



# NEW HORIZONS

## — ALLERGY —

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## Anaphylactic reactions during general anaesthesia

### Summary

Anaphylaxis during general anaesthesia is a rare but dramatic event that has been increasingly reported during the last decades. Neuromuscular blocking agents (NMBAs) represent the most frequent causes, with suxamethonium (SUX) as the prominent culprit drug. In most cases IgE-mediated mechanisms are involved, but since up to half the patients have not been previously exposed to anaesthetic drugs, other drugs or environmental chemicals sharing the quaternary ammonium ions (QAI) epitope with NMBAs are suspected of initiating IgE-sensitization. No gold standard for diagnosis exists, but most protocols include history, immunoassays for serum tryptase and IgE antibodies and skin and mediator release tests.

The calculated frequency of reactions varies considerably between countries, from about 1 in 5 000 to 1 in 20 000 anaesthetics in high prevalence countries. NMBA related anaphylaxis is much more common in Norway than in Sweden, a discrepancy at least partly explained by differently exposed and sensitized populations as indicated in a recent publication. The effect of possible IgE sensitizers was studied by testing 84 different chemicals collected from Norwegian and Swedish homes, of which several inhibited IgE binding to SUX and/or morphine (MOR). However, no difference in exposure to the above chemicals was found, except for the use of cough mixtures containing pholcodine (PHO). These are purchased without prescription (OTC) in Norway but are not available in Sweden. Further, the prevalence of IgE-sensitization to MOR, SUX and PHO in Bergen, Norway and Stockholm, Sweden was investigated. In Norway, 0.4 % of blood donors, 3.7 % of allergics and 38.5 % of NMBA anaphylactics were sensitized to SUX, as were 5.0, 10.0 and 66.7 % respectively to MOR. Among blood donors and allergics from Stockholm, no IgE antibodies to SUX or MOR were detected. IgE antibodies to PHO were present in 6.0 % of blood donors from Norway but in none from Sweden.

Additionally, in a pilot study two Norwegian individuals IgE-sensitized to PHO, MOR and SUX responded with a dramatic increase in serum IgE antibodies to 60 and 105 times the levels before exposure after one single daily dose of PHO during one week.

A PHO hypothesis is proposed, according to which the consumption of PHO-containing cough mixtures in Norway could offer one explanation both for the much higher prevalences of IgE-antibodies to PHO, MOR and SUX as well as NMBA induced anaphylaxis than in Sweden. PHO exposure could also be of relevance for the different prevalences of perianaesthetic anaphylaxis reported from other countries. However, further studies are needed.

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## Introduction

Although rare, anaphylaxis during general anaesthesia is a dramatic adverse event and a dreaded occurrence for the involved health personnel and, consequently, for the individual affected patient. Anaphylaxis not only challenges the diagnostic and therapeutic qualifications of the responsible anaesthetist, but also compromises patient safety and jeopardizes completion of the intended surgical intervention. Successful treatment is based on the early recognition and prompt administration of epinephrine (adrenaline) in addition to possible volume substitution, broncholytics, antihistamines and corticosteroids. Even when appropriately treated, mortality rates between 3.5 and 10% are reported (1-3). For the sake of safe future anaesthetics and completion of the often aborted surgical intervention, there is a need for valid identification of the cause of the reaction and its operative mechanism.

Defined as a general hypersensitivity reaction (4-5), anaphylaxis may present with several clinical manifestations and different levels of severity, but has certain characteristics. First of all the reactions are virtually unpredictable and most present themselves suddenly without forewarning during the induction phase of general anaesthesia. Although a large number of reports from several countries have been published during the past four decades or so, except for the knowledge of a previous reaction to one of the multiple drugs administered or a number of other exposures present at the operation theater, no valid predictive risk factor has been identified. The main group of victims to anaphylaxis seems to be middle aged women, while atopy, allergic diseases in general mediated by immunoglobulin E (IgE) antibodies, or previous reactions to drugs other than those administered during anaesthesia do not seem to significantly affect the risk level.

