

Danish Anaesthesia Allergy Centre – preliminary results

L. H. GARVEY¹, J. ROED-PETERSEN², T. MENNÉ² and B. HUSUM¹

Departments of ¹Anaesthesiology and ²Dermatology, Gentofte University Hospital, Copenhagen, Denmark

Background: Anaphylactoid reactions in anaesthesia are rare and should ideally be investigated in specialist centres. At Gentofte University Hospital, we established such a centre in 1998 as a joint venture between the Departments of Anaesthesiology and Dermatology. We present the methodology, diagnostic algorithm and preliminary results from our centre.

Methods: We are open for referral of patients from all of Denmark. Reactions are classified using a three-grade severity scale and all reactions ranging from mild to severe are investigated. Investigations follow a standard step-by-step protocol of *in vitro* testing and skin testing. Blood samples for tryptase analysis are taken at the time of reaction and a control sample is taken together with samples for specific IgE analysis 2–4 weeks after the reaction. Subsequent skin testing comprises both prick tests and intradermal tests in most cases. Patients are tested with all substances they were exposed to, including antibiotics, colloids, latex and chlorhexidine.

Results: A total of 68 patients have been referred to date (July 2001) and 36 have completed investigations. Positive test results were mainly seen in patients with more severe reactions, and there were more men than women in the group with the most

severe reactions. Six patients had positive specific IgE, three for penicillin, two for latex and one for thiopental. In all, 21 patients had positive skin tests to various substances, of whom four men with anaphylactic shock tested positive for chlorhexidine. Only one patient has tested positive to a neuromuscular blocking drug (NMBD) so far.

Discussion: Our preliminary results appear to differ in two ways from results usually found in this field. Firstly, only one patient has tested positive for a NMBD and secondly, we have had four patients with anaphylactic shock who have tested positive for chlorhexidine. Possible reasons for these differences are discussed.

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ANAPHYLACTOID reactions in anaesthesia are rare and it is therefore important to collect information about these reactions and to investigate patients in specialist centres. This has been done in some countries around the world (1–4). Centres have been established in France (5–7), Australia (8, 9) and the United Kingdom (10, 11), where patients are investigated to try and determine the nature and cause of anaphylactoid reactions in anaesthesia.

In Denmark such a centre, the Danish Anaesthesia Allergy Centre (DAAC), was established in 1998 as a joint venture between the Department of Anaesthesiology and the Department of Dermatology at Gentofte University Hospital, Copenhagen. A standardised investigation programme consisting of *in vitro* tests and skin testing has been established based on recommendations in the literature. This paper is a presentation of our centre and describes our methodology, diagnostic algorithm and preliminary results.

Patients and methods

The first patients were tested in the DAAC during 1999. In December 1999 information packs about anaphylactoid reactions in anaesthesia, including forms for referral and for ordering tryptase blood tests, were sent to all Departments of Anaesthesia in Denmark. Since May 2000 a senior house officer in anaesthesia has been assigned, part time, to coordinate the activities at the centre. In the Department of Dermatology a consultant dermatologist and a specially trained nurse are responsible for skin testing. The investigation programme (Fig. 1) has been devised after a thorough search of the literature, and comprises a combination of recommendations from the leading centres in this field (12–14). As terminology is not consistent in the literature, we have chosen to define all reactions which clinically have the symptomatology of allergic reactions as anaphylactoid reactions.

