

The investigation of bronchospasm during induction of anaesthesia

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Background: The aim of this study was to ascertain whether anaesthetic induction-related anaphylactic bronchospasm could be distinguished from other types of bronchospasm by clinical features and response to treatment. Such features could then be used to identify a group of patients in whom skin testing is indicated.

Methods: We retrospectively studied data from 183 patients referred to an anaesthetic allergy clinic because of bronchospasm during induction. For the analysis, the patients were divided into two groups depending on whether there was evidence suggesting immunological anaphylaxis.

Results: When the patients in whom intradermal tests were positive were compared with those in whom intradermal tests were negative, the skin test-positive patients had significantly more severe reactions, and they were

more commonly associated with other clinical signs. Mast cell tryptase (MCT) was an excellent discriminator between reactions likely to be allergic and those unlikely to be allergic.

Conclusions: Anaphylactic bronchospasm related to induction of anaesthesia is more likely to be severe than bronchospasm due to non-immune causes. An allergic cause is more likely if there are associated features of anaphylaxis (skin changes, hypotension, angioedema) or elevated MCT. Patients with any of these features should undergo immuno-allergological investigation.

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BRONCHOSPASM during anaesthesia occurs in 1.7–16% of patients depending on the patients studied and the drugs used.^{1,2} Smoking, chronic bronchitis, asthma and intubation are identifiable risk factors.¹ Up to 48% of patients with asthma developed wheezing after thiopentone in one study.² Bronchospasm occurs in 19% of patients with anaphylaxis during anaesthesia and is the only clinical feature in 4.5%.³

The main reason for undertaking this study of bronchospasm in a cohort of patients referred for investigation of an adverse event during anaesthesia was to determine if anaphylactic bronchospasm could be distinguished clinically from more common causes and whether patients who would benefit from post-operative investigation could be detected. Recently, Harper⁴ questioned which patients with bronchospasm need to be investigated, stating that the consequences of not doing so could be serious for the patient and the anaesthetist. He

noted a case in law in the United Kingdom, which emphasised the responsibility of the anaesthetist to refer such patients for expert investigation and diagnosis*.

Materials and methods

The clinical histories of 195 patients who were referred to an anaesthetic allergy clinic between 1978 and 2007 and in whom bronchospasm after induction of anaesthesia was the main clinical problem were reviewed.

Twelve patients were excluded as there was insufficient clinical information to analyse their records (eight) or if there was obvious clinical and/or radiological evidence of aspiration of gastric contents (four).

Severity was classified according to the classification of Brown,⁵ and the duration of the reaction

*Deceased

*[http://www.ipsfactoj.com/international/2005A/Part09/int2005A\(09\)-010.htm](http://www.ipsfactoj.com/international/2005A/Part09/int2005A(09)-010.htm)

was recorded as the time from first signs or symptoms until the patient was 'safe and stable'.

All patients underwent intradermal skin testing, which is the standard method of testing used in Australia.⁶ This testing used dilutions of the standard solutions of drug available in operating rooms. The dilutions used were 1:100,000 for morphine, pethidine and codeine, 1:10,000 for D-tubocurarine and atracurium, 1:1000 for all other neuromuscular blocking drugs and 1:100 for other drugs. Saline and histamine controls were used and in 1987 inability to obtain histamine led to changing the histamine test to 1:10 dilution of morphine 10 mg/ml unless morphine was a potential cause. Injections were performed using 0.01 ml of solution on the forearm at least 4 weeks after the reaction. When tests were negative, they were repeated with the dilutions decreased 10-fold. All patients with positive tests (persistent wheal >0.8 cm) in this group had positive tests at the first dilution. For analysis, patients were divided into two groups. Group 1 included patients in whom there was evidence suggesting the clinical anaphylaxis was immunologically or immunoglobulin E (IgE) mediated. This evidence included one or more positive cutaneous tests or drug-specific radioimmunoassay.⁷ Group two were patients in whom one or more of these skin tests were negative.

Mast cell tryptase⁸ (MCT) was performed in 76 patients and in 70 of these at an appropriate time for analysis (1–4 h).

