E, Alvarez FJ, Rodriguez-Ceron G, Gomez-Herreras JI, Castrodeza J. Prevalence of positive prick test to anaesthetic drugs in the general surgical population. *Allergy* 2006; 61:952-953.
9. Fisher M, Doig G. Prevention of anaphylactic reactions to anaesthetic drugs. *Drug Safety* 2004; 27:393-410.
10. Fisher MM, Baldo BA. Persistence of allergy to anaesthetic drugs. *Anaesth Intensive Care* 1992; 20:143-146.
11. Duvaldestin P, Wigdorowicz C, Inanna G. Anaphylactic shock to neuromuscular blocking agents: a familial history. *Anesthesiology* 1999; 90:1211-1212.
12. Fisher M. Anaphylactoid reactions during anaesthesia. MD Thesis. University of Otago 1986; p. 122.
13. Laforest M, More D, Fisher M. Predisposing factors in anaphylactoid reactions to anaesthetic drugs in an Australian population: the role of allergy, atopy and previous anaesthesia. *Anaesth Intensive Care* 1980; 8:454-459.
14. Fisher M, Outhred A, Bowey CJ. Can clinical anaphylaxis to anaesthetic drugs be predicted from allergic history? *Br J Anaesth* 1987; 59:690-692.

Copyright of *Anaesthesia & Intensive Care* is the property of *Anaesthesia & Intensive Care* and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.