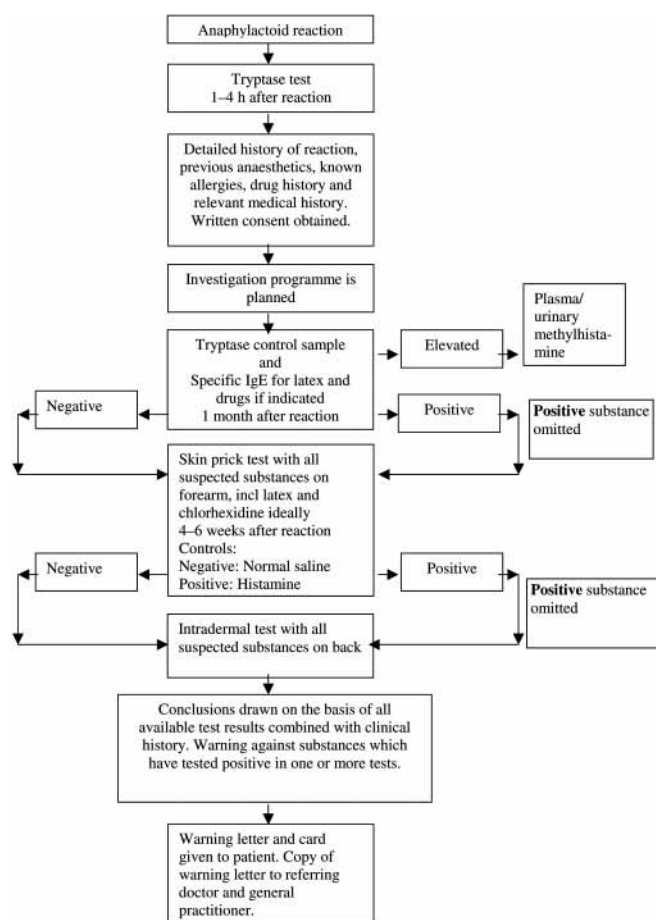


Fig. 1. Investigation programme for patients with anaphylactoid reactions in anaesthesia.

One to four hours after the anaphylactoid reaction, a blood sample is taken for tryptase analysis (Pharmacia UniCAP®). A control sample for tryptase analysis is taken approximately one month later, to record baseline levels (normal reference <13 µg/l).

On referral to the DAAC a detailed history of the reaction, including which drugs were given, the timing of symptoms, response to treatment etc. is obtained. Details of previous anaesthesia, known allergies and previous allergic reactions, drug history and relevant medical history are also obtained from the patient and medical records. Written consent from the patient is obtained on referral.

Reactions are classified into three predefined groups depending on the symptoms and severity of the reaction, modified from Galletly and Treuren 1985 (3) and Ring and Messmer 1977 (15):

Class I Mild reactions resolving spontaneously, usually only involving one organ system, e.g. urticaria, angioedema, rash;

Class II More severe reactions requiring treatment

but resolving within 10–20 min, usually involving one or more organ systems, e.g. hypotension, bronchospasm and urticaria;

Class III Very severe reactions requiring prolonged treatment, e.g. anaphylactic shock, usually, but not always, involving two or more organ systems.

Investigations usually include testing all substances to which the patient was exposed prior to the reaction, including antibiotics, colloids, latex and chlorhexidine. A blood test for specific IgE (Pharmacia UniCAP®) for latex (all patients) and some relevant drugs is obtained approximately one month after the reaction and no later than six months after, as IgE levels diminish with time. Tests for specific IgE are currently only available in the Pharmacia UniCAP® system for a few of the drugs used in anaesthesia (suxamethonium, thiopental, fentanyl, morphine and various antibiotics) but we choose to use it as an initial screening where possible. When specific IgE is *positive* we do no further tests with that particular substance and warn the patient against future exposure, but we still proceed to perform skin tests with the remaining suspected substances. In case of positive specific IgE to suxamethonium, skin testing is performed with the remaining neuromuscular blocking drugs due to the high incidence of cross-reactivity in this group of drugs. When specific IgE is *negative* we go on to perform skin testing with that substance in addition to other suspected substances (Fig. 1). Skin testing is ideally performed 4–6 weeks after the reaction, but as skin tests have been shown to remain positive for many years (16), this recommendation is rarely followed in practice.

Skin testing is performed by a specially trained nurse with the patient sitting or lying. Intravenous access is secured in all patients and there is ready access to adrenaline and resuscitation equipment. Dilutions of the suspected substances are made up the previous day by a laboratory technician; no preservatives are used. Test concentrations are made up following a standard protocol (Table 1). Where possible concentrations quoted in the literature are used (17–19). Prick testing is performed on the forearm with a device specifically made for the purpose (Prik lancet, Ewo, Sweden) (20). Negative control with normal saline and positive control with histamine is always performed.

When a substance causes a positive prick test, the test is repeated, and if still positive, no further testing is carried out with that substance and the patient is warned against future exposure.