Besides the lack of clinically useful risk factors, the concept of anaphylaxis during anaesthesia carries a number of conceptual challenges. One is the early diagnostic recognition of the reaction, and the differentiation towards drug effects like fall in blood pressure, tachycardia and flushing, and a compromised ventilation may have several explanations. Another challenge is to establish optimal diagnostic strategies and facilities to follow up reactions and to identify the mechanism and the causative drug or other antigens. This represents a profound challenge since the perioperative situation is characterized by the intravenous administration of multiple different drugs within a short time interval. In addition, the patients may be exposed to a large number of non-anaesthetic drugs and other antigens related to diagnostic and surgical procedures. Thirdly, the prevalence of anaphylactic reactions related to general anaesthesia and the associated morbidity and mortality rates are not very well established since the mere rarity of the reactions demands large population studies to allow valid statistical frequency estimates (6-7). Due to the same reasons and to the lack of sufficient specificity, to date no *in vitro* screening tests have been advocated for the identification of risk individuals.

## Definitions and classifications

For the interpretation and comparison of results from different epidemiological studies on anaphylaxis one needs to be aware of the different definitions and classifications used. Recent progress in developing an internationally accepted

terminology for allergy has provided a better framework for more precise scientific communication (4-5).

## Anaphylaxis

Anaphylaxis is described as a severe, life-threatening generalized or systemic hypersensitivity reaction, i.e. the clinical manifestation *per se*, without any direct reference to the involved initiating mechanisms. Hypersensitivity is further defined as objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons. If an IgE-mediated mechanism is documented, the reaction is termed IgE-mediated anaphylaxis, otherwise the term non-IgE-mediated anaphylaxis is proposed. Still, even in very recent publications, the term "anaphylaxis" is used for reactions mediated by IgE, and "anaphylactoid" where no IgE can be detected with the methods used.

## Grading of severity

Anaphylaxis may present with different clinical manifestations and levels of severity. There are several grading scales used in the literature. Most later studies on anaphylaxis during anaesthesia, however, apply the relatively simple and practical scale of Ring and Messmer (8) which includes skin reactions (grade 1), systemic non-life-threatening reactions (grade 2), life-threatening reactions (grade 3) and cardio-pulmonary arrest (grade 4).

## Causality

The level of causality between a certain drug and the development of anaphylaxis is of undoubted scientific value, not least since several drugs with different risk profiles are administered within a very short time span during induction of anaesthesia. Further, the sensitivity and specificity of the employed diagnostic methods may vary considerably. Most reports tend to oversee this point, although the World Health Organization has developed the appropriate terminology (9) and criteria for sorting into the causality levels of certain (which demands rechallenge information), probable, possible, unlikely, unclassified and unclassifiable. The criteria have recently been modified to fit the present diagnostic situation of perianaesthetic anaphylaxis (10).

## Diagnostic centers and networks

From the published literature and reports to national and international medicine agencies, it becomes apparent that countries like Australia, New Zealand, France, Great Britain, Ireland and Norway see relatively more anaphylactic reactions during general anaesthesia than most other countries including Sweden, Denmark and the USA (1,11-15).

It is therefore natural that diagnostic centers and networks for this specific purpose, where anaesthetists and allergologists cooperate on follow-up examinations, primarily have been established in such high prevalence countries. The most prominent is the well-organized French GERAP (Groupe d'Etudes des Reactions Anaphylactoides Peranesthésiques) counting 40 national allergeo-anaesthesia centers using standardized diagnostic protocols and publishing biannual reports on the epidemiologic situation in that country. However, even in such a well organized network, a large portion of reactions escape proper diagnostic follow-up.

## Diagnostic protocols

Most diagnostic follow-up protocols are based on a two step strategy, the first being sampling of serum timely in close relation to the acute adverse event, and later an allergological follow-up examination, ideally within 3-6 months after the event. Although no gold standard diagnostic program exists, this strategy provides results from a number of tests, including careful histories with anaesthetic charts, analyses of mast cell tryptase, skin tests (skin prick tests (SPT) and intradermal tests (IDT)), immuno-assays for detection of IgE antibodies and *in vitro* mediator release tests. Based on these results a final diagnostic conclusion is made as to the culprit drug or antigen, mechanism of action, level of causality, degree of reaction severity and, further, therapeutic strategies for the next anaesthesia are suggested.

