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## Intradermal skin testing in the investigation of suspected anaphylactic reactions during anaesthesia – a retrospective survey

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**Summary** : An anaphylactic reaction is a rare, but severe anaesthetic complication. In this retrospective survey we report on patients with a severe suspected anaphylactic reaction during anaesthesia and the investigation with intradermal skin testing of these suspected anaphylactic reactions. In the patients with an anaphylactic reaction to neuromuscular blocking drugs, the subsequent anaesthetic history was examined. Sixty-five patients suffered a suspected anaphylactic reaction between 1976 and 2001. In 47 patients skin testing was performed and 43 of these patients had positive skin tests : neuromuscular blocking drugs and succinylcholine more specifically, were the most frequently incriminated drugs. After the anaphylactic reaction 19 patients had surgery on 26 occasions with the use of a skin-test-negative neuromuscular blocking drug ; no problems occurred. Skin testing proved to be a reliable tool to investigate suspected anaphylactic reactions during anaesthesia and to guide the future use of neuromuscular blocking drugs.

**Key words** : Allergy ; Skin testing ; Anaesthesia ; Complications ; Neuromuscular blocking drugs.

### INTRODUCTION

Severe allergic reactions during anaesthesia are rare, but potentially life-threatening events (14). When the reaction is mediated by IgE-antibodies, it is defined as anaphylactic. The same clinical picture may occur as a result of a non-IgE mediated reaction (immune or non-immune) and is called anaphylactoid. IgE or other immune or non-immune mechanisms activate mast cells and basophils with the release of vasoactive and bronchoconstrictive mediators (eg. tryptase, histamine...). These mediators may cause cutaneous symptoms (generalized erythema, urticaria and angio-oedema) and symptoms involving the respiratory (bronchospasm) and the cardiovascular system (tachycardia, bradycardia, cardiovascular collapse and cardiac arrest). Treatment consists of instant interruption of contact with the possible antigens, immediate

administration of epinephrine, intubation, 100% O<sub>2</sub>, lower limb elevation, volume expansion, steroids, and H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists. The dose of epinephrine depends on the severity of the cardiovascular collapse. If necessary, external cardiac massage must be instituted immediately. To identify the causal agents and to provide precise recommendations for future anaesthetic procedures, skin testing is usually done 4-6 weeks after the event (2, 5). Cross-reactivity between neuromuscular blocking drugs (NMBDs) occurs in up to 60% of the patients (5, 14). Therefore determination of a safe NMBD for subsequent use during anaesthesia is a priority in the investigation. Nevertheless there is little information in the literature (5, 13, 15) regarding the risks of subsequent anaesthesia for patients who suffered an anaphylactic reaction to NMBDs.

The terms anaphylactic, anaphylactoid, and allergy are used inconsistently in the literature. Therefore we have chosen to define all the reactions, which clinically have the symptomatology of allergic reactions as *suspected anaphylactic reactions*, and if this is confirmed by a positive skin test to define it as an *anaphylactic reaction*.

In this retrospective survey we report on patients with a severe suspected anaphylactic reaction during anaesthesia and the investigation of these suspected anaphylactic reactions. In the patients with an anaphylactic reaction to NMBDs, the subsequent anaesthetic history was examined.

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## METHODS

Using the computer database of the department, the charts of patients with a suspected anaphylactic reaction within 10 minutes after induction of general anaesthesia, were reviewed. A suspected anaphylactic reaction was defined as a serious event during anaesthesia, thought to be allergic in nature by the attending anaesthesiologist at the time of the event. Because of the retrospective nature of the study, it was difficult to get a complete picture of all the signs and symptoms of the suspected anaphylactic reaction; to get an idea of the severity, the use and dose of epinephrine was looked up in the chart as well as whether external cardiac massage was done and whether the surgery was postponed. The following variables were recorded: age at the time of the reaction, gender, drugs given at induction of general anaesthesia, type of surgery and outcome (severe morbidity and mortality).

Since 1984, patients with a suspected anaphylactic reaction subsequently underwent intradermal skin testing after 4-6 weeks to determine the possible causal agent for the reaction. The seven patients who had the suspected anaphylactic reaction before 1984 were also invited for intradermal skin testing. Tests were done in an area where resuscitation facilities were available. Patients were tested not only for the suspected drugs, but for most of the intravenous anaesthetics available at that time. The practical aspects of performance and interpretation of the intradermal skin tests were as described in the article of M. FISHER (2). Drugs, which could modify the skin testing response such as H<sub>1</sub>-receptor antagonists, steroids, sympathomimetics, tricyclic antidepressants, were stopped prior to the testing. The test drugs were diluted in normal saline immediately before use. Table 1 shows the tested intravenous anaesthetics and their dilutions. 0.01-0.02 ml of the diluted drug was injected intradermally on the volar surface of the forearm with a 26-gauge needle to raise a 1-2 mm weal. If all tests were negative the drugs suspected of causing the reaction were retested with the dilution decreased tenfold. A negative control with normal saline to exclude dermatographism and a positive control with histamine to determine if the skin is able to react to histamine, was always performed. An intradermal skin test was considered positive if a weal and flare reaction occurred within 10 to 15 min at the injection site, resulting in a weal of greater than 8-10 mm, which persisted for more than 20 minutes. Since the available intravenous

Table 1

Drug dilutions used for intradermal skin testing.

