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CLINICAL PRACTICE

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**Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing?**

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**Background.** The aim of this retrospective survey of possible allergic reactions during anaesthesia was to investigate whether the cause suspected by anaesthetists involved corresponded with the cause found on subsequent investigation in the Danish Anaesthesia Allergy Centre (DAAC).

**Methods.** Case notes and anaesthetic charts from 111 reactions in 107 patients investigated in the DAAC were scrutinized for either suspicions of or warnings against specific substances stated to be the cause of the supposed allergic reaction.

**Results.** In 67 cases, one or more substances were suspected. In 49 of these (73%) the suspected cause did not match the results of subsequent investigation, either a different substance being the cause or no cause being found. Only five cases (7%) showed a complete match between suspected cause and investigation result. In the remaining 13 cases (19%) there was a partial match, the right substance being suspected, but investigations showed an additional allergen or several substances, including the right substance being suspected.

**Conclusions.** An informed guess is not a reliable way of determining the cause of a supposed allergic reaction during anaesthesia and may put a significant number of patients at unnecessary risk. Some patients may be labelled with a wrong allergy, leading to unnecessary warnings against harmless substances, and some patients may be put at risk of subsequent re-exposure to the real allergen. Patients with suspected allergic reactions during anaesthesia should be referred for investigation in specialist centres whenever possible.

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Anaphylactic reactions during anaesthesia are quite rare (estimates of incidence are quoted in the literature to be between 1 in 10 000 and 1 in 20 000),<sup>1,2</sup> but when they do occur they may be serious and potentially life-threatening. When a patient is suspected of having an allergic reaction during anaesthesia, the anaesthetist should ensure that the patient is not re-exposed to the suspected causative substance. A warning should be written in the case notes and anaesthetic chart and the anaesthetist should inform the patient and give him/her a temporary warning card. In

Denmark, the clinician may refer the patient to the Danish Anaesthesia Allergy Centre (DAAC) for further investigation.

At the DAAC we have recognized that anaesthetists can rarely identify the cause of a suspected allergic reaction during anaesthesia. This is important as the patient and any future anaesthetists are warned about exposure to a specific substance based only on events in a previous emergency situation. We have analysed the degree of correlation between the causes suggested by referring anaesthetists and the results of subsequent investigation at the DAAC.

## Material and methods

We carried out a retrospective survey of all patients who had completed investigations at the DAAC in the period 1999–2003. At the DAAC, patients follow a standardized investigation programme with specific immunoglobulin (IgE) analysis [Pharmacia UniCAP® for latex (all patients) and succinylcholine, thiopental, fentanyl, morphine and various antibiotics (if the patient has been exposed to these drugs before the reaction)] and skin testing [prick testing and if this is negative also intradermal testing (except latex)] with all substances the patient was exposed to before the reaction.<sup>3</sup>

All case notes and anaesthetic charts were requested from the referring anaesthetic departments and scrutinized for suspicions of or warnings against specific substances. If any suspicion or warning was identified, this was compared with the result of our subsequent investigations.

The warnings were classified as follows: 'incorrect' if no allergy or an allergen other than the suspected allergen was found; 'partly correct' if the suggestion was right but an additional allergen was found, or if two or more suggestions were made but only one was correct; and 'correct' if there was a complete match between the suspected allergen and the investigation result.

## Results

One hundred and eight patients completed testing at the DAAC in the period 1999–2003. One patient was excluded from the study as it was not possible to retrieve the case notes and anaesthetic chart relating to the allergic reaction. One patient had an anaphylactic reaction during four separate anaesthetics; another patient had an anaphylactic reaction during two separate anaesthetics. Thus, the survey included a total of 111 cases of suspected allergic reactions in 107 patients.

Suggestion of a causative allergen was made in 67 case notes and/or anaesthetic charts (60.4%) and no suggestion was made in the remaining 44 cases (39.6%). There were more allergic reactions graded as serious (grades III and III+) among the cases in which suggestions of a causative allergen were made (Table 1). In approximately half of the patients, investigations at the DAAC indicated one or more

**Table 1** Grading of reactions according to severity related to whether a suggestion of causative allergen was made. Grade I, mild self limiting reactions e.g. isolated skin symptoms; grade II, moderate reactions quickly responding to therapy, e.g. moderate hypotension or bronchospasm; grade III, severe reactions requiring prolonged treatment e.g. anaphylactic shock; grade III+, cardiac or respiratory arrest. Grades modified from Ring and Messmer<sup>10</sup> and Galletly and Treuren<sup>11</sup>