If prick test is negative, intradermal tests are per-

Table 1

Substances which have shown positive tests, showing concentrations used, test modality and number of negative tests.

Substance	Concentrations used		Positive tests			Negative tests	
	Prick	Intradermal	Specific IgE	Prick	Intradermal	Specific IgE	Skin tests
Chlorhexidine	0.5%	0.0002% ¹⁾		3	2		17
Latex	Commercial extracts	not done	2			34	33
Propofol	1:10-undiluted	1:1000–1:10			1		18
Thiopental	1:10-undiluted	1:1000–1:10	1			18	19
Fentanyl	1:10-undiluted	1:1000–1:10			1		21
Remifentanyl	1:200–1:20	1:10.000–1:200		1 ²⁾			4
Ketobemidone	1:1000–1:10	1:100.000–1:1000			1		10
Morphine	1:400–1:40	1:200.000–1:2000			2	2	4
Pethidine	1:20–1:2	1:20.000		1	1		2
Atracurium	1:100–1:10	1:100.00–1:1000					9
Cisatracurium	1:10-undiluted	1:100.00–1:100			1		8
Mivacurium	1:100	1:100.00–1:1000					8
Pancuronium	1:10-undiluted	1:100.00–1:10					10
Rocuronium	1:10-undiluted	1:100.000–1:1000					13
Suxamethonium	1:50–1:5	1:100.00–1:500				8	14
Vecuronium	1:10-undiluted	1:100.000–1:500					1 ⁵⁾
Bupivacaine	0.01%–1.0%	0.01%–1.0%			1		13
Lidocaine	0.01%–1.0%	0.01%–1.0%			1		12
Mepivacaine	0.01%–1.0%	0.01%–1.0%			2		12
Prilocaine	0.01%–1.0%	0.01%–1.0%			2		11
Methylparahydroxybenzoat	0.1%	0.1%			1 ³⁾		10
Penicillin V	Commercial extracts	Commercial extracts	2			4	0
Penicillin G	Commercial extracts	Commercial extracts	2			4	0
Hydroxyethyl starch	1:100-undiluted	1:10.000–1:100			1 ⁴⁾		4
Promiten	1:10-undiluted	1:100.000–1:1000			1		4
Atropine	1:10–1:2	1:10.000–1:2000		1 ²⁾			2
Diclofenac	1:100–1:10	1:1000–1:100			1 ⁴⁾		4
Mepyramine	1:10	1:1000–1:10			1		0
Ondansetron	1:100-undiluted	1:10000–1:1000			1		10
Oxytocin	1:10.000–1:10	1:100.000–1:100			1		10

¹⁾ We only use this concentration as higher concentrations produce false positives.²⁾ Systemic symptoms similar to initial reaction; local reaction only with atropine.³⁾ One patient had a systemic reaction 2 h after testing and positive skin tests for all local anaesthetics, preservative and an antihistamine – she is being investigated for carcinoid syndrome.⁴⁾ Atypical rash around area of testing the following day; did not occur at test sites for other substances.⁵⁾ Since January 2000 vecuronium is no longer used in Denmark; testing has therefore ceased.

formed, as a combination of the two tests has proved to increase diagnostic yield (18, 21). If a neuromuscular blocking drug is testing positive, prick tests and intradermal tests are performed with the remaining drugs in that group due to the great incidence of cross-reactivity (22, 23). Intradermal testing is carried out on the back, which means many substances can be tested on the same day. The diluted drug is injected

until a wheal of 3–4 mm diameter appears. An intradermal test is considered positive if the wheal doubles in size and surrounding erythema appears. Conclusions are drawn on the basis of *in vitro* tests, skin tests and the clinical history. A warning card and detailed letter is given to the patient containing information about the reaction, which substances were given and results of the testing. A copy is sent to the referring doctor and the patient's general practitioner. Anaesthetists are urged to give feedback about future anaesthetics to the DAAC.