Differences exist between diagnostic centers and studies as to methodological details and quality control of techniques. Accordingly, the diagnostic sensitivities may vary considerably, not least since full dose provocation tests, demanding to perform, have not been considered justified for ethical reasons.

Tryptase ImmunoCAP™ assay (Pharmacia Diagnostics AB, Uppsala, Sweden) measures both the alpha- and the beta-form. An increase of serum tryptase 2-4 h after the event to beyond the upper reference value of the laboratory or three times that of the baseline value, with successive normalization, is regarded specific for acute mast cell activation. The mechanism of activation is thereby not indicated, although some report higher tryptase levels in IgE-mediated anaphylaxis. On the other hand, cases of supposedly IgE-mediated reactions to a neuromuscular blocking agent (NMBA), where serum tryptase is not elevated, are also reported. This may in part be explained by the timing of sampling, the T<sub>1/2</sub> for tryptase is about 2.5 hrs, and test sensitivity, but may also raise questions as to the role of the basophil during anaphylaxis. To date no specific serum marker for *in vivo* basophil activation has been available.

The Norwegian Network for Anaphylactic Reactions during general Anaesthesia (NARA) is an anaesthesio-allergological cooperative network located at five University Hospitals in Norway. For evaluation of the acute reaction it has aimed at obtaining a three time point profile of tryptase in serum samples collected before the event, within 2-4 h after, and the next day to provide more reliable information. Serum samples and standardized clinical information is sent to the Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen. In addition to tryptase, routine measurements of total IgE, and IgE antibodies to relevant commercially available allergens, i.e. suxamethonium (SUX) and latex, using ImmunoCAP™ System (Pharmacia Diagnostics, Uppsala, Sweden) are done. This strategy allows the registration of most (but certainly not all) anaphylactic reactions in Norway, it ensures at least a minimum of diagnostic activity after the reactions and, since the test results are summarized and reported back to the responsible anaesthetist, enables to advise allergological follow-up examinations in relevant cases.

For follow-up examinations, most investigators use SPT as the first step in skin testing protocols. Attention is demanded to the flat dose response curve, controls, technical performance and reproducibility of SPT (16-17). A mean wheal diameter of 3 mm larger than that of the negative control is regarded positive to that particular allergen, i.e. indicating that the reaction is IgE-mediated. IDT is performed

if the SPT to a suspected allergen is negative, and for the study of NMBA cross reactivity. IDT may for some allergens improve sensitivity, but on the other hand compromises specificity. Again considerable attention is needed as to technical performance, reproducibility and defining positive responses. Another challenge relates to defining threshold test concentrations for hypersensitivity to the different drugs. Controversies exist as to what are the precise drug test concentrations that most reliably differentiate between immunological hypersensitivity reactions and those caused by pharmacological, toxic or other non-immunological mechanisms (18-20). The question also emerges whether the concentration threshold found in one study can be expected to be valid for other populations, since immunological sensitivities vary, and possibly also unspecific skin reactivity.

Direct serological measurement of IgE antibodies is another basic diagnostic step during follow-up examination. At present the commercial availability of IgE tests for specific NMBAs and other antigens relevant for the peranaesthetic exposure is restricted. Screening tests for the quaternary ammonium ions (QAI) containing allergenic epitopes have been published using either choline, P-aminophenyl-phosphoryl-choline (PAPPC) or morphine (MOR) (21-23). Although a positive screening test would increase the probability of an anaphylactic reaction related to a given NMBA to be IgE-mediated, the specificity of such tests are too low. Using additional inhibition steps with the suspected NMBA increases diagnostic performance, but demands the resources of a specialized allergy research facility that are normally not available for routine diagnostics. As a consequence of ongoing clinical studies, tests for IgE antibodies against pholcodine (PHO) and MOR, in addition to a PAPPC screening test using ImmunoCAP, have been developed and are currently under validation. Other possible incrementing agents also available in the ImmunoCAP panel are chlorhexidine, latex and thiopentone.