The data were extracted from a database composed of patients referred to a single clinician (M.F.) for evaluation of suspected anaphylaxis or anaesthetic allergies. No assumptions were made about missing data. The written records of each patient were reviewed for accuracy.

All means were compared using a *t*-test and proportions were compared using a χ^2 test.⁹ Variables with significant univariate *t*-tests or χ^2 analyses were offered to a multivariate logistic regression model to identify independent predictors of likelihood of an anaphylactic reaction. Multivariate analysis was performed using STATA 9.2 for Macintosh (Stat Corporation, College Station, TX).

Institutional Ethics Committee approval was not required under National Medical Council Guidelines.

Results

There were 183 patients enrolled in this study. In all these patients, the treating clinician had noticed clinical bronchospasm. The characteristics of the

cohort are outlined in Table 1. One hundred and fifty-one (82.5%) patients were undergoing an elective surgical procedure.

Hypotension was observed in 73 (39.9%) patients. Angioedema was seen in 22 (12.0%) patients. A skin reaction was observed in 73 (39.9%) patients. When the patients' symptom were graded by Brown's severity score,⁵ 107 (58.5%) had Grade 3 symptoms, 74 (40.4%) had Grade 2 symptoms and 2 (1.1%) patients had Grade 1 symptoms.

The symptoms lasted a median of 30 min (interquartile range, 15–60 min). One hundred and nine (59.6%) patients had a vasoactive agent administered. Eighty-one received epinephrine alone, 16 received epinephrine plus another agent, and 12 received a different vasoactive drug (ephedrine six, noradrenaline two, and metaraminol four). Eighty-five (46.4%) patients had intravenous corticosteroids. One hundred and five (57.4%) patients received a bronchodilator.

All patients underwent skin testing. Thirty-nine of the 42 skin test-positive patients had elevated MCT levels. Three patients who had a negative MCT tested positive on skin test and all 28 skin test-negative patients showed no MCT elevation. MCT appeared to clearly distinguish between immune and non-immune bronchospasm in this cohort of patients (Table 2).

Table 1 shows the differences in various parameters between skin test-positive and -negative patients, along with the *P*-value for univariate analysis.

Significant variables remaining in the multivariate model are presented in Table 3. The presence of any skin reaction, shock, an episode of desaturation and a duration of symptoms >60 min were all independent predictors of a positive skin test. Except for these four variables, no other variables (e.g. history of asthma, difficult intubation, difficulty inflating the patient prior to induction) were significant independent predictors.

Long-term outcomes were available on 105 (57.4%) of the 183 patients with regards to subsequent anaesthetics. These 105 patients were advised on the basis of the skin test what drugs to avoid and those that were 'safe'. Of these patients, 103 (98.1%) had an uneventful anaesthetic, two (1.9%) patients reported difficulties with their subsequent anaesthetic. These problems were not anaphylactic.

Discussion

This study shows that patients with severe bronchospasm, other signs of anaphylaxis or elevated

Table 1

Demographic characteristics of patients with bronchospasm and suspected anaphylaxis

	Skin test		Sens	Spec	LR+	Univariate analysis P-value*
	Positive	Negative				
Age (mean $\pm$ SD)	35.6 $\pm$ 17.2	32 $\pm$ 15.3				0.17*
Gender (male)	21/113 (25.7%)	18/70 (18.5%)	0.18	0.74	0.72	0.25
Prior history of asthma	68/113 (60.1%)	37/70 (52.8%)	0.60	0.47	1.13	0.33
Skin reaction						
Rash	11/113 (9.7%)	3/70 (4.3%)	0.09	0.95	2.27	0.18
Urticaria	16/113 (14.1%)	2/70 (2.9%)	0.14	0.97	4.96	0.034
Erythema	45/113 (39.8%)	11/70 (15.7%)	0.40	0.84	2.53	0.001
Any skin change	72/113 (63.7%)	15/70 (21.4%)	0.63	0.79	2.97	<0.0001
NMB use	93/113 (82.3%)	57/70 (81.4%)	0.82	0.19	1.01	0.88
Hypotension	64/113 (56.6%)	9/70 (12.9%)	0.57	0.87	4.4	<0.0001
Desaturation observed†	45/48 (93.7%)	16/51 (31.3%)	0.94	0.69	2.99	<0.0001
Angioedema observed	22/113 (19.4%)	0/70 (0%)	0.19	1.0	∞	<0.0001
Difficult ventilation pre-intubation	26/113 (23.0%)	13/70 (18.6%)	0.23	0.81	1.23	0.476
Difficult intubation	2/113 (1.8%)	46/70 (65.6%)	0.02	0.58	0.04	<0.0001
Surgery was aborted due to symptoms	60/113 (53.1%)	59/70 (84.3%)	0.53	0.16	0.63	<0.0001
Received vasoactive drugs	89/113 (78.7%)	20/70 (28.6%)	0.78	0.71	2.76	<0.0001
Received corticosteroids	66/113 (77.7%)	19/70 (22.3%)	0.58	0.73	2.15	<0.0001
Bronchodilators, not adrenaline	67/113 (59.2%)	38/70 (54.2%)	0.59	0.45	1.09	0.505
Duration in minutes (mean $\pm$ SD)	88 $\pm$ 106	28.9 $\pm$ 37				<0.0001*