	Suggestion made (67 cases)	No suggestion made (44 cases)
Grade I (38 cases)	17/38 (44.7%)	21/38 (55.3%)
Grade II (25 cases)	14/25 (56.0%)	11/25 (44.0%)
Grades III and III+ (48 cases)	36/48 (75.0%)	12/48 (25.0%)

allergies; in the other half no allergy was found. This was the case both for reactions where a causative allergen had been suggested and for reactions where no suggestion was made. In 49 of the 67 cases (73.1%), where a suggestion of a causative allergen was made, the suspected cause was not confirmed by subsequent investigations at the DAAC, either because other allergens were found (18 cases) or because no allergy was confirmed (31 cases). In only five of the 67 cases (7.5%) was there a complete match between the suspected substance and the investigation result. In the remaining 13 cases (19.4%) there was only a partial match, either because the right substance was suspected [but investigations showed an additional allergen (five cases)] or two or more substances, including only one right substance (eight cases), had been suspected. The average number of suggested causes in these eight cases was more than four compared with two for the other cases.

The median number of potential allergens to which the patients were exposed from induction of anaesthesia, including premedication when given, until the suspected allergic reaction occurred was nine for all cases and seven for the five cases where a correct suggestion of a causative allergen was made (Table 2).

In four out of the five cases with a correct suggestion of the causative allergen, the time between exposure to the allergen and recognition of the reaction was  $\leq 5$  min. In the group with incorrect suggestions of causative allergen, only two out of 17 reactions appeared within 5 min (Table 3). The substances most frequently suspected by anaesthetists

**Table 2** Number of potential allergens the patients were exposed to from induction of anaesthesia (including latex, chlorhexidine, volatile anaesthetics and premedication when given) until the suspected allergic reaction occurred

	Median	Range
All cases	9	3–19
Cases where allergy was found	9	3–19
Cases where no allergy was found	9	3–18
Cases where suggestion of causative allergen was made	9	3–19
Cases where no suggestion of causative allergen was made	9	3–18
Cases with incorrect suggestion	9	4–17
Cases with partly correct suggestion	10	4–19
Cases with correct suggestion	7	3–9

**Table 3** Time between exposure to the causative allergen and recognition of the allergic reaction (for latex and chlorhexidine the time of exposure is estimated to be between induction of anaesthesia and start of surgery). \*In the Incorrect suggestion group, one case is excluded, as the time of exposure cannot be determined

	Correct suggestion of causative allergen (cases)	Partly correct suggestion of causative allergen (cases)	Incorrect suggestion of causative allergen (other allergen found) (cases)
5 min or less	4 (80%)	8 (62%)	2 (12%)
More than 5 min	1 (20%)	5 (38%)	15 (88%)
	5 (100%)	13 (100%)	17* (100%)

**Table 4** Allergens suspected by the referring anaesthetists in the 67 cases (66 patients) where a suggestion of causative allergen was made. NSAID, non-steroidal anti-inflammatory drug

Allergen	No. of cases
Opioids	27
Alfentanil	2
Fentanyl	11
Morphine	5
Pethidine	2
Remifentanil	6
Sufentanil	1
Antibiotics	26
Cefuroxime	9
Dicloxacillin	1
Gentamicin	5
Mecillinam	1
Metronidazole	4
Penicillin	4
Vancomycin	2
NMBAs	21
Atracurium	3
Cisatracurium	2
Mivacurium	2
Rocuronium	11
Succinylcholine	2
Vecuronium	1
Propofol	12
Thiopental	11
Local anaesthetics	10
Local anaesthetics (group)	2
Bupivacaine	3
Lidocaine	3
Lidocaine + epinephrine	1
Mepivacaine + epinephrine	1
Colloids	9
Hydroxyethyl starch	1
Dextran 70 (Macrodex®)	6
Dextran 1 (Promit®)	2
NSAIDs	4
NSAID (group)	2
Diclofenac	1
Ketorolac	1
Volatile anaesthetics	3
Desflurane	1
Sevoflurane	2
Latex	8
Chlorhexidine	8
Others	5
Diazepam	1
Lorazepam	1
Ondansetron	1
Acetaminophen	1
Patent Blue	1
Total	144

as having caused the supposed allergic reactions were opioids (19%), antibiotics (18%) and neuromuscular blocking agents (15%) (Table 4).

The allergies identified in the group of 67 cases where a suggestion of causative allergen was made are shown in Table 5.