*In vitro* mediator release tests monitoring either the increase of histamine or leuko-trienes after stimulation of blood basophils with allergen are used in several studies for the indirect documentation of IgE-mediated mechanisms. In general, methods relying on quantification of the released mediators are hampered by low sensitivities, although the specificities are reported acceptable. Studies using flow cytometric measurements of the up-regulated basophil cell surface markers CD63 and CD203c have recently been published, but even after such methodological refinements sensitivities still seem unsatisfactory (24-26). Again, these test modalities are accessible only in specialized laboratories.

## Prevalences of anaphylaxis

The general frequencies of anaphylaxis during anaesthesia are reported to be between 1 reaction in 10 000 to 20 000 general anaesthetics (12). In France from 1994 to 1996 the overall prevalence was 1 reaction in 13 000 anaesthetics, while for NMBAs the frequency was 1 in 6 500 NMBA exposed (27). A recent 6-year single-center follow-up study from Norway estimated 1 in-hospital IgE-mediated NMBA anaphylactic reaction per 5 200 general anaesthetics where NMBAs had been administered (95% CI 1:14 285-1: 3 125) (10). For specific NMBAs like rocuronium, the Norwegian Medicines Agency in 2001 estimated a frequency of 1 in 5 000, a more than 20-fold higher number than for the rest of Scandinavia (6).

Besides the varying frequencies between countries, published reports also indicate relative differences in the causes of reactions. In most reports 60-70 % of the reactions are characterized as “anaphylactic” in the sense that they are IgE-mediated, and about 30 % as “anaphylactoid” meaning non-IgE-mediated according to comprehensive nomenclature. Furthermore, 54-66 % of the reactions are caused by an NMBA (table 1) with SUX as the most frequently incriminated drug, 37.6 % in France and 36.1 % in Norway, followed by rocuronium in France (26.2 %) and Norway (20.5 %). Depending in part on anaesthetic practices other NMBA reactions are caused by vecuronium, pancuronium and atracurium, however considerably less frequently reported. In France 22.3 % of reactions are caused by IgE-mediated allergy to natural rubber latex, while this only applies to 3.6 % in Norway (10,12). In a preliminary report from the Danish Anaesthesia Allergy Centre, the ubiquitously used disinfectant chlorhexidine has emerged as a prominent cause of anaphylaxis surpassing the role of NMBAs (28).

**Table 1.** Prevalence of substances found to cause an anaphylactic reaction during anaesthesia. The figures are those reported from the respective national centre for the last years.

Substance	France (29)	Norway (10)	Denmark (30)
NMBA	54.0 %	66.2 %	8.7 %
Latex	22.3 %	3.6 %	13.8 %
Antibiotics	14.7 %	-	15.0 %
Opioids	2.4 %	-	17.5 %
Chlorhexidine	-	-	11.2 %
Others	6.6 %	30.2 %	33.8 %

In addition to the anaesthetic drug combinations used, a considerable number of other drugs and antigens like antibiotics, opioids, colloid solutions, radiocontrast media, intravenously administered dyes (isosulphan blue), disinfectants, latex, and even extremely rarely local anaesthetics, must be considered as possible causative agents. This not only challenges the thoroughness of history taking in identifying all possible perianaesthetic exposures, but consecutively also the performance of the available diagnostic test methods.

The differences in reported prevalences and the relative distribution of causative agents may be explained by several factors. First of all by statistics, since the very rare occurrences demand large numbers of study objects to achieve sufficient statistical power. In such cases reporting bias, both the underreporting of reactions to well known substances like SUX and latex, and possible overreporting of reactions to new drugs on the market may severely influence the results. In addition, genetically different populations and different anaesthetic practices may influence the results, and so may the availability of diagnostic networks for follow-up investigations, different diagnostic protocols and variations in methodological techniques. Finally it must be recognized that surveys from different countries may reflect differently exposed and sensitized populations.