*t-test, otherwise results are from χ^2 .

†Data not available in all cases.

Sens, sensitivity; spec, specificity; LR, likelihood ratio of a positive test; NMB, neuromuscular blocker; SD, standard deviation.

MCT during anaesthesia induction are likely to have allergic bronchospasm. These patients should be investigated in a clinic with interest in anaesthetic anaphylaxis.

To place the findings of our multi-variate analysis in a clinical context, a patient with bronchospasm after the commencement of general anaesthesia, who develops hypotension is 27 times more likely to return a positive skin test compared to those who do not develop hypotension as part of the clinical presentation. If they develop an episode of desaturation, they are 21 times more likely to be skin test positive. In contrast, if they develop skin changes only (rash or urticaria) they are only twice as likely as those who don't develop any skin changes.

A plan for investigation is shown in Table 4.

There is no gold standard diagnostic test to distinguish immune from non-immune symptoms and signs of anaphylaxis.^{10,11}

Intradermal testing is the most utilised diagnostic test in Australia but because of inconsistent methodology and reported incidences of positive tests in controls,^{12,13} it remains controversial. Although all authorities agree that MCT is of value, there is controversy as to whether it distinguishes IgE-mediated reactions from non-immune reactions. MCT is released directly during *in vitro* studies^{14,15} but the results, for vancomycin in particular, do not correlate with *in vivo* studies.^{16,17} MCT levels show strong correlation with evidence for IgE involvement during anaesthetic reactions,⁸ and the validity of extrapolation of negative *in vivo*

Table 2

Mast cell tryptase in immune and non-immune bronchospasm on induction			
	Immune	Non-immune	Total
MCT elevated	39	0	39
MCT not elevated	3	28	31
Total	42	28	70
<i>P</i> -value (Fisher's exact test): <i>P</i> < 0.0001			
	Value	95% confidence intervals	
Sensitivity	100%	91–100%	
Specificity	90.3%	74.2–98%	
Likelihood ratio (+)	10.3	3.53–30.3	
Likelihood ratio (–)	0	–	
ROC area	0.95	0.9–1.0	
Positive-predictive value	92.9%	80.5–98.5%	
Negative-predictive value	100%	87.7–100%	

MCT, mast cell tryptase; ROC, receiver-operating characteristic.

Table 3

Multivariate logistic regression model predicting a positive test for anaphylaxis			
Predictor	Odds ratio (adjusted*)	95% confidence interval	<i>P</i>
Any skin reaction	2.3	1.5–5.7	0.0009
Shock	27.3	4.7–27.0	<0.00001
Desaturation	21.1	8.9–121.6	<0.00001
Episode duration > 60 min	6.9	1.8–10.4	<0.0003

*Adjusted for all the other covariates in the model.

results to the clinical situation has been questioned.¹⁷ While some authorities suggest elevated MCT levels *in vitro* usually can distinguish immune and non-immune anaphylaxis,¹⁷ others dispute this.¹¹

We believe that in this study the comparison based on MCT and intradermal tests is valid as they are the tests most likely to be performed if anaphylaxis is suspected. Thus, the literature reflects that subsequent anaesthesia is usually uneventful when based on the results of these tests.¹⁸