Drug	Concentration in vial	Dilution for skin testing
Histamine	1 mg/ml	1 : 20
Normal saline 0.9%	90 mg/ml	1 : 1
Etomidate	2 mg/ml	1 : 100
Propofol	10 mg/ml	1 : 100
Thiopental*	25 mg/ml	1 : 100
Succinylcholine	50 mg/ml	1 : 1.000
Gallamine*	40 mg/ml	1 : 1.000
d-Tubocurare*	10 mg/ml	1 : 10.000
Pancuronium*	2 mg/ml	1 : 1.000
Vecuronium*	4 mg/ml	1 : 1.000
Rocuronium	10 mg/ml	1 : 1.000
Mivacurium	2 mg/ml	1 : 10.000
Cisatracurium	2 mg/ml	1 : 1.000
Atracurium	10 mg/ml	1 : 10.000
Sufentanil	0.005 mg/ml	1 : 100
Morphine HCl	10 mg/ml	1 : 100.000
Meperidine	50 mg/ml	1 : 10.000
Cefazoline	200 mg/ml	1 : 100

\* no longer used in clinical practice; testing has ceased.

anaesthetics changed over time, the tested intravenous anaesthetics changed accordingly.

The percentage of patients in whom intradermal skin testing was done, was determined. In the patients with a positive skin test to an intravenous anaesthetic, we checked if this agent was given during the suspected anaphylactic reaction. The most frequently incriminated agent, the incidence per year of the agents responsible for the anaphylactic reaction and cross-reactivity (positive skin test to more than one agent) between NMBDs were determined.

In the subset of patients with a positive intradermal skin test to NMBDs (Fig. 1), the charts were reviewed for surgery after the anaphylactic reaction; type of anaesthesia (general versus locoregional), use of NMBDs and outcome were recorded.

## RESULTS

The charts of 65 patients from 1976 to 2001 with a suspected anaphylactic reaction were reviewed. The distribution of the suspected anaphylactic reactions according to age and gender is shown in Figure 2. Mean age was 40 years. Eighteen (28%) patients were male, 47 were female (72%). Twenty-four patients were scheduled for gynaecological surgery, 10 for vascular, 6 for dental, 5 for abdominal, 5 for back, 5 for ear, nose and throat, 4 for orthopaedic, 4 for eye and 2 for general surgery.

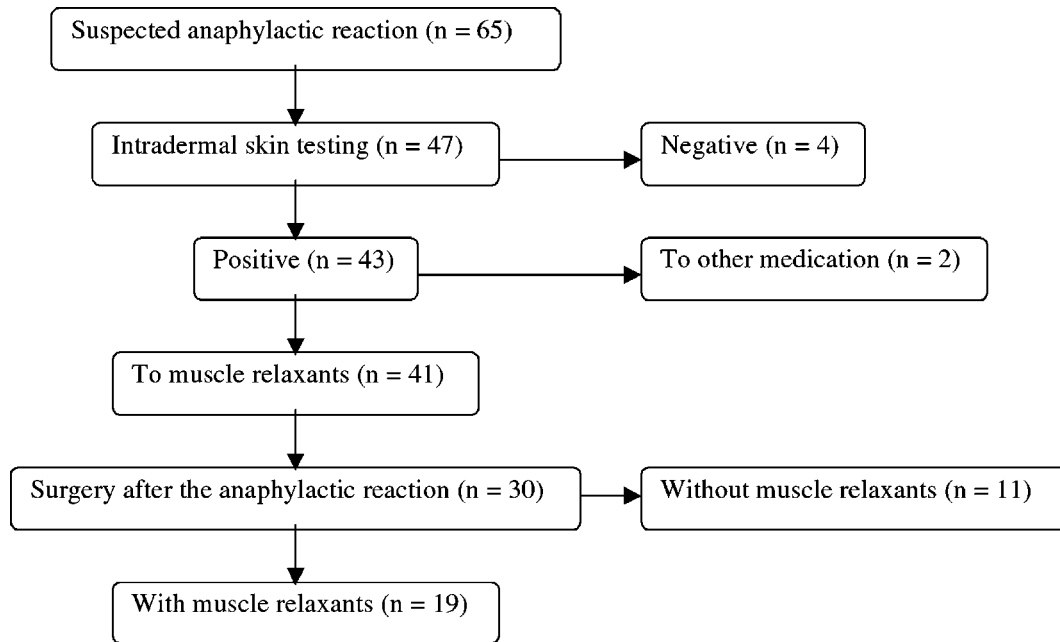


Fig. 1. — Flow diagram showing the investigation of patients with a suspected anaphylactic reaction (n = number of patients)