In a relatively large portion of reactions, about 30%, the causing agent or pathogenetic mechanisms could not be identified. This is in itself an interesting research field that may comprise immunological hypersensitivity mechanisms not detected with the diagnostic methods used (low sensitivity), dose dependent side effects of anaesthetic drugs, non

immunological activation of effector systems like direct histamine release and, probably reactions caused by other presently unknown antigens and mechanisms.

## The allergenic epitope – the quaternary ammonium ion

Studies several years ago identified the QAI as the most likely allergenic epitope for the specific binding of IgE to the NMBA (31). However, other amines, especially tertiary structures, have been shown both to function as haptens and being capable of inhibiting the QAI-specific reaction. To be capable of initiating an IgE-mediated anaphylactic reaction the NMBAs have at least to be bi-valent for the QAI epitope in order to cross-link IgE antibodies on sensitized mast cells and basophils, and thus trigger the release of inflammatory mediators.

To screen for individuals IgE-sensitized to the QAI epitope, MOR has been suggested (23). MOR has an unusual alkaloid structure with only one QAI epitope that actually is a tertiary amine. It can therefore not by itself trigger mast cells or basophils sensitized with IgE antibodies to QAI, but has been suggested to be used for the detection of an IgE-sensitization to QAI. However, the presence of IgE antibodies to MOR has a low specificity for IgE-sensitization to SUX (see below) and thus a low predictive value for an allergic reaction upon exposure. A MOR positive serum must be further tested against the NMBA intended to be used to allow a risk assessment. Although very little is known about the clinical significance of risk thresholds for serum levels of IgE antibodies to QAI, it is known that an individual with high serum levels of IgE antibodies to a classical allergen ( $>3.5 \text{ kU}_A/\text{L}$ ) is at great risk of a severe reaction when exposed. An additional risk factor for severity by itself is the intravenous administration of anaesthetic drugs.

## Norway and Sweden – similarities and differences

As stated above, reports indicate that anaphylactic reactions caused by NMBAs are much more common in Norway than in Sweden. To explore this intriguing finding, the two countries were considered suitable study objects. Not only are they closely located geographically, but also climatic conditions, the standard of living, population genetics and constitution are very similar. The anaesthetic practices are also much the same and there is little reason to believe that reporting bias alone would affect reporting frequency significantly, even if diagnostic follow-up services so far are more available in Norway. The hypothesis was that differently exposed and sensitized populations could explain the discrepancies between the countries. Since up to half of the patients are reported not to have been anaesthetically exposed (12), other drugs or environmental substances sharing allergenic epitopes with the NMBAs must have initiated the sensitization, the prerequisite for an allergic reaction. A study was performed to document the prevalence of IgE-sensitization to MOR and PHO, recently developed for ImmunoCAP, together with SUX. Comparable populations in Bergen, Norway and Stockholm, Sweden were selected and attempts were made to identify factors in the environment that might explain the geographical differences (14).

A total of 300 superfluous volumes of “allergic” sera were consecutively sampled from the allergy diagnostic laboratories at the Haukeland and Karolinska University Hospitals, in Bergen and Stockholm, respectively. Further, sera from 500 blood donors were collected and, in Bergen, sera from 65 patients having previously reacted anaphylactically to NMBAs during anaesthesia, were included. The serum samples were tested for IgE antibodies to MOR, SUX and PHO, using ImmunoCAP Specific IgE assay. In summary the results showed that in Norway 0.4 % of blood donors, 3.7 % of allergics and 38.5 % of anaphylactics were IgE-sensitized to SUX, as were 5.0, 10.0 and 66.7 % respectively to MOR. In sera from the blood donors and allergics from Stockholm, no IgE antibodies to SUX or MOR were detected. IgE antibodies to PHO were present in 6.0 % of blood donors from Norway but in none from Sweden. Approx. 65 % of the anaphylactics were sensitized to PHO. The majority of those sensitized (69 %) were women. About 70 % of the sera with IgE antibodies to MOR/PHO in the allergic group did not react with SUX, and the IgE antibodies could be inhibited by MOR but not by SUX.