The overlooked allergies, i.e. the allergies identified in the groups 'incorrect suggestion (other allergen found)' and 'partly correct suggestion (additional allergen found)' were to latex (27%), chlorhexidine (27%), low molecular weight heparins (11%), local anaesthetics (8%) and others (27%).

**Table 5** Allergens identified in 36 cases (35 patients) out of the group of 67 cases where a suggestion of causative allergen was made by the referring anaesthetist. NSAIDs, non-steroidal anti-inflammatory drugs

Allergen	No. of cases
Opioids	5
Fentanyl	1
Ketobemidone	1
Morphine	1
Pethidine	1
Remifentanil	1
Antibiotics	4
Cefuroxime	3
Penicillin	1
NMBAs	2
Cisatracurium	1
Mivacurium	1
Propofol	1
Thiopental	3
Local anaesthetics	2
Bupivacaine	1
Mepivacaine	1
Colloids	1
Dextran 1 (Promit®)	1
NSAIDs	1
Diclofenac	1
Latex	8
Chlorhexidine	9
Others	6
Atropine	1
Enoxaparin	1
Ondansetron	1
Patent Blue	1
Tinzaparin	2
Total	42

## Discussion

Correctly identifying the causative substance in a suspected allergic reaction during anaesthesia is obviously very difficult, as 73% of the suggestions made were not confirmed on subsequent testing at the DAAC, and only five out of 67 suggestions were completely correct. We are aware that investigation at the DAAC may in some cases produce false-negative or false-positive results, as they are based on skin testing and IgE testing, which, despite their limitations, are the mainstay of investigation in the field of anaesthesia allergy.<sup>4,5</sup>

Diagnosing an allergic reaction and distinguishing it from other symptoms occurring during anaesthesia is difficult, since almost all symptoms of allergic reactions are also common side-effects of anaesthesia, e.g. hypotension at induction of anaesthesia, tachycardia at intubation and start of surgery, and bronchospasm after mechanical stimulation of the airways. This may explain why an allergen was not found in a substantial number of the 'incorrect suggestion' cases. Another reason why an allergen was not found in these cases may be that some of the reactions resulted from non-specific histamine release, which has a non-IgE-mediated mechanism and may lead to a negative result on conventional allergy investigation.<sup>3</sup> The only way of finding the causative substance in such reactions would be a full-dose drug provocation test,<sup>6</sup> which is rarely done in

conventional allergy testing. That our investigations at the DAAC indicated an allergy in only about half of the cases referred is in accordance with results from other centres with a similar investigation programme.<sup>2,7</sup>

Identifying the correct causative substance is also difficult because, during anaesthesia and operation, patients are often exposed to a large number of potential allergens in a very short time. Thus, in the present study the median number of potential allergens was nine for all cases and only seven in the five cases where a correct suggestion of causative allergen was made. This may suggest that the smaller the number of potential allergens the greater the chance of a correct identification.

The time between exposure to the allergen and appearance of allergic symptoms is also important. The longer the time lapse, the more difficult it appears to identify the causative allergen correctly. The time of exposure to the patients' immune system is often difficult to pinpoint in cases of reactions to latex, chlorhexidine and drugs administered epidurally or subcutaneously, e.g. low molecular weight heparins and local anaesthetics. This might explain why in this study the most frequently overlooked allergies were chlorhexidine and latex. In Denmark, we systematically test all patients for chlorhexidine, and thus we seem to have a higher incidence of allergy to this substance than centres that do not test for it.<sup>8</sup>

Not surprisingly, this study also indicated that the more serious the reaction (grades III and III+), the more likely the anaesthetist was to document his/her warning to the patient against re-exposure to the suspected causative substance.

In conclusion, the present study indicates that relying on an informed guess as to the cause of suspected allergic reactions under anaesthesia can put a significant number of patients at unnecessary risk. Some patients may be labelled with an allergy they do not have, leading to unnecessary warnings against harmless substances. Other patients may be put at risk of subsequent re-exposure to the real allergen. Determining the cause of a suspected allergic reaction during anaesthesia is a specialist task, and it is not reasonable to expect clinicians to come up with the right answer in the clinical situation.

Reports of allergic reactions during anaesthesia reported to national medicines agencies may be of questionable value

if based only on observations and guesses made in the emergency situation. Our findings thus corroborate the view expressed in a recent editorial by Axon and Hunter,<sup>9</sup> in which they emphasized that all patients with suspected allergic reactions during anaesthesia should be referred to investigation in specialist centres. If this is not possible, we advise that the patient is given a letter describing the reaction that occurred during anaesthesia and listing all substances the patient was exposed to.

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