Results

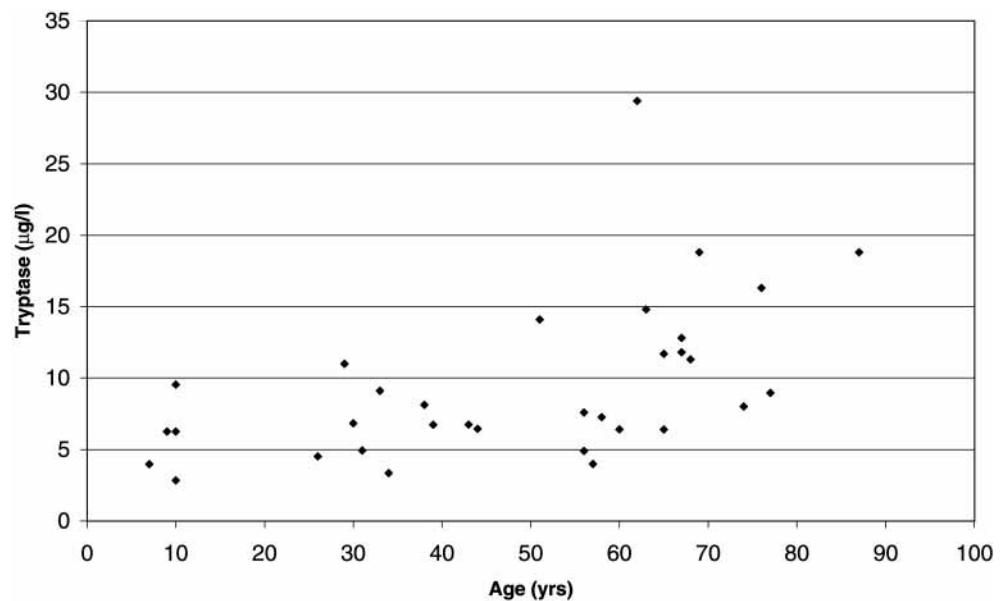
To date (July 2001), 68 patients have been referred and 36 have completed investigations (19 m/17 f), median age 49.5 years (range 7–87 years). Of these, there were 13 patients with class I reactions (5 m/8 f), 11 patients

Table 2

Test results divided into classes according to severity of reactions (n=36).

	Class I n=13	Class II n=11	Class III n=12
Negative n=15 (42%)	8	4	3
Positive n=21 (58%)	5	7	9

Fig. 2. Control serum concentrations of tryptase plotted against patient age ($n=33$). Tryptase normal reference value $<13 \mu\text{g/l}$.



with class II reactions (4 m/7 f) and 12 patients with class III reactions (10 m/2 f). A total of 21 out of 36 patients tested positive (58%) comprising five out of 13 tested in class I, seven out of 11 tested in class II and nine out of 12 tested in class III (Table 2).

Table 1 shows a list of the substances which have tested positive. Results are divided into the different test modalities and information on test concentrations used and number of negative tests is also included for skin tests and specific IgE where available. Two patients had specific IgE to latex, three patients had specific IgE to either penicillin V or G or both and one patient had specific IgE to thiopental. Skin tests have been positive to a variety of substances, including opioids and local anaesthetics, and only one patient has tested positive to a neuromuscular blocking drug (cisatracurium). Perhaps surprisingly four patients have tested positive to chlorhexidine, which is a widely used antiseptic around the world. These cases have been described separately (24).

Patients referred to DAAC have a control blood sample taken for tryptase analysis, whether or not a sample was taken in connection with their reaction. Only 8 of the 36 patients had a sample taken in connection with the reaction; six were taken at the recommended time 1–4 h after the reaction. Only one sample was greatly elevated at $155 \mu\text{g/l}$, this sample having been taken at 6 h after the reaction. In all, 33 out of 36 had control samples taken (three of our early patients did not have samples taken) and six results out of these 33 lie above the quoted reference value of $13 \mu\text{g/l}$. It is noticeable that the higher values are

found almost exclusively in patients aged 60 and over (Fig. 2).

Discussion

In Denmark we have tested patients with anaphylactoid reactions in anaesthesia for a couple of years. Prior to this only a few Danish case reports have been published (25–27). Our results are only preliminary, but there are two important findings:

We have so far found only one patient testing positive to a neuromuscular blocking drug (NMBD), and we have found 4 cases of anaphylactic shock caused by chlorhexidine.