The role of direct histamine release (DHR) in the aetiology of bronchospasm during anaesthesia is also unclear. Studies of DHR in volunteers and patients rarely show evidence of airway involvement.¹⁹ The *in vitro* studies by Marone's group^{14,20} using pooled mast cells from different sites show that anaesthetic drugs release histamine from different mast cell groups. Morphine and thiopentone, for example, release histamine from skin mast cells only and therefore only a small portion reaches the bronchial musculature.²⁰ Other drugs such as pro-

Table 4

Indications for investigation of bronchospasm during induction	
All patients should have Mast cell tryptase performed at 1 h	
1. Patients who should be investigated	• Severity • Duration longer than 60 min • Desaturation • Need for sympathomimetics
2. Associated symptoms of anaphylaxis	
3. Difficult ventilation before intubation or LMA	
4. Elevated mast cell tryptase	
Patients who may be given a letter only	
	• Difficult intubation • Duration < 60 min • Response to simple measures, i.e. volatile anaesthetics • MCT not elevated

LMA, laryngeal mask airway; MCT, mast cell tryptase.

pofol, ketamine, atracurium, and vecuronium release histamine directly from lung mast cells in addition.¹⁴

The association with clinical findings is tenuous. While atracurium may increase bronchial tone, propofol and ketamine are bronchodilators effective in the prevention and treatment of bronchospasm^{2,21–23} although preparations of propofol containing metabisulphite may increase bronchial tone.²⁴

The clinical situation is compounded by the release of endogenous catecholamines (which may be broncho-protective) in association with DHR.^{25,26}

Histamine is a potent constrictor of bronchial muscle, particularly when nebulised into the airway, but its effects are reduced when it is given by infusion or released into the circulation.²⁷ A study of histamine infusion in non-atopic patients only produced changes in airways resistance after β -blockade, reflecting the small amount delivered by the bronchial circulation and the protective effect of sympathomimetics.²⁸ Indeed one of the factors making bronchospasm more serious in anaphylaxis or increasing the risk of bronchospasm during anaesthesia in asthmatics may be the impaired catecholamine response which occurs in asthmatics.²⁹ We suspect the histamine releasing properties of anaesthetic drugs may be an over-rated cause of bronchospasm on induction.

All of our patients received at least one and often two or more drugs capable of direct histamine release, but in this study we were unable to confirm or reject a role for direct histamine release in producing bronchospasm.

The reported incidence of wheezing or bronchospasm during induction of anaesthesia are between 1.7% and 16%,^{1,2} and anaphylaxis is a relatively rare

cause. In the bronchospasm component of the Australian Incident Monitoring study (AIMS) six of 42 cases of bronchospasm during induction were attributed to anaphylaxis; 23 were attributed to airway irritation.³⁰ Known risk factors include smoking, obstructive airways disease including asthma, obesity, upper respiratory tract infection, laryngoscopy, endotracheal tubes, laryngeal masks and acute respiratory illness in children.^{1,2}

The high specificity and sensitivity of MCT suggest it should be measured in all cases (at 1 h) and further investigation performed in anyone who has an elevated MCT and anyone with predictors of a positive skin test (a skin reaction, shock, desaturation or prolonged bronchospasm of longer than 60 min). Although failing to reach significance as independent predictors of anaphylaxis, it would also seem sensible to investigate those with other features that appear from our clinical experience to be suspicious for allergy, such as angioedema, a requirement for catecholamines or where bronchospasm has occurred before instrumentation of the airway. A resting MCT level should be performed 24 h later to exclude mastocytosis although in some patients with severe reactions elevated levels may persist longer than 24 h.

Conversely, patients in whom the reaction is the sole feature, of low severity and in whom the reaction occurs after airway instrumentation do not need referral, unless MCT is elevated.

We recommend, based on experience with a clinic studying such patients, that all patients should be given a letter describing the event and the investigations where performed. Anaesthetists should update the note after subsequent anaesthesia. This practise avoids the not uncommon problem of the patient's records being in another hospital and improves both patient safety and anaesthetist stress. This data and previously published data¹⁸ suggest this approach usually leads to safe subsequent anaesthesia.

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