A large number of regular household chemicals are known to carry QAI structures similar to those present in NMBAs. Therefore, a total of 84 different household and other environmental chemicals (skin care ointments, hair care products, cough syrups, lozenges, tooth pastes, cleansers and motor oils) from Norwegian and Swedish homes were tested for SUX and MOR content using IgE antibody inhibition analyses. Although several of the environmental chemicals inhibited the IgE binding to SUX and/or MOR, no definite difference in exposure could be found, except for the use of cough mixtures containing PHO. These are obtained OTC and widely consumed in Norway but are not available at all in Sweden. The results raise the possibility that the consumption of PHO in Norway could explain the much higher prevalence of IgE-sensitization to MOR and SUX and thereby also the higher frequency of anaphylactic reactions to NMBAs. Interestingly, PHO is used in decreasing doses *per capita*, in Ireland, France, Norway, U.K., New Zealand, Australia, Finland and Belgium. Most of these countries report high prevalences of anaphylactic shock during general anaesthesia. In contrast PHO is not available, or used very rarely (<1/1000 of Norway), in Sweden, Germany, USA and Denmark, which seemingly are low prevalence countries for NMBA anaphylaxis.

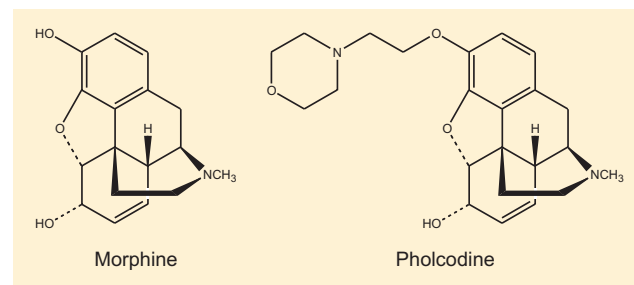
Cross-inhibition results indicate that MOR has at least two non-cross reacting allergenic epitopes, one of which is shared by SUX. The latter is most likely the QAI related allergen, while the former does not seem to be shared by the NMBAs. It is also indicated that MOR and PHO share not only the QAI related allergenic epitope, but also the non-QAI related allergen (figure 1). Since PHO seems to share most allergenic epitopes with MOR, an IgE-sensitization to PHO would in most cases be picked up with a MOR assay.

The possible sensitizing role of PHO was further addressed in a pilot study (32). Two Norwegian individuals IgE-sensitized to MOR, PHO and SUX, and two non-sensitized controls, were given a standard single dose of a PHO-containing cough syrup once daily for a week. After 7 days exposure, no effect of PHO was seen in the controls but the two sensitized participants experienced general itching and localized urticaria, respectively, and it was found that their serum IgE had increased dramatically: the IgE levels were 60 and 105

times higher than before exposure, respectively. This remarkable effect of PHO on IgE production and its possible clinical importance certainly warrants further studies.

## The pholcodine hypothesis

The following available data allows to propose a possible hypothesis for the different degrees of IgE-sensitization and NMBA related anaphylaxis reported for Sweden and Norway, possibly also relevant for the differences observed between other countries: Exposure to PHO in Norway, but not in Sweden, may explain the different degrees of sensitization to PHO, MOR and SUX in the two countries. Exposure to PHO can in susceptible individuals initiate a remarkably strong stimulation of IgE synthesis. IgE antibodies against PHO and MOR are of lesser clinical significance since both drugs are monovalent, but IgE binding to SUX bivalent for the QAI epitope may initiate release of mediators and cause anaphylaxis. Internationally, PHO sales seem quite well to match national reporting frequencies of anaphylaxis caused by NMBAs. Additional studies are mandatory to further test the hypothesis.



**Figure 1.** In addition to the QAI, marked in the figure, morphine and pholcodine share an additional allergenic epitope, the structure of which is not known.

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