Table 2  
Incidence per year of anaphylactic reactions

Cause of the reaction :	76	77-81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01
Succinylcholine	1		1	1		2	2	1	1	1	2	1	3	2	5	7	1	2				
Succinylcholine + Gallamine					1					1		1										
Other agents			1				1				2										2	1
Total	1	0	2	1	1	2	3	1	1	2	4	2	3	2	5	7	1	2	0	0	2	1

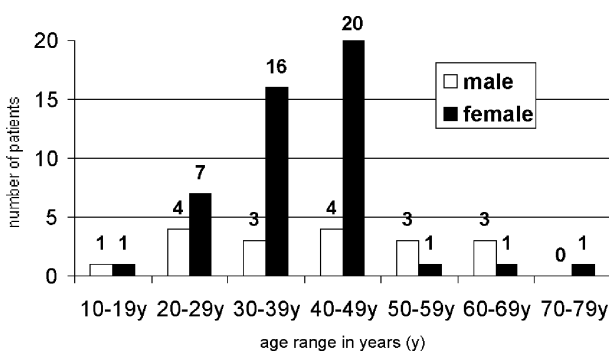


Fig. 2. — Distribution of the suspected anaphylactic reactions according to age and gender.

Fifty patients (77%) received epinephrine IV or/and SC ; when recorded, the mean dose per case was 1.3 mg. In 12 patients (18%) external cardiac massage was done. In 22 patients (34%) surgery was postponed. There was no severe morbidity or mortality.

In 47 patients (72%) intradermal skin testing was done. Six of the 7 patients who had a suspec-

ted anaphylactic reaction before 1984 were tested. In 4 patients (9%) intradermal skin testing was negative. Forty-three patients (91%) had positive intradermal skin tests. The incidence of the anaphylactic reactions was one to four reactions per year, except for 1994 and 1995 (Table 2). In all cases, at least one of the intravenous anaesthetics that tested positive, was used during the suspected anaphylactic reaction. Table 3 shows the agents identified by skin testing as the cause of the anaphylactic reaction. Forty-one patients had a positive intradermal skin test to NMBDs. Of these, succinylcholine (with or without gallamine) was identified as the cause in 36 cases (84%). NMBDs as a group were responsible for 95% of the reactions. Nine of the 41 patients (22%) tested positive for more than one NMBD (Table 4).

Of the 41 patients who tested positive for NMBDs, 30 had surgery since the anaphylactic reaction. In 11 patients NMBDs were avoided (general anaesthesia without the use of a NMBD in 9 patients, regional anaesthesia in 2 patients). The

Table 3

Agents identified by skin testing as the cause of the anaphylactic reaction

	Total = 43	Percentage
Succinylcholine	33	77
Gallamine	2	5
Succinylcholine and Gallamine	3	7
d-Tubocurare	1	2
Atracurium	1	2
Pancuronium	0	0
Vecuronium	0	0
Rocuronium	1	2
Fentanyl	1	2
Cefazoline	1	2

Table 4

Cross-reactivity between NMBDs

Positive intradermal skin test for :	Number of patients
Succinylcholine and Gallamine	4
Succinylcholine and d-Tubocurare	1
Succinylcholine, Pancuronium and Vecuronium	4

other 19 patients received NMBDs during 26 surgical procedures. In these cases, a NMBD that tested negative during intradermal skin testing, was chosen for muscle relaxation (Table 5). In all cases anaesthesia was uneventful.

## DISCUSSION

An anaphylactic reaction is a severe anaesthetic complication. In this survey 77% of the patients received epinephrine with a mean dose of 1.3 mg, in 18% external cardiac massage was done and in 34% of the patients surgery was postponed. Fortunately, there was no severe morbidity or mortality. An anaphylactic reaction to intravenous anaesthetic drugs is a rare event. The incidence in this survey was 1 in 2800 (65 suspected anaphylactic reactions in 26 years ; about 7000 general anaesthetics per year). The reported incidence in the literature varies from 1 in 1750 (8) to 1 in 20000 (4). Our results show a large female predominance

(2.6 females/1 male) and this is consistent with the findings from other studies (11, 12).