There may be several explanations for our apparent lack of reactions to NMBDs. The most obvious explanation is that our numbers are small and that there is a definite underreporting of anaphylactoid reactions. On the other hand it may be that comparatively fewer anaesthetics include a NMBD in Denmark and therefore risk of sensitisation is less. Sensitisation is postulated to be caused by some environmental substance which may cross-react with NMBDs – perhaps this environmental substance is not very prevalent in Denmark. It is also interesting that the sex distribution in our results is quite different from that seen in other centres (7), with relatively fewer females having class III reactions.

Four patients with class III reactions subsequently tested positive for chlorhexidine on either prick test with 0.5% or intradermal test with 0.0002% chlorhexidine. Although no direct comparison can be made,

only 5 out of 565 patients (0.9%) referred to the Department of Dermatology, Gentofte University Hospital, for investigation of skin complaints in 1999 and 2000, tested positive on prick test with chlorhexidine 0.5%. We think that allergy to chlorhexidine might be more prevalent in surgical patients and we now routinely test all patients referred to us with chlorhexidine, to try and determine the incidence in this population. It may be that in future chlorhexidine will become as important as latex in postoperative investigation of patients with anaphylactoid reactions under anaesthesia. Latex allergy in patients undergoing surgery and anaesthesia is well described (28, 29) and as a consequence all patients referred to us are tested with latex (Fig. 1). We have found two cases of latex allergy so far, where both had positive blood tests for specific IgE to latex.

Another interesting finding relates to collection of control samples for tryptase analysis. Although only preliminary, our results suggest that patients aged 60 and over have slightly higher tryptase baseline levels than the population under 60 years of age (Fig. 2). In fact half of the patients over 60 years of age had baseline levels over the quoted reference value. This finding has not been reported before and the significance is unclear, but warrants further investigation, as it can have implications for the validity of the quoted reference value in this age group.

Only few doctors remember to take a blood sample for tryptase analysis at the time of the reaction, and when samples have been taken within the appropriate time interval most have been negative. So far, we test patients regardless of tryptase result, as we have seen several cases of positive skin tests or specific IgE despite a negative tryptase test.

The preliminary results from the Danish Anaesthesia Allergy Centre appear to differ from results traditionally found in this field. There may be several reasons for this.

Firstly, we get most referrals from hospitals in the vicinity and our results therefore mainly reflect the anaesthetic practice of the University Hospitals around Copenhagen. We are quite sure that a number of reactions occurring further away have so far not been reported to us.

Secondly, in addition to testing patients with serious and life-threatening reactions, we have chosen to test a number of patients with milder reactions to try and determine whether positive tests are found in this group of patients. It seems from our early results that patients with mild reactions are less likely to test positive (Table 2), which confirms findings in the literature (1). It is our belief, however, that some mild reactions

may be significant. We have found that some cases of postoperative rash/urticaria or facial oedema retrospectively have proven to be a forerunner of anaphylactic shock to chlorhexidine. We will continue to test patients with milder reactions until we have sufficient numbers to classify these reactions and thereby prove or disprove their relevance.

Thirdly, we test a wider range of substances than many other centres, as we test all substances including antibiotics, colloids, chlorhexidine and latex. All substances given prior to the reaction are tested and not just substances given within minutes of the reaction. We might therefore identify positive tests which may be missed by centres with a more restrictive testing protocol.

Fourthly, we accept a positive test in one test modality and do not go on to test further with that substance. We realise that we will incur some false positive tests this way, but feel that we would put the patient at unnecessary risk by testing with a substance that in most cases has produced a true positive. By investigating patients in a step-by-step fashion (Fig. 1) a negative test will usually mean that two or three test modalities have tested negative, which decreases the risk of false negatives. In this field, a false negative test may lead to the patient being put at serious risk at a subsequent anaesthetic. A false positive test, on the other hand, means restriction of the choice of drugs for an anaesthetic in future, which in most cases is harmless. For this reason we also warn against substances which cause non-specific systemic reactions or atypical skin reactions, as we cannot be sure how to interpret these findings.

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Address:

Lene Heise Garvey, MB, ChB
 Danish Anaesthesia Allergy Centre
 Dept. of Anaesthesiology
 Gentofte University Hospital
 Niels Andersens Vej 65
 DK-2900 Hellerup
 Denmark
 e-mail: daac@gentoftehosp.kbhamt.dk