Only 72% of the patients were tested. In the remaining 28%, in one patient only one product (thiopental) was used and intradermal skin testing was deemed unnecessary. One patient refused. For the majority of patients no reason was given in the chart for not testing. On closer examination of these reactions, it was notable that epinephrine was used in fewer patients, that the mean dose of epinephrine was lower (0.4 mg), that less operations were cancelled and that external cardiac massage was performed less often. Perhaps because of a less severe reaction, the attending anaesthesiologist did not stress the importance of skin testing to the patient as strongly.

In 4 patients intradermal skin testing was negative. Three of these patients were not tested 4-6 weeks after the suspected anaphylactic reaction, but respectively 4, 11 and 4 years after the suspected anaphylactic reaction. Although skin testing may be positive up to 29 years after a reaction (3), increasing the interval between the reaction and skin testing, leads to a possible spontaneous decrease in specific IgE antibodies and as a consequence to more false negative skin tests (14).

Ninety-five percent of the anaphylactic reactions were due to NMBDs. The ammonium ions of the NMBDs are the main antigenic determinants involved in the generation of specific IgE antibodies. Since most NMBDs have 2 quaternary ammonium ions per molecule, bridging between two IgE antibodies, which is required to elicit anaphylaxis, is facilitated and explains the higher incidence of anaphylactic reactions to NMBDs compared to other anaesthetic drugs (14). The contribution of NMBDs in this study was higher than reported in other reports (95% vs. 70%) (11, 12). A possible explanation for this difference is that we only looked at possible anaphylactic reactions taking place within 10 min after the induction of anaesthesia and these reports looked at all possible anaphylactic reactions during anaesthesia. As a

Table 5

Type and frequency of NMBDs used after the anaphylactic reaction

	Gall.	Panc.	Vec.	Roc.	Atr.	Mivac.
Positive intradermal skin test for :						
Succinylcholine		1	9	4	5	1
Gallamine					1	
Succinylcholine and Gallamine			1		2	
Succinylcholine and d-Tubocurare					1	
Succinylcholine, Pancuronium and Vecuronium	1					

Gall. = Gallamine ; Panc. = Pancuronium ; Vec. = Vecuronium ; Roc. = Rocuronium ; Atr. = Atracurium ; Mivac. = Mivacurium.

consequence some reactions are not included : eg. anaphylaxis to latex tends to occur later during surgery (9) and colloids are mostly given during the maintenance of anaesthesia. The incidence of cross-reactivity between NMBDs in this study is lower than reported in the literature (22% vs. 60%) (5, 14).

In this survey anaphylactic reactions have been increasing in frequency over the years, with the highest incidence in 1994 and 1995. This increase could be due to a better recognition of an anaphylactic reaction or in case of NMBDs, to a gradual sensitization of the population to quaternary ammonium ions, which are widely present in foods, cosmetics and disinfectants. Sensitized individuals can thus react to NMBDs at their first contact (1). As most anaphylactic reactions were caused by succinylcholine the sharp decrease after 1995 is explained by the introduction of mivacurium, a short acting NMBD, and at the same time the diminished use of succinylcholine.

Every patient with a suspected anaphylactic reaction during anaesthesia should be investigated to determine the allergic nature of the reaction and to identify the responsible drug with the aim of providing a safe and documented advice for future administration of anaesthetics. Currently, we measure the serum concentration of mast cell tryptase 1 hour after the suspected anaphylactic reaction and perform skin testing 4 to 6 weeks after the reaction. The results of the serum concentration of mast cell tryptase were not reported in this paper, because it is a rather new technique (6, 10) which was introduced only the last couple of years in our hospital.

All NMBDs should be tested because of the high incidence of cross-reactivity. If a NMBD caused the anaphylactic reaction, a NMBD that tested negative during skin testing should be used during subsequent anaesthesia. In this retrospective survey, none of the patients with an anaphylactic reaction to a NMBD developed a second anaphylactic reaction to a skin-test-negative NMBD. One should remember, however, that using a NMBD that tested negative during skin testing is no absolute guarantee for prevention of an anaphylactic reaction and that the safest approach is to avoid all NMBDs if possible (7, 15). A warning card and a detailed letter containing information about the anaphylactic reaction and the results of the investigation should be given to the patient and sent to the general practitioner.

Anaphylactic reactions during anaesthesia are potentially lethal events (14). For this reason it is important to investigate the cause of these reactions

in order to guide the administration of safe anaesthesia in the future. Because anaphylactic reactions are so rare, every anaesthesia department sees at most a few reactions a year and it is difficult to get sufficient expertise in allergy testing. Ideally the investigation should be coordinated in a few specialized centres, as is done in France, Australia, New Zealand, the United Kingdom and Denmark. Centralisation has the additional advantage that proper epidemiological studies could be performed and that the results could be made available to the anaesthesia community.

In conclusion, in this retrospective survey skin testing proved to be a reliable tool to investigate suspected anaphylactic reactions during anaesthesia and to guide the future use of NMBDs.

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